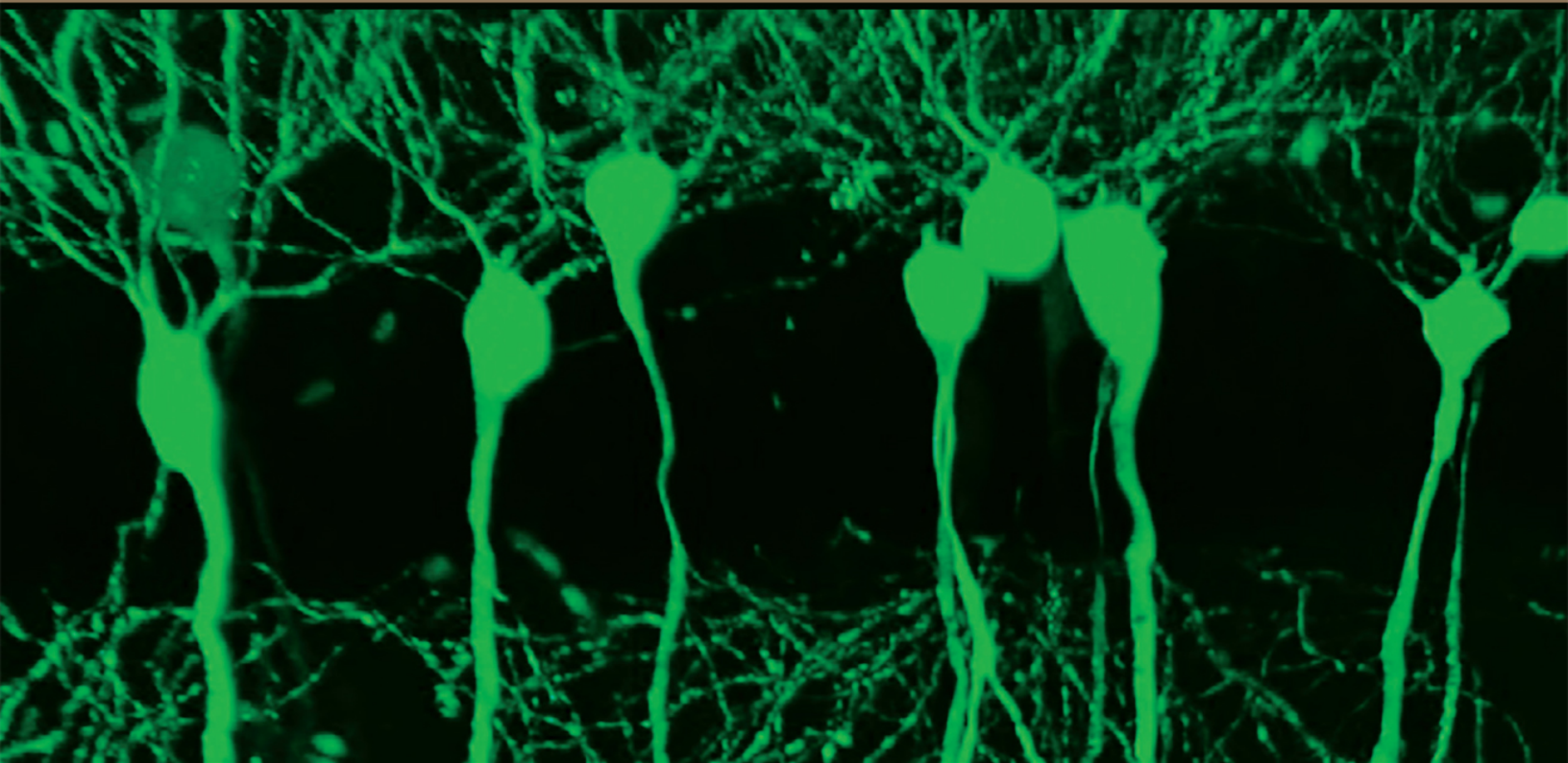


F I F T H   E D I T I O N

The American Psychiatric Association Publishing

TEXTBOOK of

# PSYCHOPHARMACOLOGY



**DSM-5**  
EDITION

EDITED BY

Alan F. Schatzberg, M.D.

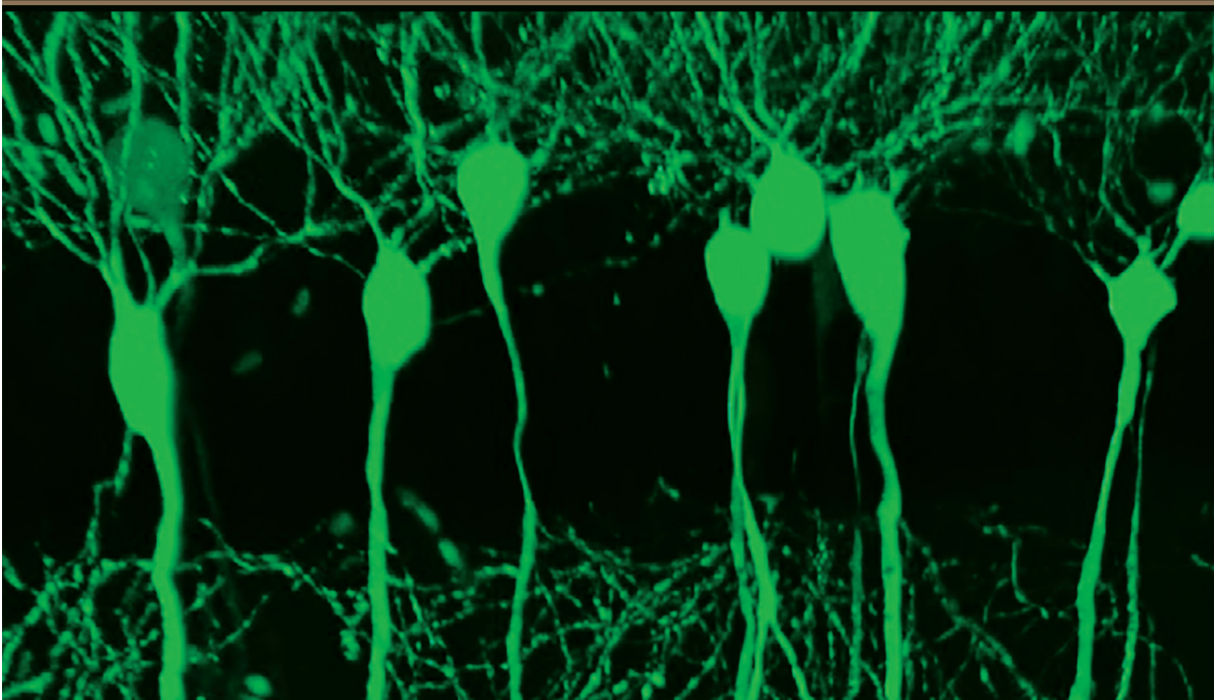
Charles B. Nemeroff, M.D., Ph.D.

F I F T H   E D I T I O N

The American Psychiatric Association Publishing

TEXTBOOK of

# PSYCHOPHARMACOLOGY



**DSM-5**  
EDITION

EDITED BY

Alan F. Schatzberg, M.D.



Charles B. Nemeroff, M.D., Ph.D.

The American Psychiatric Association  
Publishing

TEXTBOOK OF  
**PSYCHOPHARMACOLOGY**

FIFTH EDITION

The American Psychiatric Association  
Publishing

TEXTBOOK OF  
**PSYCHOPHARMACOLOGY**

FIFTH EDITION

EDITED BY

**Alan F. Schatzberg, M.D.**  
**Charles B. Nemeroff, M.D., Ph.D.**

AMERICAN  
PSYCHIATRIC  
ASSOCIATION  

---

PUBLISHING





**Note:** The authors have worked to ensure that all information in this book is accurate at the time of publication and consistent with general psychiatric and medical standards, and that information concerning drug dosages, schedules, and routes of administration is accurate at the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice continue to advance, however, therapeutic standards may change. Moreover, specific situations may require a specific therapeutic response not included in this book. For these reasons and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of physicians directly involved in their care or the care of a member of their family.

Books published by American Psychiatric Association Publishing represent the findings, conclusions, and views of the individual authors and do not necessarily represent the policies and opinions of American Psychiatric Association Publishing or the American Psychiatric Association.

If you wish to buy 50 or more copies of the same title, please go to [www.appi.org/specialdiscounts](http://www.appi.org/specialdiscounts) for more information.

Copyright © 2017 American Psychiatric Association Publishing  
ALL RIGHTS RESERVED

Manufactured in the United States of America on acid-free paper

21 20 19 18 17 5 4 3 2 1

Fifth Edition

American Psychiatric Association Publishing  
1000 Wilson Boulevard  
Arlington, VA 22209-3901  
[www.appi.org](http://www.appi.org)

### **Library of Congress Cataloging-in-Publication Data**

Names: Schatzberg, Alan F., editor. | Nemeroff, Charles B., editor. | American Psychiatric Association Publishing, publisher.

Title: The American Psychiatric Association Publishing textbook of psychopharmacology / edited by Alan F. Schatzberg, Charles B. Nemeroff.

Other titles: American Psychiatric Publishing textbook of psychopharmacology | Textbook of psychopharmacology

Description: Fifth edition. | Arlington, Virginia : American Psychiatric Association Publishing, [2017] | Preceded by The American Psychiatric Publishing textbook of psychopharmacology / edited by Alan F. Schatzberg, Charles B. Nemeroff. 4th ed. 2009. | Includes bibliographical references and index.

Identifiers: LCCN 2017004876 (print) | LCCN 2017005663 (ebook) | ISBN 9781585625239 (hardcover : alk. paper) | ISBN 9781615371228 (ebook)

Subjects: | MESH: Psychotropic Drugs—pharmacology | Psychotropic Drugs—therapeutic use | Mental Disorders—drug therapy | Psychopharmacology

Classification: LCC RM315 (print) | LCC RM315 (ebook) | NLM QV 77.2 | DDC 615.7/8—dc23

LC record available at <https://lccn.loc.gov/2017004876>

**British Library Cataloguing in Publication Data**

A CIP record is available from the British Library.

*Dedicated to  
our wives, children, and grandchildren,  
who bring us much joy  
and give us great support.*



# Contents

Contributors

Introduction

## PART I

### Principles of Pharmacology

#### 1 Basic Principles of Molecular Biology and Genomics

*Jiang-Zhou Yu, MD., Ph.D.*

*Mark M. Rasenick, Ph.D.*

#### 2 Neurotransmitters and Receptors in Psychiatric Disorders

*Carolyn M. Drazinic, M.D., Ph.D.*

*Steven T. Szabo, M.D., Ph.D.*

*Todd D. Gould, M.D.*

*Husseini K. Manji, M.D., F.R.C.P.C.*

#### 3 Genetics and Genomics

*Jessica Keverne, Ph.D.*

*Darina Czamara, Ph.D.*

*Joseph F. Cubells, M.D., Ph.D.*

*Elisabeth B. Binder, M.D., Ph.D.*

#### **4** Psychoneuroendocrinology

***Roxanne Keynejad, M.A., M.B.B.S., M.R.C.P.***

***Ania Korszun, Ph.D., M.D., F.R.C.Psych.***

***Carmine M. Pariante, Ph.D., M.D., F.R.C.Psych.***

#### **5** Brain-Immune System Interactions Relevance to the Pathophysiology and Treatment of Neuropsychiatric Disorders

***Firdaus S. Dhabhar, Ph.D.***

***Charles L. Raison, M.D.***

***Andrew H. Miller, M.D.***

#### **6** Principles of Pharmacokinetics and Pharmacodynamics

***C. Lindsay DeVane, Pharm.D.***

#### **7** Brain Imaging in Psychopharmacology

***Ebrahim Haroon, M.D.***

***Helen Mayberg, M.D.***

## **PART II**

### **Classes of Psychiatric Treatments**

#### **Antidepressants and Anxiolytics**

#### **8** Monoamine Oxidase Inhibitors

***K. Ranga Rama Krishnan, M.D.***

#### **9** Tricyclic and Tetracyclic Drugs

***J. Craig Nelson, M.D.***

**10** Fluoxetine

***Jerrold F. Rosenbaum, M.D.***

***Dawn F. Ionescu, M.D.***

**11** Sertraline

***Linda L. Carpenter, M.D.***

***Alan F. Schatzberg, M.D.***

**12** Paroxetine

***Jonathon R. Howlett, M.D.***

***Murray B. Stein, M.D., M.P.H.***

***Charles B. Nemeroff, M.D., Ph.D.***

**13** Fluvoxamine

***Elias Aboujaoude, M.D.***

***Lorrin M. Koran, M.D.***

**14** Citalopram and Escitalopram

***Patrick H. Roseboom, Ph.D.***

***Ned H. Kalin, M.D.***

**15** Trazodone and Nefazodone

***Robert N. Golden, M.D.***

***Karon Dawkins, M.D.***

***Linda Nicholas, M.D.***

**16** Vortioxetine

***Pierre Blier, M.D., Ph.D.***



**17** Mirtazapine

***Alan F. Schatzberg, M.D.***

**18** Bupropion

***David V. Hamilton, M.D., M.A.***  
***Anita H. Clayton, M.D.***

**19** Venlafaxine and Desvenlafaxine

***Michael E. Thase, M.D.***

**20** Duloxetine, Milnacipran, and Levomilnacipran

***Sandhya Norris, M.D.***  
***Pierre Blier, M.D., Ph.D.***

**21** Ketamine

***David S. Mathai, B.S.***  
***Sanjay J. Mathew, M.D.***

**22** Benzodiazepines

***David V. Sheehan, M.D., M.B.A.***

**23** Buspirone

***Donald S. Robinson, M.D.***  
***Karl Rickels, M.D.***

## **Antipsychotics**

**24** Classic Antipsychotic Medications

***Henry A. Nasrallah, M.D.***  
***Rajiv Tandon, M.D.***

**25** Clozapine

***Stephen R. Marder, M.D.***  
***Yvonne S. Yang, M.D., Ph.D.***

**26** Olanzapine

***Amy L. Silberschmidt, M.D.***  
***Jacob S. Ballon, M.D.***  
***S. Charles Schulz, M.D.***

**27** Quetiapine

***Peter F. Buckley, M.D.***  
***Adriana E. Foster, M.D.***  
***Matthew Byerly, M.D.***

**28** Risperidone and Paliperidone

***Michele Hill, M.R.C.Psych.***  
***Donald C. Goff, M.D.***

**29** Aripiprazole and Brexpiprazole

***Rolando Gonzalez, M.D.***  
***Martin T. Strassnig, M.D.***

**30** Ziprasidone

***John W. Newcomer, M.D.***  
***Elise Fallucco, M.D.***  
***Martin T. Strassnig, M.D.***

**31** Asenapine

***Leslie L. Citrome, M.D., M.P.H.***

**32** Iloperidone

***Peter F. Buckley, M.D.***

***Adriana E. Foster, M.D.***

***Oliver Freudenreich, M.D.***

***Scott Van Sant, M.D.***

**33** Lurasidone

***Philip D. Harvey, Ph.D.***

**34** Cariprazine

***Sultan Albrahim, M.D.***

***Joseph H. Henry, M.D.***

***Charles B. Nemeroff, M.D., Ph.D.***

**35** Drugs to Treat Extrapyramidal Side Effects

***Joseph K. Stanilla, M.D.***

***George M. Simpson, M.D.***

**Drugs for Treatment of Bipolar  
Disorder**

**36** Lithium

***Masoud Kamali, M.D.***

***Venkatesh Basappa Krishnamurthy, M.D.***

***Raman Baweja, M.D.***

***Erika F.H. Saunders, M.D.***

***Alan J. Gelenberg, M.D.***



**37** Valproate

***Charles L. Bowden, M.D.***

**38** Carbamazepine, Oxcarbazepine, and Lincarbazepine

***Po W. Wang, M.D.***

***Terence A. Ketter, M.D.***

***Robert M. Post, M.D.***

**39** Gabapentin and Pregabalin

***Mark A. Frye, M.D.***

***Katherine Marshall Moore, M.D.***

***Alan F. Schatzberg, M.D.***

**40** Lamotrigine

***David E. Kemp, M.D., M.S.***

***Marc L. van der Loos, M.D., Ph.D.***

***Keming Gao, M.D., Ph.D.***

***Joseph R. Calabrese, M.D.***

**41** Topiramate

***Susan L. McElroy, M.D.***

***Paul E. Keck Jr., M.D.***

## **Other Agents**

**42** Agents for Cognitive Disorders

***Frank W. Brown, M.D.***

**43** Sedative-Hypnotics

***Seiji Nishino, M.D., Ph.D.***  
***Noriaki Sakai, D.V.M., Ph.D.***  
***Kazuo Mishima, M.D., Ph.D.***  
***Emmanuel Mignot, M.D., Ph.D.***  
***William C. Dement, M.D., Ph.D.***

**44** Psychostimulants and Wakefulness-Promoting Agents

***Charles DeBattista, D.M.H., M.D.***

**45** Electroconvulsive Therapy and Other Neuromodulation Therapies

***William M. McDonald, M.D.***  
***Thomas W. Meeks, M.D.***  
***Linda L. Carpenter, M.D.***  
***W. Vaughn McCall, M.D., M.S.***  
***Charles F. Zorumski, M.D.***

## **PART III**

### **Psychopharmacological Treatment**

**46** Treatment of Depression

***William V. Bobo, M.D., M.P.H.***  
***Richard C. Shelton, M.D.***

**47** Treatment of Bipolar Disorder

***Paul E. Keck Jr., M.D.***  
***Susan L. McElroy, M.D.***

**48** Treatment of Anxiety and Related Disorders

***Daniella David, M.D.***  
***Jonathan R.T. Davidson, M.D.***

**49** Treatment of Schizophrenia

***Tsung-Ung W. Woo, M.D., Ph.D.***  
***Carla M. Canuso, M.D.***  
***Joanne D. Wojcik, Ph.D., P.M.H.C.N.S.-B.C.***  
***Douglas Noordsy, M.D.***  
***Mary F. Brunette, M.D.***  
***Alan I. Green, M.D.***

**50** Treatment of Substance-Related Disorders

***Brian J. Sherman, Ph.D.***  
***Karen J. Hartwell, M.D.***  
***Aimee L. McRae-Clark, Pharm.D.***  
***Kathleen T. Brady, M.D., Ph.D.***

**51** Treatment of Personality Disorders

***Marissa Miyazaki, M.D.***  
***Daphne Simeon, M.D.***  
***Eric Hollander, M.D.***

**52** Treatment of Eating Disorders

***W. Stewart Agras, M.D.***

**53** Treatment of Insomnia

***Andrew D. Krystal, M.D., M.S.***

**54** Treatment of Chronic Pain

***Kurt Kroenke, M.D.***

**55** Treatment of Child and Adolescent Disorders

***Karen Dineen Wagner, M.D., Ph.D.***

***Steven R. Pliszka, M.D.***

**56** Treatment During Late Life

***Steven P. Roose, M.D.***

***Bruce G. Pollock, M.D., Ph.D.***

***D. P. Devanand, M.D.***

**57** Psychopharmacology During Pregnancy and Lactation

***Shona L. Ray-Griffith, M.D.***

***D. Jeffrey Newport, M.D.***

***Zachary N. Stowe, M.D.***

**58** Treatment of Psychiatric Emergencies

***Steven J. Garlow, M.D., Ph.D.***

***Margaret B. Weigel, M.D.***

***Barbara D'Orio, M.D., M.P.A.***

**59** Treatment of Agitation and Aggression in the Elderly

***Carl Salzman, M.D.***

Appendix—Psychiatric Medications

***Robert H. Chew, Pharm.D.***

Index

# Contributors

**Elias Aboujaoude, M.D.**

Clinical Professor, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

**W. Stewart Agras, M.D.**

Professor of Psychiatry Emeritus, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

**Sultan Albrahim, M.D.**

Resident in Psychiatry, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine/Jackson Memorial Hospital, Miami, Florida

**Jacob S. Ballon, M.D., M.P.H.**

Clinical Assistant Professor and Director, INSPIRE Clinic, Stanford University Department of Psychiatry and Behavioral Sciences, Stanford, California

**Raman Baweja, M.D.**

Assistant Professor, Department of Psychiatry, Penn State College of Medicine and Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania

**Elisabeth B. Binder, M.D., Ph.D.**

Director, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany; Professor, Department of Psychiatry and

Behavioral Sciences, Department of Human Genetics,  
Emory University School of Medicine, Atlanta, Georgia

**Pierre Blier, M.D., Ph.D.**

Professor, Departments of Psychiatry and Cellular and  
Molecular Medicine, University of Ottawa, The Royal  
Institute of Mental Health Research Institute, Ottawa,  
Ontario, Canada

**William V. Bobo, M.D., M.P.H.**

Associate Professor, Psychiatry and Psychology, Mayo Clinic,  
Rochester, Minnesota

**Charles L. Bowden, M.D.**

Clinical Professor, Departments of Psychiatry and  
Pharmacology, University of Texas Health Science Center at  
San Antonio, San Antonio, Texas

**Kathleen T. Brady, M.D., Ph.D.**

Distinguished University Professor, Addiction Sciences  
Division, Department of Psychiatry and Behavioral Sciences,  
Medical University of South Carolina; Staff Psychiatrist,  
Ralph H. Johnson VA Medical Center, Charleston, South  
Carolina

**Frank W. Brown, M.D.**

Associate Chief Quality Officer, Emory University Hospital;  
Associate Professor and Vice-Chairman of Clinical  
Operations, Department of Psychiatry and Behavioral  
Sciences, Emory University School of Medicine, Atlanta,  
Georgia

**Mary F. Brunette, M.D.**

Associate Professor of Psychiatry, Psychiatric Research  
Center and Psychopharmacology Research Group, Geisel  
School of Medicine at Dartmouth, Concord, New Hampshire

**Peter F. Buckley, M.D.**

Dean, Medical College of Georgia, Augusta University,  
Augusta, Georgia

**Matthew Byerly, M.D.**

Professor of Cell Biology and Neuroscience, Montana State  
University, Bozeman, Montana

**Joseph R. Calabrese, M.D.**

Director, Mood Disorders Program, University Hospitals  
Case Medical Center, Bipolar Disorders Research Chair and  
Professor of Psychiatry, Case Western Reserve University  
School of Medicine, Cleveland, Ohio

**Carla M. Canuso, M.D.**

Senior Director, Neuroscience Clinical Development,  
Janssen Research and Development, Titusville, New Jersey

**Linda L. Carpenter, M.D.**

Professor, Department of Psychiatry and Human Behavior,  
The Warren Alpert Medical School of Brown University;  
Chief, Butler Hospital Mood Disorders Program; Director,  
Butler TMS Clinic and Neuromodulation Research Facility,  
Providence, Rhode Island

**Robert H. Chew, Pharm.D.**

Psychiatric Pharmacist Specialist, Sacramento, California

**Leslie L. Citrome, M.D., M.P.H.**

Clinical Professor of Psychiatry and Behavioral Sciences,  
New York Medical College, Valhalla, New York

**Anita H. Clayton, M.D.**

Chair and David C. Wilson Professor, Department of  
Psychiatry and Neurobehavioral Sciences, University of  
Virginia, Charlottesville, Virginia

**Joseph F. Cubells, M.D., Ph.D.**

Associate Professor, Department of Psychiatry and Behavioral Sciences, Departments of Human Genetics and of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

**Darina Czamara, Ph.D.**

Staff Scientist, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

**Daniella David, M.D.**

Chief, Psychiatry Service, and Medical Director, PTSD Program, Bruce W. Carter VA Medical Center, Miami, Florida; Professor of Clinical Psychiatry and Associate Director of Psychiatry Residency Training Program, Department of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, Florida

**Jonathan R.T. Davidson, M.D.**

Professor Emeritus, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina

**Karon Dawkins, M.D.**

Associate Professor and Director of General Psychiatry Residency Training Program, Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, North Carolina

**Charles DeBattista, D.M.H., M.D.**

Professor of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

**William C. Dement, M.D., Ph.D.**

Lowell W. and Josephine Q. Berry Professor, Department of Psychiatry and Behavioral Sciences, Stanford University



School of Medicine, Stanford, Palo Alto, California

**D.P. Devanand, M.D.**

Professor of Psychiatry and Neurology and Director of Geriatric Psychiatry, Columbia University Medical Center, New York, New York

**C. Lindsay DeVane, Pharm.D.**

Professor, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina

**Firdaus S. Dhabhar, Ph.D.**

Professor, Department of Psychiatry and Behavioral Sciences, Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, Florida

**Barbara D'Orio, M.D., M.P.A.**

Associate Professor, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

**Carolyn M. Drazinic, M.D., Ph.D.**

Associate Professor, Department of Psychiatry and Behavioral Sciences, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida; Chief Medical Officer of Psychiatry, Jackson Health System, Miami, Florida

**Elise Fallucco, M.D.**

Director, North Florida Center for Collaborative Care; Adjunct Assistant Professor, Department of Psychiatry (Child), University of Florida College of Medicine-Jacksonville, Jacksonville, Florida

**Adriana E. Foster, M.D.**

Professor and Vice Chair for Clinical and Research Programs, Herbert Wertheim College of Medicine, Florida

International University, Miami, Florida

**Oliver Freudenreich, M.D.**

Associate Professor of Psychiatry, Harvard Medical School,  
Boston, Massachusetts

**Mark A. Frye, M.D.**

Professor and Chair, Department of Psychiatry and  
Psychology, Mayo Clinic, Rochester, Minnesota

**Keming Gao, M.D., Ph.D.**

Professor of Psychiatry, Department of Psychiatry; Clinical  
Director, Mood and Anxiety Clinic in the Mood Disorders  
Program, University Hospitals Case Medical Center/Case  
Western Reserve University School of Medicine, Cleveland,  
Ohio

**Steven J. Garlow, M.D., Ph.D.**

Professor, Department of Psychiatry, University of Wisconsin  
School of Medicine and Public Health, Madison, Wisconsin

**Alan J. Gelenberg, M.D.**

Professor Emeritus of Psychiatry, University of Arizona,  
Tucson, Arizona

**Donald C. Goff, M.D.**

Marvin Stern Professor of Psychiatry and Vice Chair for  
Research, Department of Psychiatry, NYU Langone Medical  
Center, New York, New York

**Robert N. Golden, M.D.**

Dean and Professor of Psychiatry, School of Medicine and  
Public Health; Vice Chancellor for Medical Affairs,  
University of Wisconsin–Madison, Madison, Wisconsin

**Rolando Gonzalez, M.D.**

Resident in Psychiatry, Department of Psychiatry and  
Behavioral Sciences, University of Miami Miller School of

Medicine, Miami, Florida

**Todd D. Gould, M.D.**

Associate Professor, Departments of Psychiatry, Pharmacology, and Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, Maryland

**Alan I. Green, M.D.**

Raymond Sobel Professor of Psychiatry, Professor of Molecular and Systems Biology, Chairman, Department of Psychiatry, Director, Dartmouth SYNERGY: The Dartmouth Clinical and Translational Science Institute; Primary Institutional Affiliation: The Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire

**David V. Hamilton, M.D., M.A.**

Assistant Professor, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, Virginia

**Ebrahim Haroon, M.D.**

Assistant Professor, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

**Karen J. Hartwell, M.D.**

Associate Professor, Addiction Sciences Division, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina; Medical Director, Substance Abuse Treatment Center, Ralph H. Johnson VA Medical Center, Charleston, South Carolina

**Philip D. Harvey, Ph.D.**

Leonard M. Miller Professor of Psychiatry and Behavioral Science, University of Miami Miller School of Medicine, Miami, Florida

**Joseph H. Henry, M.D.**

Assistant Professor, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, Florida

**Michele Hill, M.R.C.Psych.**

Consultant Psychiatrist, St Michael's Psychiatric Unit, Mercy University Hospital, Cork, Ireland

**Eric Hollander, M.D.**

Clinical Professor of Psychiatry and Behavioral Sciences; Director, Autism and Obsessive Compulsive Spectrum Program and Anxiety and Depression Program, Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York

**Jonathon R. Howlett, M.D.**

Associate Physician, Department of Psychiatry, University of California San Diego, La Jolla, California; Resident Physician, VA San Diego Healthcare System, San Diego, California

**Dawn F. Ionescu, M.D.**

Assistant in Psychiatry, Massachusetts General Hospital, and Assistant Professor, Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

**Ned H. Kalin, M.D.**

Hedberg Professor and Chair, Department of Psychiatry; Director, HealthEmotions Research Institute, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

**Masoud Kamali, M.D.**

Assistant Professor, Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

**Paul E. Keck Jr., M.D.**

Lindner Professor and Executive Vice Chair, Department of Psychiatry and Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio

**David E. Kemp, M.D., M.S.**

Associate Professor of Psychiatry, University of Illinois at Chicago; Co-Medical Director, Behavioral Health Service Line, Advocate Health Care, Downers Grove, Illinois

**Terence A. Ketter, M.D.**

Professor of Psychiatry and Behavioral Sciences and Chief, Bipolar Disorders Clinic, Stanford University School of Medicine, Stanford, California

**Jessica Keverne, Ph.D.**

Scientist, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

**Roxanne Keynejad, M.A., M.B.B.S., M.R.C.P.**

Academic Clinical Fellow in General Adult Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London

**Lorrin M. Koran, M.D.**

Professor (Clinical) of Psychiatry and Behavioral Sciences, Emeritus, Stanford University School of Medicine, Stanford, California

**Ania Korszun, Ph.D., M.D., F.R.C.Psych.**

Professor of Psychiatry, Centre for Psychiatry, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, London

**Venkatesh Basappa Krishnamurthy, M.D.**

Assistant Professor, Department of Psychiatry, Penn State College of Medicine and Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania

**K. Ranga Rama Krishnan, M.D.**

Dean, Rush Medical College, Chicago, Illinois

**Kurt Kroenke, M.D.**

Director of Education and Training Programs, Regenstrief Institute, Inc.; Professor of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

**Andrew D. Krystal, M.D., M.S.**

Professor of Psychiatry and Behavioral Sciences; Director, Brain Stimulation Program, Sleep Research Laboratory, Insomnia Clinic, and Quantitative EEG Laboratory, Duke University Medical Center, Durham, North Carolina

**Husseini K. Manji, M.D., F.R.C.P.C.**

Global Therapeutic Head for Neuroscience, Janssen Pharmaceutical Research and Development, Johnson & Johnson, Titusville, New Jersey

**Stephen R. Marder, M.D.**

Professor of Psychiatry, Semel Institute for Neuroscience at UCLA, Los Angeles, California

**David S. Mathai, B.S.**

Medical Student, Baylor College of Medicine, Houston, Texas

**Sanjay J. Mathew, M.D.**

Marjorie Bintliff Johnson and Raleigh White Johnson Jr. Chair for Research in Psychiatry, Professor of Psychiatry and Behavioral Sciences, Menninger Department of

Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas

**Helen Mayberg, M.D.**

Professor, Department of Psychiatry, Neurology, and Radiology; Dorothy C. Fuqua Chair, Psychiatric Neuroimaging and Therapeutics, Emory University School of Medicine, Atlanta, Georgia

**W. Vaughn McCall, M.D., M.S.**

Case Distinguished University Chair, Department of Psychiatry and Health Behavior, Medical College of Georgia at Augusta University, Augusta, Georgia

**William M. McDonald, M.D.**

J.B. Fuqua Chair for Late-Life Depression and Professor of Psychiatry and Behavioral Sciences; Vice-Chair for Education; Director, Geriatric Psychiatry Services and ECT and Neuromodulation Services, Emory University School of Medicine, Atlanta, Georgia

**Susan L. McElroy, M.D.**

Professor, Department of Psychiatry and Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio

**Aimee L. McRae-Clark, Pharm.D.**

Professor, Addiction Sciences Division, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina

**Thomas W. Meeks, M.D.**

Assistant Professor of Psychiatry, Uniformed Services University of the Health Sciences, Naval Medical Center San Diego, San Diego, California

**Emmanuel Mignot, M.D., Ph.D.**

Craig Reynolds Professor of Sleep Medicine; Professor of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, California; Director, Stanford Center for Sleep Sciences and Medicine, Palo Alto, California

**Andrew H. Miller, M.D.**

William P. Timmie Professor, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

**Kazuo Mishima, M.D., Ph.D.**

Director, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

**Marissa Miyazaki, M.D.**

Staff Psychiatrist, Columbia University Student Mental Health Service, Columbia University Medical Center, New York, New York

**Katherine Marshall Moore, M.D.**

Assistant Professor, Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota

**Henry A. Nasrallah, M.D.**

Professor and Chairman, Department of Psychiatry and Behavioral Neuroscience, and Sydney W. Souers Endowed Chair, Saint Louis University School of Medicine, Saint Louis, Missouri

**J. Craig Nelson, M.D.**

Leon J. Epstein Professor of Psychiatry and Director of Geriatric Psychiatry, Department of Psychiatry, University of California-San Francisco, San Francisco, California

**Charles B. Nemeroff, M.D., Ph.D.**



Leonard M. Miller Professor and Chairman, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, University of Miami, Miami, Florida

**John W. Newcomer, M.D.**

Vice Dean for Research and Innovation, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida

**D. Jeffrey Newport, M.D.**

Director, Women's Reproductive Mental Health; Medical Director, Health and Recovery Center, Jackson Behavioral Health Hospital; Professor, Departments of Psychiatry and Behavioral Sciences and of Obstetrics and Gynecology, University of Miami Miller School of Medicine, Miami, Florida

**Linda Nicholas, M.D.**

Professor of Psychiatry (retired), University of North Carolina School of Medicine, Chapel Hill, North Carolina

**Seiji Nishino, M.D., Ph.D.**

Professor of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California; Director, Sleep and Circadian Neurobiology Laboratory, Stanford Sleep Research Center, Palo Alto, California

**Douglas Noordsy, M.D.**

Clinical Professor, Director of Sports Psychiatry Initiative, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

**Sandhya Norris, M.D.**

Assistant Professor, Department of Psychiatry, University of Ottawa; Staff Psychiatrist, The Royal—Institute of Mental

Health Research, Ottawa, Ontario, Canada

**Carmine M. Pariante, Ph.D., M.D., F.R.C.Psych.**

Professor of Biological Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London

**Steven R. Pliszka, M.D.**

Dielmann Distinguished Professor and Chair, Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, Texas

**Bruce G. Pollock, M.D., Ph.D.**

Vice President, Research and Director, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health; Professor of Psychiatry and Pharmacology and Director, Division of Geriatric Psychiatry, University of Toronto Faculty of Medicine, Toronto, Ontario, Canada

**Robert M. Post, M.D.**

Clinical Professor of Psychiatry, George Washington School of Medicine, Washington, D.C.; Head, Bipolar Collaborative Network, Chevy Chase, Maryland

**Charles L. Raison, M.D.**

Professor, Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin

**Mark M. Rasenick, Ph.D.**

Distinguished UIC Professor, Departments of Physiology and Biophysics and Psychiatry, University of Illinois, Chicago, and Jesse Brown VAMC, Chicago, Illinois

**Shona L. Ray-Griffith, M.D.**

Assistant Professor, Departments of Psychiatry and of Obstetrics and Gynecology, University of Arkansas for

Medical Sciences, Psychiatric Research Institute, Little Rock, Arkansas

**Karl Rickels, M.D.**

Stuart and Emily B.H. Mudd Professor of Behavior and Reproduction in Psychiatry, Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania

**Donald S. Robinson, M.D.**

Consultant, Worldwide Drug Development, Shelburne, Vermont

**Steven P. Roose, M.D.**

Professor of Clinical Psychiatry, College of Physicians and Surgeons, Columbia University; Director, NeuroPsychiatry Research Clinic, New York State Psychiatric Institute, New York, New York

**Patrick H. Roseboom, Ph.D.**

Senior Scientist in Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

**Jerrold F. Rosenbaum, M.D.**

Chief of Psychiatry, Massachusetts General Hospital; Stanley Cobb Professor of Psychiatry, Harvard

**Noriaki Sakai, D.V.M., Ph.D.**

Basic Life Science Research Associate, Department of Psychiatry and Behavioral Sciences, Sleep and Circadian Neurobiology Laboratory, Stanford University School of Medicine, Palo Alto, California

**Carl Salzman, M.D.**

Professor of Psychiatry, Harvard Medical School, Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Boston, Massachusetts

**Erika F. H. Saunders, M.D.**

Associate Professor and Chair, Department of Psychiatry,  
Penn State College of Medicine and Penn State Milton S.  
Hershey Medical Center, Hershey, Pennsylvania

**Alan F. Schatzberg, M.D.**

Kenneth T. Norris Jr. Professor, Department of Psychiatry  
and Behavioral Sciences, Stanford University School of  
Medicine, Stanford, California

**S. Charles Schulz, M.D.**

Emeritus Professor, Department of Psychiatry, University of  
Minnesota School of Medicine, Minneapolis; Psychiatrist,  
PrairieCare Medical Group, Brooklyn Park, Minnesota

**David V. Sheehan, M.D., M.B.A.**

Distinguished University Health Professor Emeritus,  
University of South Florida College of Medicine, Tampa,  
Florida

**Richard C. Shelton, M.D.**

Charles B. Ireland Professor and Vice Chair for Research;  
Director, Mood Disorders Program, University of Alabama  
at Birmingham School of Medicine, Birmingham, Alabama

**Brian J. Sherman, Ph.D.**

Postdoctoral Fellow, Addiction Sciences Division,  
Department of Psychiatry and Behavioral Sciences, Medical  
University of South Carolina, Charleston, South Carolina

**Amy L. Silberschmidt, M.D.**

Resident, University of Pittsburgh Medical Center,  
Pittsburgh, Pennsylvania

**Daphne Simeon, M.D.**

Associate Professor of Psychiatry; Co-Director, Compulsive  
and Impulsive Disorders Research Program; Director,  
Depersonalization and Dissociation Research Program;

Clinical Director, Center of Excellence for Compulsive and Impulsive Disorders (CECID), Department of Psychiatry, Mount Sinai School of Medicine, New York, New York

**George M. Simpson, M.D.**

Professor of Psychiatry Emeritus, Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles

**Joseph K. Stanilla, M.D.**

Associate Professor of Psychiatry, Cooper School of Medicine at Rowan University, Camden, New Jersey

**Murray B. Stein, M.D., M.P.H.**

Distinguished Professor, Departments of Psychiatry and of Family Medicine and Public Health, University of California San Diego, La Jolla, California; Staff Psychiatrist, VA San Diego Healthcare System, San Diego, California

**Zachary N. Stowe, M.D.**

Professor, Departments of Psychiatry, Obstetrics and Gynecology, and Pediatrics, University of Arkansas for Medical Sciences, Psychiatric Research Institute, Little Rock, Arkansas

**Martin T. Strassnig, M.D.**

Associate Director, Clinical and Translational Research Core; Associate Professor, Department of Integrated Medical Science, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida

**Steven T. Szabo, M.D., Ph.D.**

Assistant Professor, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina; Attending Psychiatrist, Mental

Health Service Line, Veterans Affairs Medical Center,  
Durham, North Carolina

**Rajiv Tandon, M.D.**

Professor and Executive Vice Chair, Department of  
Psychiatry, University of Florida College of Medicine,  
Gainesville, Florida

**Michael E. Thase, M.D.**

Professor, Department of Psychiatry, Perelman School of  
Medicine at the University of Pennsylvania, Philadelphia,  
Pennsylvania

**Marc L. van der Loos, M.D., Ph.D.**

Psychiatrist, Department of Psychiatry, Isala Klinieken,  
Zwolle, The Netherlands

**Scott Van Sant, M.D.**

Clinical Assistant Professor, Department of Psychiatry and  
Health Behavior, Medical College of Georgia, Augusta  
University, Augusta, Georgia

**Karen Dineen Wagner, M.D., Ph.D.**

Titus Harris Chair and Professor and Chair, Department of  
Psychiatry and Behavioral Sciences, The University of Texas  
Medical Branch, Galveston, Texas

**Po W. Wang, M.D.**

Clinical Professor of Psychiatry and Behavioral Sciences,  
Stanford University School of Medicine, Stanford, California

**Margaret B. Weigel, M.D.**

Assistant Professor, Department of Psychiatry and  
Behavioral Sciences, Emory University School of Medicine,  
Atlanta, Georgia

**Joanne D. Wojcik, Ph.D., P.M.H.C.N.S.-B.C.**

Associate Director, Commonwealth Research Center,  
Instructor in Psychiatry, Harvard Medical School; Beth  
Israel Deaconess Medical Center Department of Psychiatry,  
The Division of Massachusetts Mental Health Center Public  
Psychiatry, Boston

**Tsung-Ung W. Woo, M.D., Ph.D.**

Director, Program in Cellular Neuropathology, Medical  
Director, Harvard Brain Tissues Resource Center, McLean  
Hospital; Assistant Professor of Psychiatry, Harvard Medical  
School, Boston, Massachusetts

**Yvonne S. Yang, M.D., Ph.D.**

Health Sciences Assistant Clinical Professor, Semel Institute  
for Neuroscience at UCLA, Los Angeles, California

**Jiang-Zhou Yu, M.D., Ph.D.**

Research Assistant Professor, Departments of Physiology  
and Biophysics and of Surgery, University of Illinois,  
Chicago

**Charles F. Zorumski, M.D.**

Samuel B. Guze Professor and Head, Department of  
Psychiatry; Professor of Neuroscience; Director, Taylor  
Family Institute for Innovative Psychiatric Research,  
Washington University School of Medicine, St. Louis,  
Missouri

## **Disclosure of Interests**

*The following contributors to this textbook have indicated a financial interest in or other affiliation with a commercial supporter, manufacturer of a commercial product, and/or provider of a commercial service as listed below:*

**Jacob S. Ballon, M.D.** *Research Funding:* Novartis, Otsuka.

**Elisabeth B. Binder, M.D., Ph.D.** *Grant/Research Support:* Basic Science Grant from Boehringer Ingelheim.

**Pierre Blier, M.D., Ph.D.** *Grant Funding/Lecture Honoraria/Advisory Boards:* AstraZeneca, Bristol Myers Squibb, Eli Lilly, Forest, Euthymics Bioscience, Janssen, Lundbeck, Merck, Otsuka, Pfizer, Pierre Fabre, Servier, Shire, Takeda, and Valeant.

**William V. Bobo, M.D., M.P.H.** *Grant/Research Support:* Brain & Behavior Research Foundation (formerly NARSAD), Cephalon, Mayo Foundation, NIMH; *Speakers' Bureau:* Janssen, Pfizer.

**Mary F. Brunette, M.D.** *Grant/Research Support:* Alkermes.

**Peter F. Buckley, M.D.** *Grant/Research Support:* Ameritox, AstraZeneca, Eli Lilly, Janssen, NIMH, Pfizer, Posit Science, Sunovion; *Consultant:* AstraZeneca, Eli Lilly, Janssen, NIMH, Pfizer.

**Matthew Byerly, M.D.** *Speakers' Bureau/Research/Grant Support:* Otsuka America.

**Joseph R. Calabrese, M.D.** *Research Funding:* U.S. Department of Defense, Health Resources and Services Administration, National Institute of Mental Health; *Grant Support:* Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Cephalon (now Teva), Dainippon Sumitomo, GlaxoSmithKline, Janssen, Eli Lilly, Intra-Cellular Therapies, Pfizer, H. Lundbeck A/S, Sunovion, Takeda; *Consultant/Advisory Board Member/Speaker:* Abbott Laboratories, Allergan, AstraZeneca, Bristol-Myers Squibb,



Cephalon (now Teva), Dainippon Sumitomo, GlaxoSmithKline, Janssen, H. Lundbeck A/S, Merck, Otsuka, Pfizer, Repligen, Servier, Sunovion, Solvay, Takeda.

**Carla M. Canuso, M.D.** *Employment and Stock/Equity Holdings:* Dr. Canuso is a full-time employee of Janssen Research & Development, LLC, and a shareholder of Johnson & Johnson stock.

**Linda L. Carpenter, M.D.** *Grant/Research Support:* Cervel, Neuronetics, NeoSync; *Consultant:* MagStim Ltd.

**Les L. Citrome, M.D., M.P.H.** *Consultant:* Actavis (Forest), Alexza, Alkermes, Bristol-Myers Squibb, Eli Lilly, Forum, Genentech, Janssen, Jazz, Lundbeck, Merck, Medivation, Mylan, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, Teva, Valeant; *Speakers' Bureau:* Actavis (Forest), AstraZeneca, Janssen, Jazz, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva; *Stock (small number of shares of common stock):* Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer (purchased >10 years ago).

**Anita H. Clayton, M.D.** *Grant/Research Support:* Auspex, Forest Research Institute, Palatin Technologies; *Advisory Board/Consultant:* Forest Labs, Lundbeck, Naurex, Otsuka, Palatin Technologies, Roche, S1 Biopharmaceuticals, Sprout Pharmaceuticals; *Royalties/Copyright:* Ballantine Books/Random House, Guilford Publications ("Changes in Sexual Functioning Questionnaire"); *Shares/Restricted Stock Units:* Euthymics, S1 Biopharmaceuticals.

**Jonathan R. T. Davidson, M.D.** *Consultant/Advisory Services:* Edgemont, Lundbeck, Tonix; *Data and Safety Monitoring Board:* University of California, San Diego; *Speaker Honorarium:* University of Tennessee; *Royalties*

*(Assessment Instruments):* Connor-Davidson Resilience Scale; Davidson Trauma Scale, Social Phobia Inventory (SPIN), and Mini-SPIN); *Royalties (Authored Books/Chapters):* Guilford Publications, McFarland Publishers, and Springer.

**Charles DeBattista, D.M.H., M.D.** *Grant/Research Support:* Assurex Health, AstraZeneca, Brain Resources, CNS Response, Janssen, NIMH, St. Jude, Takeda; *Advisory Board:* Genentech, Pfizer.

**D. P. Devanand, M.D.** *Consultant (Scientific Advisory Board):* AbbVie, Astellas, Lundbeck; *Consultant:* Intra-Cellular Therapies.

**Oliver Freudenreich, M.D.** *Grant/Research Support:* Psychogenics; *Consultant:* Beacon Health Strategies, Optimal Medicine; *Honoraria:* Global Medical Education, Med-IQ, Oakstone Medical Education; *Royalties:* UpToDate.

**Mark A. Frye, M.D.** *Grant/Research Support (36 months):* Assurex Health, Janssen Research & Development, Mayo Foundation, Myriad, National Institute of Alcohol Abuse and Alcoholism (NIAAA), National Institute of Mental Health (NIMH), Pfizer; *Consultant (Mayo) (36 months):* Janssen R&D, Mitsubishi Tanabe Pharma, Myriad Genetics, Neuralstem, Sunovion, Supernus, Teva; *CME/Travel Support (36 months):* American Physician Institute, CME Outfitters.

**Keming Gao, M.D., Ph.D.** *Grant/Research Support:* AstraZeneca, Brain & Behavior Research Foundation, Cleveland Foundation; *Speaker/Advisory Board:* AstraZeneca, Pfizer, Sunovion.

**Alan J. Gelenberg, M.D.** *Consultant:* Zynx Health; *Major Stock Ownership:* Healthcare Technology Systems, Inc.

**Alan I. Green, M.D.** *Grant/Research Support:* Alkermes, National Institute on Drug Abuse, National Institute of Alcohol Abuse and Alcoholism, Novartis; *Consultant (Unpaid):* Alkermes, Otsuka; *Data and Safety Monitoring Board:* Eli Lilly; *Patent (U.S.):* Treatment of Substance Abuse.

**Philip D. Harvey, Ph.D.** *Grant/Research Support:* Takeda; *Consultant:* Acadia, Boehringer-Ingelheim, Forum, Lundbeck, Otsuka America, Sanofi, Sunovion, Takeda.

**Eric Hollander, M.D.** *Grant/Research Support:* Past research funding from Abbott.

**Jonathon R. Howlett, M.D.** *Grant/Research Support:* Investigator in multicenter clinical trial funded by Janssen.

**Ned H. Kalin, M.D.** *Scientific Advisory Board:* Corcept Therapeutics, Skyland Trail—George West Mental Health Foundation; *Research/Grant Support:* National Institute of Mental Health, Stanley Medical Research Institute; *Honoraria:* CME Outfitters, Elsevier, Pritzker Neuropsychiatric Disorders Research Consortium; *Editor:* *Psychoneuroendocrinology* (Elsevier); *Stock/Equity Holdings:* Corcept Therapeutics; *Patents:* U.S. Patent Nos. 7,071,323 and 7,531,356—Kalin NH, Roseboom PH, Landry CF, Nanda SA: Promoter sequences for corticotropin-releasing factor CRF2alpha and method of identifying agents that alter the activity of the promoter sequences; U.S. Patent No. 7,087,385—Kalin NH, Roseboom PH, Nanda SA: Promoter sequences for urocortin 2 and the use thereof; U.S. Patent No. 7,122,650—Roseboom PH, Kalin

NH, Nanda SA: Promoter sequences for corticotropin-releasing factor binding protein and use thereof.

**Masoud Kamali, M.D.** *Grant/Research Support:* Assurex Health, Janssen. The studies conducted with these funds were unrelated to the current chapter, not part of the references, and pose no competing interest.

**Paul E. Keck Jr., M.D.** *Employers:* University of Cincinnati College of Medicine and Lindner Center of HOPE; *Research Sponsorship:* Cephalon, Marriott Foundation, National Institute of Mental Health, and Shire; *Consultant (2014):* Merck, Otsuka, ProPhase, Shire, Supernus; *Patent:* Co-inventor on U.S. Patent No. 6,387,956—Shapira NA, Goldsmith TD, Keck PE Jr. (University of Cincinnati): Methods of treating obsessive-compulsive spectrum disorder comprises the step of administering an effective amount of tramadol to an individual. Filed March 25, 1999; approved May 14, 2002. (Dr. Keck has received no financial gain from this patent.)

**David E. Kemp, M.D.** *Speakers' Bureau:* AstraZeneca, Sunovion, Takeda/Lundbeck.

**Terence A. Ketter, M.D.** *Grant/Research Support:* Sunovion; *Consultant/Advisory Board:* Janssen, Myriad Genetic Laboratories, Sunovion, Teva; *Lecture Honoraria (NOT Speakers' Bureau):* GlaxoSmithKline, Sunovion; *Royalties:* American Psychiatric Publishing; *Employment (Nzeera Ketter, MD, Spouse):* Janssen Pharmaceuticals; *Stock Ownership (Nzeera Ketter, MD, Spouse):* Janssen Pharmaceuticals.

**Lorin M. Koran, M.D.** *Consultant:* F. Hoffmann-La Roche Ltd; *Royalties:* Cambridge University Press.

**K. Ranga Rama Krishnan, M.D.** *Advisory Board:* Chairman, National Research Council, Singapore; *Stock Ownership:* Atentiv, Corcept, Orexigen.

**Andrew D. Krystal, M.D., M.S.** *Grant/Research Support:* Azevan, Brainsway, Eisai, Janssen, NeoSync, NIH, Novartis, Stanley Foundation, Sunovion, Teva; *Consultant:* Atentiv, BioExcel, GlaxoSmithKline, Jazz, Lundbeck, Merck, Neurocrine, Novartis, Otsuka, Paladin Labs, Pernix, Pfizer, Sunovion.

**Husseini K. Manji, M.D.** *Employment:* Dr. Manji is a full-time employee of Janssen Research & Development, LLC, of the Johnson & Johnson Pharmaceuticals Group.

**Stephen R. Marder, M.D.** *Grant/Research Support:* Forum, Neurocrine, Synchroneuron; *Consultant:* Allergan, Forum, Genentech, Lundbeck, Otsuka, Roche, Takeda, Teva.

**Sanjay J. Mathew, M.D.** *Consultant:* Naurex, Teva.

**Helen S. Mayberg, M.D.** Dr. Mayberg consults and receives licensing fees for intellectual property related to deep brain stimulation for depression from St. Jude Medical, Inc.

**W. Vaughn McCall, M.D., M.S.** *Grant/Research Support:* MECTA Corporation, NIMH; *Honoraria:* Wolters Kluwer Publishing.

**William M. McDonald, M.D.** *Grant/Research Support:* Cervel Neurotherapeutics, National Institute of Mental Health, National Institute of Neurological Disease and Stroke, Neuronetics, Soterix, Stanley Foundation; *Consultant:* Neurological Devices Panel of the Medical Devices Advisory Committee, Center for Devices and Radiological Health, U.S. Food and Drug Administration.

**Susan L. McElroy, M.D.** *Employers:* University of Cincinnati College of Medicine, University of Cincinnati Physicians, and the Lindner Center of HOPE; *Consultant/Scientific Advisory Board:* Bracket, F. Hoffmann-La Roche Ltd., MedAvante, Myriad, Naurex, Novo Nordisk, Shire, Sunovion; *Research Sponsorship:* Agency for Healthcare Research and Quality, Alkermes, Cephalon, Forest, Marriott Foundation, National Institute of Mental Health, Naurex, Orexigen Therapeutics, Shire, Sunovion, Takeda; *Patents:* Inventor on U.S. Patent No. 6,323,236 B2 (Use of Sulfamate Derivatives for Treating Impulse Control Disorders), and, along with the patent's assignee (University of Cincinnati, Cincinnati, OH), has received payments from Johnson & Johnson Pharmaceutical Research & Development LLC, which has exclusive rights under the patent.

**Henry A. Nasrallah, M.D.** *Grant/Research Support:* Forest, Forum, Genentech, Otsuka, Shire; *Advisory Boards/Consultant:* Acadia, Alkermes, Boehringer-Ingelheim, Forum, Genentech, Janssen, Lundbeck, Merck, Otsuka, Sunovion, Teva, Vanda; *Speakers' Bureau:* Alkermes, Janssen, Lundbeck, Otsuka, Sunovion.

**J. Craig Nelson, M.D.** *Grant/Research Support:* Avid Radiopharmaceuticals, HRSA, NIMH; *Consultant:* Corcept, Janssen, Lundbeck, Otsuka; *Lecture Honoraria:* Otsuka (Asia); *Advisory Board:* Otsuka, Sunovion; *Stock Ownership:* Atossa Genetics.

**Charles B. Nemeroff, M.D., Ph.D.** *Grant/Research Support:* National Institutes of Health (NIH); *Consultant (2013-2016):* Bracket (Clintara), Fortress Biotech, Gerson Lehrman Group (GLG) Healthcare & Biomedical Council, Lundbeck, Mitsubishi Tanabe Pharma Development

America, Prismic Pharmaceuticals, Sumitomo Dainippon Pharma, Sunovion Pharmaceuticals Inc., Taisho Pharmaceutical Inc., Takeda, Total Pain Solutions (TPS), Xhale; *Stock Holdings*: AbbVie, Bracket Intermediate Holding Corp., Celgene, Network Life Sciences Inc., OPKO Health, Inc., Seattle Genetics, Titan Pharmaceuticals, Xhale; *Scientific Advisory Boards*: American Foundation for Suicide Prevention (AFSP), Anxiety Disorders Association of America (ADAA), Bracket (Clintara), Brain & Behavior Research Foundation (formerly NARSAD), Laureate Institute for Brain Research, Inc., RiverMend Health LLC, Skyland Trail, Xhale; *Board of Directors*: ADAA, AFSP, Gratitude America; *Income Sources/Equity Holdings*  $\geq \$10,000$ : American Psychiatric Publishing, Bracket (Clintara), CME Outfitters, Takeda, Xhale; *Patents*: U.S. Patent No. 6,375,990B1—Method and devices for transdermal delivery of lithium; U.S. Patent No. 7,148,027B2—Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay.

**John W. Newcomer, M.D.** *Grant/Research Support*: Foundation2Recovery, National Institutes of Health, Otsuka America; *Data and Safety Monitoring Board*: Amgen; *Consultant*: Reviva, Rutgers, The State University of New Jersey.

**D. Jeffrey Newport, M.D.** *Grant/Research Support*: Eli Lilly, GlaxoSmithKline (GSK), Janssen, National Alliance for Research on Schizophrenia and Depression (NARSAD), National Institutes of Health (NIH), Takeda, Wyeth; *Speakers' Bureaus/Honoraria*: AstraZeneca, Eli Lilly, GSK, Pfizer, Wyeth; *Advisory Board*: GSK.

**Douglas Noordsy, M.D.** *Grant/Research Support:* Alkermes; *Consultant:* Alkermes, Otsuka.

**Carmine M. Pariante, Ph.D., M.D., F.R.C.Psych.** *Research Funding:* GlaxoSmithKline, Lundbeck, Johnson & Johnson; *Research Funding (Consortium):* Medical Research Council and the Wellcome Trust.

**Steven R. Pliszka, M.D.** *Grant/Research Support:* Ironshore, Purdue Pharma, Shire; *Consultant:* Ironshore.

**Robert M. Post, M.D.** *Speakers' Honoraria:* AstraZeneca, Sunovion, Validus.

**Mark M. Rasenick, Ph.D.** *Grant/Research Support:* Eli Lilly, Lundbeck; *Honoraria/Consulting:* Eli Lilly, Pfizer; *Financial Interest:* Pax Neuroscience.

**Shona L. Ray-Griffith, M.D.** *Research Support:* Sage Therapeutics (paid travel and meals to attend investigator meeting).

**Patrick H. Roseboom, Ph.D.** *Patents:* U.S. Patent Nos. 7,071,323 and 7,531,356—Kalin NH, Roseboom PH, Landry CF, Nanda SA: Promoter sequences for corticotropin-releasing factor CRF2alpha and method of identifying agents that alter the activity of the promoter sequences; U.S. Patent No. 7,087,385—Kalin NH, Roseboom PH, Nanda SA: Promoter sequences for urocortin 2 and the use thereof; U.S. Patent No. 7,122,650—Roseboom PH, Kalin NH, Nanda SA: Promoter sequences for corticotropin-releasing factor binding protein and use thereof.

**Alan F. Schatzberg, M.D.** *Consultant:* Alkermes, Forum (En Vivo), Lundbeck/Takeda, McKinsey, Myriad, Naurex, Neuronetics, One Carbon, Pfizer, Sunovion; *Honoraria:* Pfizer; *Grants:* Janssen; *Equity Holdings:* Amnestix, Cervel,



Corcept (co-founder), Delpor, Merck, Neurocrine, Titan, Xhale; *Intellectual Property*: Named inventor on pharmacogenetic and antiglucocorticoid use patents on prediction of antidepressant response.

**S. Charles Schulz, M.D.** *Grant/Research Support*: Myriad/RBM, NIMH, Otsuka; *Consultant*: FORUM, Lundbeck, Myriad.

**David V. Sheehan, M.D., M.B.A.** *Grant/Research Support*: Abbott Laboratories, American Medical Association, Anclore Foundation, AstraZeneca, Avera, Bristol-Myers Squibb, Burroughs Wellcome, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Glaxo-Wellcome, International Clinical Research (ICR), Janssen, Jazz, Kali-Duphar, Labopharm-Angellini, Lundbeck, Mead Johnson, MediciNova, Merck Sharp & Dohme, National Institute of Drug Abuse, National Institutes of Health, Novartis, Parke-Davis, Pfizer, Quintiles, Sandoz, Sanofi-Aventis, Sanofi-Synthelabo Recherche/Sanofi Aventis, Shire Laboratories, SmithKlineBeecham, Sunovion, Takeda, TAP, Tonix, United Bioscience, University of South Florida Psychiatry Center, Upjohn, Warner Chilcott, Worldwide Clinical Trials, Wyeth-Ayerst, Zeneca; *Consultant*: Abbott Laboratories, Actavis/Allergan, Ad Hoc Committee, Treatment Drug & Assessment Research Review, Alexza, ALZA, Applied Health Outcomes/xCenda, AstraZeneca, Avera, BioMarin, Bionomics, Bristol-Myers Squibb, Cephalon, Cortex, Cypress Bioscience, Daiichi Sankyo Pharma Development, Daiichi Sankyo/MMS Holdings, Eisai, Eli Lilly, Faxmed, Forest Laboratories, GlaxoSmithKline, INC Research, International Society for CNS Drug Development (ISCDD), Janssen, Jazz, Labopharm-Angellini, Layton Bioscience, Lilly

Research Laboratories, Lundbeck, MAPI, MediciNova, National Anxiety Awareness Program, National Anxiety Foundation, National Depressive and Manic Depressive Association, Neuronetics, NovaDel, Novartis, Organon, Orion, Otsuka, Parexel International, Pfizer, Pharmacia & Upjohn, PharmaNeuroBoost, PH&T, Pierre Fabre France, ProPhase, Roche, Sagene, Sanofi-Aventis, Sanofi-Synthelabo Recherche/Sanofi Aventis, Sepracor, Shire Laboratories, SmithKlineBeecham, Solvay, Takeda, Targacept, Tikvah Therapeutics, Titan, Turing, United Bioscience, Upjohn, World Health Organization, Wyeth-Ayerst, ZARS; *Lectures/Presentations/Royalties*: Abbott Laboratories, Apsen, AstraZeneca, Boehringer Ingelheim, Boots, Bristol-Myers Squibb, Burroughs Wellcome, Charter Hospitals, Ciba Geigy, Dista Products, Eli Lilly, Excerpta Medica Asia, Forest Laboratories, Glaxo, GlaxoSmithKline, Hikma, Hospital Corporation of America, Humana, ICI, INC Research, Janssen, Kali-Duphar, Labopharm-Angellini, Lundbeck, Macmillan, Marion Merrill Dow, McNeil, Mead Johnson, Merck Sharp & Dohme, Novo Nordisk, Organon, Parke-Davis, Pfizer, Pharmacia & Upjohn, PharmaNeuroBoost, Rhone Laboratories, Rhone-Poulenc Rorer, Roerig, Sandoz, Sanofi-Aventis, Schering, Simon & Schuster, SmithKlineBeecham, Solvay, Sunovion, Takeda, TAP, TGH-University Psychiatry Center, Titan, United Bioscience, Upjohn, Warner Chilcott, Wyeth-Ayerst; *Stock Holdings*: Medical Outcome Systems.

**Richard C. Shelton, M.D., M.P.H.** *Grant/Research Support*: Alkermes, Actavis, Assurex Health, Avanir, Cerecor, Janssen, Naurex, Novartis, Otsuka, Pamlab, Takeda; *Consultant*: Allergan, Bristol-Myers Squibb, Cerecor, Clintara, Janssen, Medtronic, MSI Methylation

Sciences, Naurex, PamLab, Pfizer, Ridge Diagnostics, Shire Plc, Takeda.

**Murray B. Stein, M.D., M.P.H.** *Grant/Research Support:* Investigator in multicenter clinical trial funded by Janssen. *Consultant:* Actelion, Janssen, Oxeia Biopharmaceuticals, Resilience Therapeutics.

**Zachary N. Stowe, M.D.** *Research Support/Consultant:* GlaxoSmithKline, Pfizer, Wyeth; *Speakers' Honoraria:* Eli Lilly (prior to 2008), Forest (prior to 2008), GlaxoSmithKline, Pfizer, Wyeth; *Clinical Trial Support:* Janssen Pharmaceuticals, Sage Therapeutics.

**Martin T. Strassnig, M.D.** *Consultant/Honoraria:* Janssen.

**Michael E. Thase, M.D.** *Consultant (as of August 25, 2015):* Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb, Cerecor, Eli Lilly, Fabre-Kramer, Forest, Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, LLC (Nestle), MedAvante, Merck, Moksha8, Naurex, Neuronetics, Novartis, Ortho-McNeil (Johnson & Johnson; Janssen), Otsuka, PamLab, Pfizer, Shire US, Sunovion, Takeda, and Trius Therapeutics; *Grant Funding:* Agency for Healthcare Research and Quality, Alkermes, Assurex Health, Avanir, Forest, Janssen, Eli Lilly, National Institute of Mental Health, and Otsuka. *Equity Holdings:* MedAvante; *Royalties:* American Psychiatric Foundation, Guilford Publications, Herald House, Oxford University Press, and W.W. Norton. *Employment (Spouse):* Dr. Thase's wife is employed as Group Scientific Director for Peloton Advantage, which does business with Pfizer.

**Karen Dineen Wagner, M.D., Ph.D.** *Honoraria:* UBM Medica, Nebraska Psychiatric Association.

**Charles F. Zorumski, M.D.** *Scientific Advisory Board:*  
Sage Therapeutics.

*The following contributors stated that they had no competing interests during the year preceding manuscript submission:*

Elias Aboujaoude, M.D.; W. Stewart Agras, M.D.; Sultan Albrahim, M.D.; Raman Baweja, M.D.; Charles L. Bowden, M.D.; Kathleen T. Brady, M.D., Ph.D.; Frank W. Brown, M.D.; Joseph F. Cubells, M.D., Ph.D.; Darina Czamara, Ph.D.; Daniella David, M.D.; Karon Dawkins, M.D.; William C. Dement, M.D., Ph.D.; C. Lindsay DeVane, Pharm.D.; Firdaus S. Dhabhar, Ph.D.; Barbara D’Orio, M.D., M.P.A.; Carolyn M. Drazinic, M.D., Ph.D.; Elise M. Fallucco, M.D.; Adriana E. Foster, M.D.; Steven J. Garlow, M.D., Ph.D.; Donald C. Goff, M.D.; Robert N. Golden, M.D.; Rolando Gonzalez, M.D.; Todd D. Gould, M.D.; David V. Hamilton, M.D., M.A.; Ebrahim Haroon, M.D.; Karen Hartwell, M.D.; Joseph H. Henry, M.D.; Michele Hill, M.R.C.Psych.; Dawn F. Ionescu, M.D.; Jessica Keverne, Ph.D.; Roxanne Keynejad, M.A. (Oxon), M.B.B.S., M.R.C.P.; Ania Korszun, Ph.D., M.D., F.R.C.Psych.; Venkatesh Basappa Krishnamurthy, M.D.; Kurt Kroenke, M.D.; David S. Mathai, B.S.; Aimee L. McRae-Clark, Pharm.D.; Thomas W. Meeks, M.D.; Emmanuel Mignot, M.D., Ph.D.; Andrew H. Miller, M.D.; Kazuo Mishima, M.D., Ph.D.; Marissa Miyazaki, M.D.; Katherine Marshall Moore, M.D.; Linda Nicholas, M.D.; Seiji Nishino, M.D., Ph.D.; Sandhaya Norris, M.D.; Bruce G. Pollock, M.D., Ph.D., F.R.C.P.; Charles L. Raison, M.D.; Karl Rickels, M.D.; Donald S. Robinson, M.D.; Steven P. Roose, M.D.; Jerrold F. Rosenbaum, M.D.; Noriaki Sakai, D.V.M., Ph.D.; Carl Salzman, M.D.; Erika F. H. Saunders, M.D.; Brian J. Sherman, Ph.D.; Amy L. Silberschmidt, M.D.; Daphne

Simeon, M.D.; George M. Simpson, M.D.; Joseph K. Stanilla, M.D.; Steven T. Szabo, Ph.D.; Rajiv Tandon, M.D.; Marc L. van der Loos, M.D., Ph.D.; Scott Van Sant, M.D.; Po W. Wang, M.D.; Margaret B. Weigel, M.D.; Joanne D. Wojcik, Ph.D., A.P.R.N., B.C.; Tsung-Ung W. Woo, M.D., Ph.D.; Yvonne S. Yang, M.D., Ph.D.; Jiang-Zhou Yu, M.D., Ph.D.

# Introduction

Psychopharmacology has developed as a medical discipline over approximately the past five decades. The discoveries of the earlier effective antidepressants, antipsychotics, and mood stabilizers were invariably based on serendipitous observations. The repeated demonstration of efficacy of these agents then served as an impetus for considerable research into the neurobiological bases of their therapeutic effects and of emotion and cognition themselves, as well as the biological bases of the major psychiatric disorders. Moreover, the emergence of an entire new multidisciplinary field, neuropsychopharmacology, leading to the development of specific agents to alter maladaptive central nervous system processes or activity, was another by-product of these early endeavors. The remarkable proliferation of information in this area—coupled with the absence of any comparable, currently available text—led us to edit the first edition of *The American Psychiatric Press Textbook of Psychopharmacology*, published in 1995. The response to that edition was overwhelmingly positive. In the second edition, published in 1998, we expanded considerably on the first edition, covering a number of areas in much greater detail, adding several new chapters, and updating all of the previous material. Again, the response was positive. We then presented third and fourth editions, in 2004 and 2009, respectively, with updated and expanded

material. These have continued to be very popular, and the past three editions of the *Textbook* have each been followed, after an interval of approximately 2 years, with a distilled *Essentials* volume—in essence an updated but abridged version of the *Textbook* in paperback format.

We now come to the fifth edition of this work, *The American Psychiatric Association Publishing Textbook of Psychopharmacology*. Again, all of the material has been updated, and several new authors and chapters have been added, covering new key areas in the specialty. To aid the reader in absorbing and integrating the vast amount of information presented, we have attempted in all editions to provide sufficient foundational material to support a sound understanding of how drugs work, and why, when, and in whom they should be used.

Each successive edition has understandably become larger as we have attempted to keep pace with the ever-growing body of knowledge in the field. In contrast, over the past 20 years, reading preferences have changed, with handiness and portability now being primary requirements. With this in mind, American Psychiatric Association Publishing decided to apply uniformity to textbook sizes and page counts to bring them into line with the more compact format used for the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5). Therefore, this revised, fifth edition of the *Textbook of Psychopharmacology* has been designed to be more accessible, with fewer overall chapters than in the last edition, while still covering the depth of information the reader needs.

The *Textbook* has three parts. [Part I, “Principles of Psychopharmacology,”](#) contains 7 chapters that provide a theoretical background for the ensuing parts. Topics

include molecular biology, neurotransmitters and receptors, genetics and genomics, psychoneuroendocrinology, brain-immune system interactions, pharmacokinetics and pharmacodynamics, and brain imaging.

[Part II, “Classes of Psychiatric Treatments,”](#) presents information by classes of drugs. For each drug within a class, data are reviewed on history and discovery, preclinical and clinical pharmacology, pharmacokinetic parameters, mechanism of action, indications and efficacy, side effects and toxicology, and drug-drug interactions. This section is pharmacopoeia-like, encompassing 38 chapters generally dedicated to individual agents (e.g., paroxetine, venlafaxine, vortioxetine, lurasidone, cariprazine). We include data not only on drugs currently available in the United States but also on medications that will in all likelihood become available in the near future. On many chapters we have invited new authors to provide fresh insights.

[Part III, “Psychopharmacological Treatment,”](#) includes 14 chapters that review state-of-the-art pharmacotherapeutic approaches to patients with major psychiatric disorders as well as those in specific age groups (e.g., pediatric populations, elderly patients) or circumstances (e.g., psychiatric emergencies, chronic pain). Here, too, new contributors provide fresh looks at important clinical topics. Chapters in this section provide the reader with specific information about drug selection and prescription.

Finally, an [Appendix—“Psychiatric Medications”](#)—provides key information on indications (both approved and off-label) and dosages (both adult and pediatric) for individual agents covered in the *Textbook*, presented in a convenient tabular format.



This *Textbook* would not have been possible without the superb editorial work of our managing editor, Rebecca Wyse, who organized the coordination of chapter authors' efforts and time lines. In addition, we wish to thank John McDuffie, Associate Publisher, Acquisitions and Development, of American Psychiatric Association Publishing and his staff for their efforts. In particular, we appreciate the major efforts of Bessie Jones, Acquisitions Coordinator; Greg Kuny, Managing Editor; Tammy J. Cordova, Graphic Design Manager; Rebecca Richters, Senior Editor; and Judy Castagna, Assistant Director of Production Services.

*Alan F. Schatzberg, M.D.*

*Charles B. Nemeroff, M.D., Ph.D.*

# **PART I**

## Principles of Pharmacology

# CHAPTER 1

## Basic Principles of Molecular Biology and Genomics

Jiang-Zhou Yu, MD., Ph.D.

Mark M. Rasenick, Ph.D.

In June 2000, it was announced that both a corporate effort and a government consortium had succeeded in sequencing all of the human genome. This was followed by the publication of that sequence in February 2001 ([Lander et al. 2001](#); [Venter et al. 2001](#)). For anyone involved in biology or medicine, these events represented a revolution in the technical and conceptual approach to both research and therapy.

It seems that humans are far less complex than most scientists had previously thought. Rather than having 100,000–150,000 genes, as was once the belief, humans may have only about 20,000 genes. At present, not all of

those genes have an identified function, and it is becoming clear that many gene products have more than one function. Perhaps more important, genes that have been identified in a single cell type may have an entirely different function in other cell types. Some other genes may enjoy a brief and transient expression during the process of embryonic development, only to play an entirely different role in the adult. Truly understanding those genes and gene products will revolutionize all of science, and this may be especially true for psychiatry.

Consider that prior to identification of the genome, psychiatric genomics was limited to studies of chromosomal linkage wherein a putative gene for a disorder could be roughly localized to a given region of a chromosome. This burgeoning understanding of the human genome has led to a rudimentary understanding of genetic variation among humans. In many humans, a single base or single nucleotide is modified, and it is a combination of knowing the entire genetic code and determining aberrations in individuals with disease that will allow the pinpointing of specific genes associated with psychiatric diseases.

Sometimes during a disease process, inappropriate genes are activated or inactivated. Identifying these genes helps to shed light on the disease process and on possible therapy.

At the same time that rapid advances are being made in understanding the genome, rapid advances in molecular biology are allowing the manipulation of genes and proteins in individual nerve cells. The development of molecular and cellular models for neuropsychiatric disease has also permitted tremendous advancement in understanding both the biochemical defects and possible new approaches toward ameliorating those defects.

In this chapter, we present information about genetics, genomics, and the genome, as well as explain modern molecular biology and the investigative methods used in that field. We also discuss pathophysiology, as related to neuropsychiatry and molecular strategy, and introduce findings from studies on the cell biology of the neuron that help us to understand both psychopharmacology and the biology of the brain and mind. Remarkable progress has been made in the 6 years since the publication of the previous edition of this book. Epigenetics has become important to psychiatry and has sparked new understanding of gene regulation as well as new mechanisms for monitoring this. Gene editing has gone from an in vitro phenomenon to a straightforward technique employed in intact mammals. Optogenetics has revolutionized the tracing of neural circuits, and the study of microRNAs has revealed a great deal about the regulatory potential of noncoding regions of the genome. We discuss these advances in this chapter, but we caution readers that the half decade following publication of this book is likely to bring a new tsunami of discovery to be discussed in the subsequent edition.

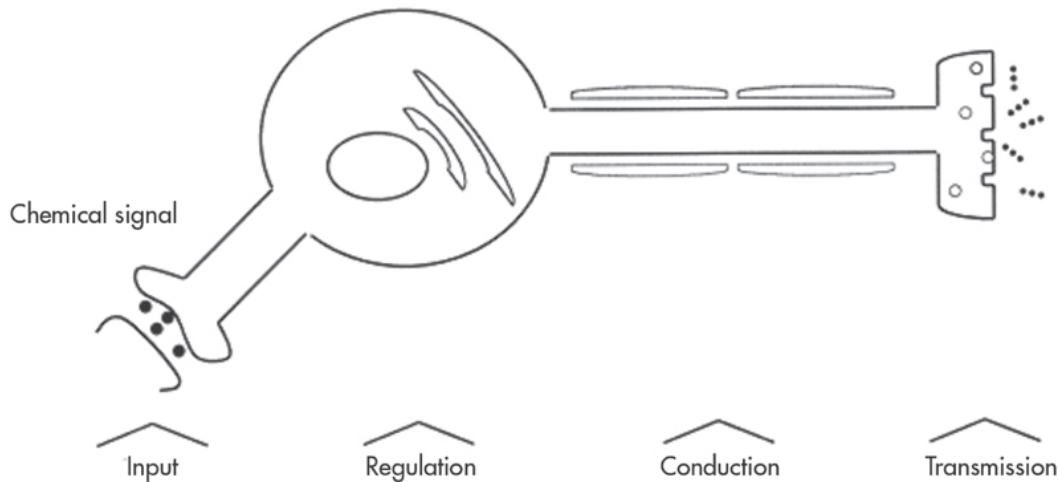
---

## **Cell Biology of Neurons and Glia**

---

To appreciate the molecular biology described in this chapter, one needs to understand the aspects of the neurons that process signals that directly or indirectly modify the aspects of the genome described below. Neurons are specialized cells that function to transmit signals to other neurons, muscles, and secretory cells. Neurons

contain four basic domains (Figure 1-1), which serve to receive signals, process and integrate signals, conduct impulses, and transmit signals.



**FIGURE 1-1.** Diagram of a typical neuron.

As described in the text, this neuron is divided into zones for reception of signals (input=dendrites), integration of signals (regulation=nucleus and soma), conduction of signals (axon), and transmission of signals (axon terminal).

The nucleus resides in the cell body (the signal processing domain) and contains the DNA that codes for the genes expressed by neurons. Activation of a given gene results in the generation of a messenger RNA (mRNA), which is then translated into a protein (see below). Although such events are common to all cells, neural cells are unique in some aspects of molecular signaling. Notably, the variety of gene expression is far greater in the brain than in any other organ or tissue. Some estimates are that in aggregate, the brain expresses up to 10 times the number of genes expressed in any other tissue. This does not mean that individual cells undergo a much greater gene expression.

Rather, it suggests an extraordinary heterogeneity among neurons and glia, which allows for a rich regulation when those neurons and glia assemble into the elaborate network of the human brain.

mRNA molecules exported from the nucleus are translated into proteins by ribosomes in the endoplasmic reticulum. Most of the protein production occurs in the cell body, although there is some mRNA in the dendrites as well ([Steward and Wallace 1995](#)). This means that newly made proteins must be transported from that cell body to the axon terminal, a distance as great as 1 meter. These proteins are often packaged in vesicles, and specialized “motor” molecules transport packaged proteins down microtubule “tracks” at the cost of adenosine triphosphate (ATP) hydrolysis ([Setou et al. 2000](#)).

---

## Essential Principles of Gene Expression

---

### Genes and DNA

The DNA double helix transmits genetic information from generation to generation and is the repository of information required to guide an organism’s development and interaction with the environment. The role of DNA in storing and transferring hereditary information depends on the innate properties of its four constituent bases: the two purine bases, adenine (A) and guanine (G), and the two pyrimidine bases, cytosine (C) and thymine (T). Within the DNA double helix, A is complementary to T, and G is

complementary to C. Each block of DNA that codes for a single RNA or protein is called a *gene*, and the entire set of genes in a cell, organelle, or virus forms its *genome*. Cells and organelles may contain more than one copy of their genome. When “unraveled,” the total DNA of a single cell is approximately 1 meter in length. Such a large amount of genetic material is effectively packaged into a cell nucleus, which is also the site of DNA replication and transcription. Only a small percentage of chromosomal DNA in the human genome is responsible for encoding genes that act as a template for RNA strands; there are approximately 20,000 human genes, but modifications such as alternative splicing and RNA editing may lead to a larger number of proteins.

Among RNA strands, only ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), and microRNA (miRNA) have independent cellular functions. The most abundant cellular RNA, mRNA, serves as a template for protein synthesis. RNA, like DNA, is composed of four nucleotide building blocks. However, in RNA, the nucleotide uracil (U) takes the place of thymine (T), and RNA is a flexible single strand that is free to fold into a variety of conformations. Thus, the functional versatility of RNA greatly exceeds that of DNA.

Chromosomal DNA contains both genes and more extensive intergenic regions. Some regions of DNA in genes act as the template for RNA, but some regions are responsible for regulatory functions. The distribution of genes on chromosomes is not uniform; some chromosomal regions, and indeed whole chromosomes, are richly endowed with genes, whereas other regions are more amply supplied with noncoding DNA (although some nongenomic DNA codes for miRNA). Regulation of gene expression conferred by the nucleotide sequence of a DNA



molecule is referred to as *cis*-regulation, because the regulatory and transcribed regions occur on the same DNA molecule. *cis*-Regulatory elements that determine the transcription start site of a gene are called *basal* (or *core*) *promoters*; other *cis*-regulatory elements are responsible for tethering different activators and repressor proteins to DNA. There are specific regions of DNA that bind to regulatory proteins. These regulatory proteins may be encoded at any region in the genome, and because they are not coded by the stretch of DNA to which they bind, they are sometimes called *trans*-acting factors. *Trans*-acting factors that regulate the transcription of DNA are also called *transcription factors*.

## DNA Replication

Chromosomal DNA must be replicated to coordinate with cell division. Replication begins at a sequence called the *origin of replication*. It involves the separation of the double helix DNA strands over a short length and the binding of enzymes, including DNA and RNA polymerases. During DNA replication, each existing strand of DNA serves as a template for the synthesis of a new double helix that contains one old strand and one strand that is newly synthesized but complementary. This process is known as *semiconservative replication*. In the process of cell division, each of the 46 double helices is replicated and folded into chromosomes.

## Transcription

Only a fraction of all the genes in a genome are expressed in a given cell or at a given time. These genes undergo the process of transcription, in which an RNA molecule complementary to one of the gene's DNA strands is synthesized in a 5' to 3' direction, using nucleotide triphosphates. Transcription can be classified into three discrete steps: initiation, mRNA chain, elongation, and chain termination. Transcriptional regulation may occur at any step in the process; however, initiation appears to be the primary control point because, in a sense, it is the rate-limiting step. Localization of the transcription start site and regulation of the rate of transcription are essential to initiation. The *cis*- and *trans*-acting factors described earlier in this section all regulate the initiation of transcription.

## Translation

Each mRNA in a cell can code for the primary amino acid sequence of a protein, using a triplet of nucleotides (codon) to represent each of the amino acids. Some amino acids are represented by more than one codon, because there are more triplet codons than there are amino acids. The codons in mRNA do not interact directly with the amino acids they specify. The translation of the individual codons of mRNA into protein depends on the presence of another RNA molecule, tRNA, which has a cloverleaf structure. On the top leaf of the tRNA structure, three nucleotides form a complementary codon, an anticodon, to each mRNA nucleotide triplet. Thus, each mRNA nucleotide triplet can code for a specific amino acid. Each tRNA carries an amino acid corresponding to its anticodon, and when thus "charged," the complex is termed *aminoacyl-tRNA*.

Anticodons of aminoacyl-tRNA bind with mRNA codons in ribosomes. Ribosomes, a complex of rRNA and enzymes needed for translation, provide the structure on which tRNA can bind with the codons of mRNA in sequential order.

Initiation of protein synthesis involves the assembly of the components of the translation system. These components include the two ribosomal subunits, the mRNA to be translated, the aminoacyl-tRNA specified by the first codon in the message, guanosine triphosphate (GTP), and initiation factors that facilitate the assembly of this initiation complex. In eukaryotes, there are at least 12 distinct translation initiation factors ([Roll-Mecak et al. 2000](#)). After the ribosome recognizes the specific start site on the mRNA sequence, which is always the codon AUG coding for methionine, it slides along the mRNA molecule strand and translates the nucleotide sequence one codon at a time, adding amino acids to the growing end of the polypeptide chain (the elongation process). During elongation, the ribosome moves from the 5' end to the 3' end of the mRNA that is being translated. The binding of GTP to the elongation factor tu (EFtu) promotes the binding of aminoacyl-tRNA to the ribosome ([Wieden et al. 2002](#)). When the ribosome finds a stop codon (UAA, UGA, or UAG) in the message RNA, the mRNA, the tRNA, and the newly synthesized protein are released from ribosomes with the help of release factors that also bind GTP. The translation process is stopped, and a nascent protein exists.

It is noteworthy that initiation, elongation, and release factors undergo a conformational change upon the binding of GTP. In this regard, they are similar to the G proteins (both heterotrimeric G proteins and small "ras-like" G proteins) involved in cellular signaling, and regions of

amino acid sequence homology in the GTP-binding domains have been identified ([Halliday et al. 1984](#); [Kaziro et al. 1991](#)).

---

## Regulation of Gene Expression

---

### Chromatin and DNA Methylation

Biophysics and molecular biology have revealed that chromatin consists of a repetitive nucleoprotein complex, the nucleosome. This particle comprises a histone octamer, with two copies of each of the histones H2A, H2B, H3, and H4, wrapped by 147 base pairs of DNA. In the octamer, histones H3 and H4 are assembled in a tetramer, which is flanked by two H2A-H2B dimers. A variable length of DNA completes the second turn around the histone octamer and interacts with a fifth histone, H1. H2A, H2B, H3, and H4 are variously modified at their amino- and carboxyl-terminal tails to influence the dynamics of chromatin structure and function ([Ballestar and Esteller 2002](#); [Keshet et al. 1986](#); [Kornberg and Lorch 1999](#); [Strahl and Allis 2000](#)). Although chromatin provides structure to chromosomes, it also plays a critical role in transcriptional regulation in eukaryotes because it can repress gene expression by inhibiting the ability of transcription factors to access DNA. In fact, chromatin ensures that genes are inactive until their expression is commanded. In the activation process, cells must attenuate nucleosome-mediated repression of an appropriate subset of genes by means of activator proteins that modify chromatin structure. An activator protein displaces nucleosomes, which permits a complex of proteins

(general transcription factors) to bind DNA at a promoter and to recruit RNA polymerase.

Cytosine methylation at CpG dinucleotides is the most common modification of the eukaryotic genome, which is catalyzed by a family of DNA methyltransferases including Dnmt1, Dnmt3a, and Dnmt3b. CpG islands are CpG-rich regions in the genome, which are often but not always located in the promoter regions of genes and some regulatory elements ([Jones 2012](#)). Methylation of cytosines at CpG inhibits gene expression either by directly interfering with transcription factor binding to DNA ([Ballestar and Esteller 2002](#)) or by recruiting methyl-CpG binding domain proteins, which complex with histone deacetylase (HDAC) to transform chromatin to a repressive state ([Ballestar and Esteller 2002](#); [Keshet et al. 1986](#)). Dnmt1 expression is remarkably high in the embryonic nervous system, consistent with the proposed role for Dnmt1 in maintaining DNA methylation in dividing neural progenitor cells ([Cedar and Bergman 2009](#)).

In addition to alterations in DNA methylation, epigenetic modifications to histone tails are thought to regulate a range of cellular functions, including transcription, replication, chromosome condensation, recombination, DNA repair, and the organization of higher-order chromatin within the nucleus ([Strahl and Allis 2000](#)). Acetylation and methylation of lysine at histone tails are the two most common histone modifications ([Jenuwein and Allis 2001](#)). Hyperacetylation of nucleosomes was strongly associated with transcription, which is considered a hallmark of transcriptional activity, acting to weaken the polar interaction between the negatively charged DNA and the positively charged histone proteins and resulting in a relaxed chromatin state ([Dindot et al. 2009](#); [Ruthenburg et](#)

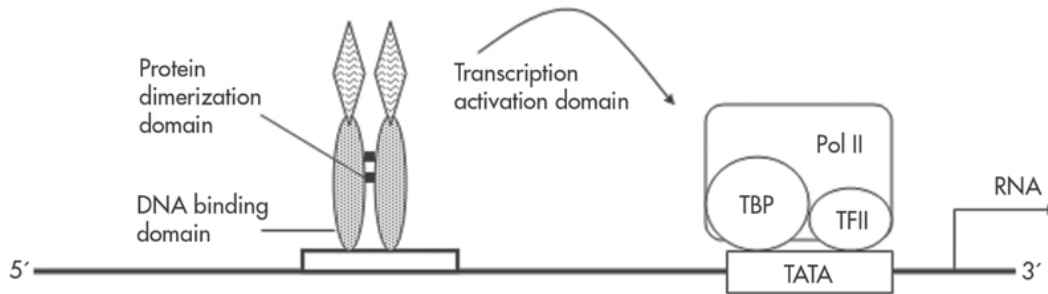
al. 2007). Integral components of the transcriptional machinery include histone acetyltransferase and histone deacetylase enzymes, which regulate, respectively, the addition of acetyl groups to and removal of acetyl groups from histone proteins.

The effects of histone methylation on gene function and chromatin state are mainly dependent on the specific residue that is modified. Generally, in activated gene regions, there is an enrichment of histone methylation at H3K4me, H3K36me, or H3K79me (Guenther et al. 2007; Heintzman et al. 2007; Steger et al. 2008). In contrast, the enrichment of histone methylation at H3K9me, H3K20me, or H4K27me is implicated in gene inactivation or silencing (Kouzarides 1999; Ruthenburg et al. 2007). Studies also revealed that the degree of histone methylation plays a role in gene expression activity. The tri-methylation at residues of H3K9, H3K2, and H4K20 is associated with transcription repression (Barski et al. 2007; Mikkelsen et al. 2007; Vakoc et al. 2006). However, the mono-methylation at these residues represented the gene activation (Barski et al. 2007; Vakoc et al. 2006). These DNA modifications form the basis of epigenetics, which has taken on a prominent role in relating experience to psychiatric phenotypes (Klengel and Binder 2015).

## RNA Polymerases

There are three distinct classes of RNA polymerase—RNA polymerase I (Pol I), RNA polymerase II (Pol II), and RNA polymerase III (Pol III)—in the nucleus of eukaryotic cells, and they are designed to carry out transcription. RNA Pol I synthesizes large rRNA molecules. RNA Pol II is mainly

used to yield mRNA and, subsequently, proteins. RNA Pol III produces small RNA, including rRNA and tRNA molecules. Each class of RNA polymerase recognizes particular types of genes. However, RNA polymerases do not bind to DNA directly. Rather, they are recruited to DNA by other proteins that bind to promoters (Figure 1-2).



**FIGURE 1-2.** Transcription factors and RNA polymerase II (Pol II) complex.

Typical transcription factors contain DNA binding domains, dimerization domains, and transcription activation domains. Some transcription factors (e.g., cAMP response element-binding protein [CREB]) may be modified by phosphorylation. The transcription activation domain interacts with an RNA Pol II complex to induce transcription. TATA binding protein (TBP) binds to the TATA box element and associates with general transcription factors (TFII). This gene transcription apparatus recruits Pol II to the appropriate gene.

mRNA is transcribed from DNA by RNA Pol II, with heterogeneous nuclear RNA (hnRNA), an intermediate product. The core promoter recognized by Pol II is the TATA box (Hogness box), a sequence rich in nucleotides A and T, which is usually located 25–30 bases upstream of the transcription start site. The TATA box determines the start site of transcription and orients the basal transcription

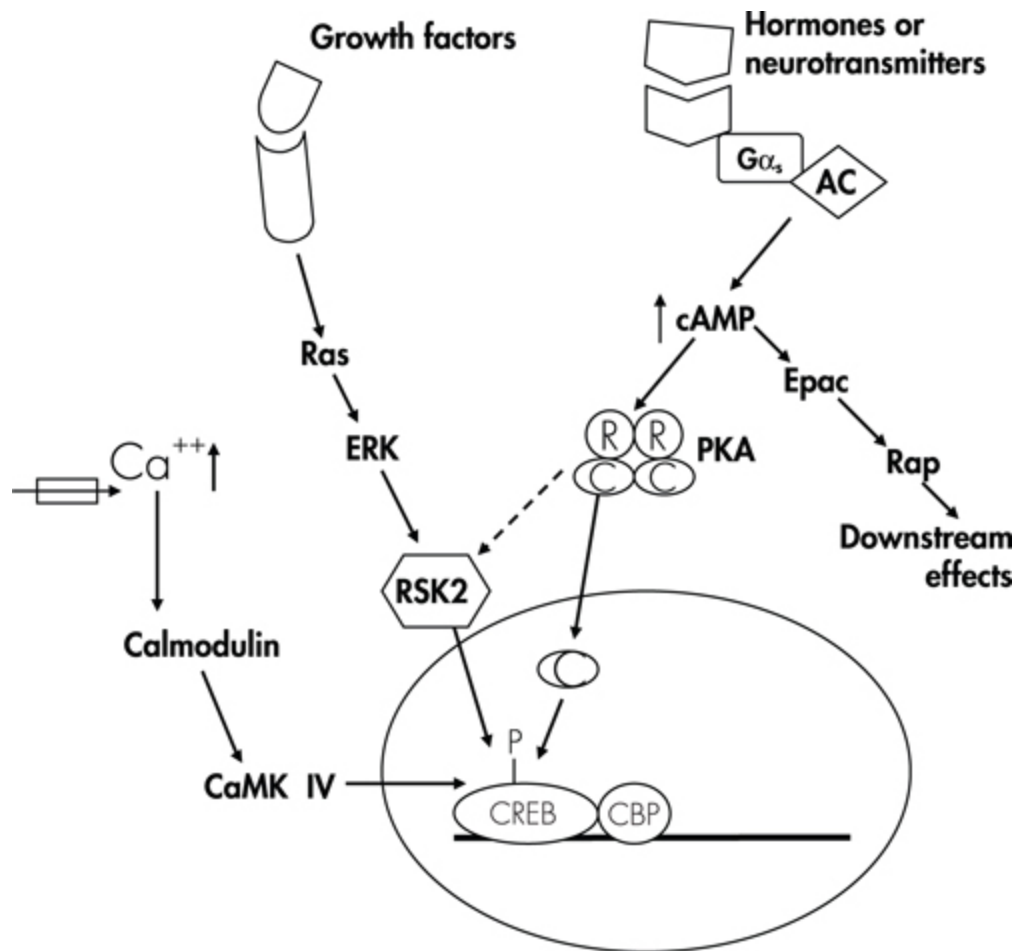
complex that binds to DNA and recruits RNA Pol II to the TATA box; thus, it establishes the 5' to 3' direction in which Pol II synthesizes RNA. The formation of the basal transcription complex is promoted by a TATA box binding protein (TBP) that binds core promoter together with multiple TBP-associated factors and other general transcription factors. *Enhancers* are DNA sequences that increase the rate of initiation of transcription by RNA Pol II through its interaction with transcription factors, which can be located “upstream” or “downstream” of the transcription start site. Enhancer elements are important to cell-specific and stimulus-dependent expression of hnRNA. Some Pol II species, including those for many genes that are expressed in neurons, lack a TATA box and possess instead an *initiator*, a poorly conserved genetic promoter element.

## Transcription Factors

Transcription factors act as the key regulators of gene expression. Sequence-specific transcription factors typically contain physically distinct functional domains (see [Figure 1-2](#)). Numerous transcription factors have been found. Some of them translocate to the nucleus to bind their *cis*-regulatory elements in response to their activation reaction, such as nuclear factor  $\kappa$ B (NF- $\kappa$ B). However, some transcription factors are already bound to their cognate *cis*-regulatory elements in the nucleus under basal conditions and are converted into transcriptional activators by phosphorylation. cAMP (cyclic 3'-5'-adenosine monophosphate) response element-binding protein (CREB), for example, is bound to regions of DNA, called *cAMP response elements* (CREs), before cell stimulation.



CREB can promote transcription when it is phosphorylated on a serine residue (ser133), because phosphorylated CREB can interact with a coactivator, CREB-binding protein (CBP), which in turn contacts and activates the basal transcription complex. Of interest, CBP possesses intrinsic histone acetyltransferase activity. The activity of most transcription factors is regulated through second-messenger pathways. CREB can be activated via phosphorylation at ser133 by second messengers such as cAMP,  $\text{Ca}^{++}$ , and growth factors (Kandel 2012) (Figure 1-3).



**FIGURE 1-3.** Activation of cAMP response element-binding protein (CREB) via different signal

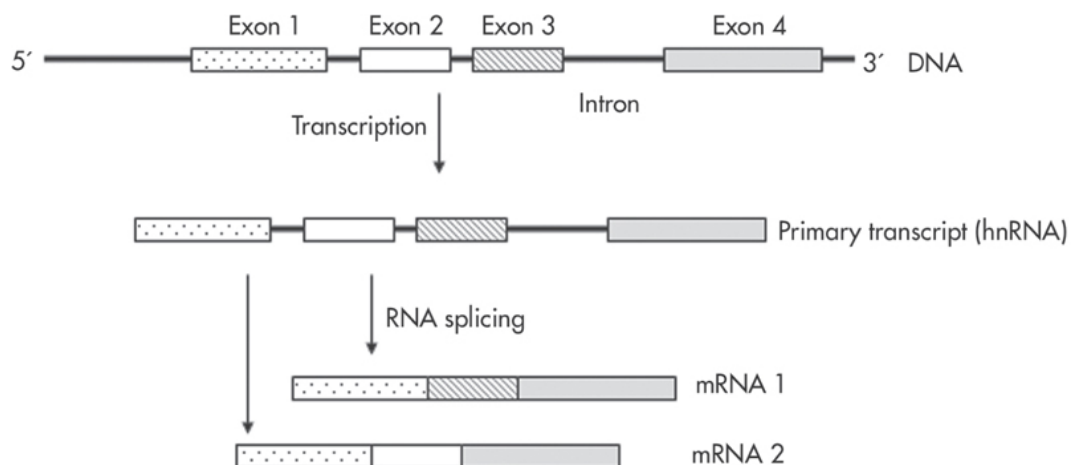
## transduction pathways.

Signal cascades are activated by external stimuli, such as hormones or neurotransmitters and growth factors. *Arrows* indicate the interaction between pathways. AC=adenylyl cyclase; C=catalytic subunits of PKA;  $Ca^{++}$ =calcium; CaMK IV=calmodulin-dependent kinase IV; cAMP=cyclic 3'-5'-adenosine monophosphate; CBP=CREB-binding protein; Epac=exchange protein activated by cAMP; ERK=extracellular-regulated kinase;  $G\alpha_s$ = $\alpha$  subunit of the stimulatory G protein; P=phosphorylation; PKA=cAMP-dependent protein kinase; R=regulatory subunits of PKA; Rap and Ras=small GTPases (small proteins that bind to guanosine triphosphate [GTP]); RSK2=ribosomal S6 kinase 2.

CREB is a molecule that is widely implicated in learning and memory in many species. Mice expressing mutant CREB isoforms show impaired memory, but this is dependent on the genetic background of the mice ([Graves et al. 2002](#)). CBP is a transcriptional coactivator with CREB. A partial-knockout mouse model, in which CBP activity is lost, exhibits learning deficiencies ([Oike et al. 1999](#)). Furthermore, Rubinstein-Taybi syndrome (RTS) is an autosomal-dominant dysmorphic syndrome that results in severe impairment of learning and memory. The RTS gene has been mapped to chromosome 16 and identified as CBP. Loss of the function of CBP is likely one important contributing factor to the learning and memory defects seen in RTS ([Murata et al. 2001](#); [Oike et al. 1999](#); [Petrij et al. 1995](#)).

## Posttranscriptional Modification of RNA

The mRNA of prokaryotes can be used without any modification to direct protein synthesis, but posttranscriptional processing of mRNA is required in eukaryotes. The DNA sequences that code for mRNA (exons) are frequently interrupted by intervening DNA sequences (introns). When a protein-coding gene is first transcribed, the hnRNA contains both exons and introns. Before the transcript exits the nucleus, its introns are removed and its exons are spliced to form mature mRNA (Figure 1-4.) The hnRNA that is synthesized by RNA polymerase has a 7-methyl-guanosine “cap” added at the 5’ end. The cap appears to facilitate the initiation of translation and to help stabilize the mRNA. In addition, most eukaryotic mRNA has a chain of 40-200 adenine nucleotides attached to the 3’ end of mRNA. The poly (A) tail is not transcribed from DNA; rather, it is added after transcription by the nuclear enzyme poly (A) polymerase. The poly (A) tail may help stabilize the mRNA and facilitate mRNA exit from the nucleus. After the mRNA enters the cytoplasm, the poly (A) tail is gradually shortened.



**FIGURE 1-4.** Transcription and RNA splicing.

The horizontal black line between exons indicates intron. The region before the first exon is the 5' regulatory region of the gene, such as a TATA box. There also are *cis*-regulatory elements in introns and downstream of the last exon. The heterogeneous nuclear RNA (hnRNA), containing both exons and introns, is spliced to form mRNA. mRNAs are then exported from the nucleus to the cytoplasm, where they will direct the synthesis of distinct proteins.

## RNA Editing

RNA editing has been observed in eukaryotes ranging from protozoa to mammals and is now recognized as a type of RNA process (posttranscriptional modification of RNA) that differs from the well-known processes of RNA splicing, 5' end formation, and 3' endonucleolytic cleavage and polyadenylation ([DeCerbo and Carmichael 2005](#); [Kable et al. 1997](#)). The conversion of adenosine to inosine was observed first in yeast tRNA ([Grosjean et al. 1996](#)) but has since been detected in viral RNA transcripts and mammalian cellular RNA ([Bass 1997](#); [Simpson and Emeson 1996](#)). The inosine residues generated from adenosines can alter the coding information of the transcripts, as inosine is synonymous for guanosine during transcript translation. For example, upon A-to-I editing the CAC codon for histamine is transformed to CIC, coding for arginine. RNA editing can have dramatic consequences for the expression of genetic information, and in a number of cases it has been shown to lead to the expression of proteins not only with altered amino acid sequences from those predicted from the DNA sequence but also with altered biological functions ([Bass 2002](#); [Burns et al. 1997](#)).

The enzymes for RNA editing are referred to as *adenosine deaminases that act on RNA* (ADARs). ADARs target double-stranded RNA (dsRNA) and convert adenosines to inosines by catalyzing a hydrolytic deamination at the adenine base ([Bass 2002](#)). Mammals have several ADARs, of which two, ADAR1 and ADAR2, are expressed in most tissues of the body ([Seeburg and Hartner 2003](#)). RNA editing may also catalyze the conversion of a small number of adenosines in a transcript to inosines ([Stuart and Panigrahi 2002](#)). On the other hand, RNA editing can convert numerous adenosines to inosines in RNA. This type of editing is thought to be the result of aberrant production of dsRNA ([DeCerbo and Carmichael 2005](#)) and has been suggested to lead to RNA degradation ([Scadden and Smith 2001](#)), nuclear retention ([Zhang and Carmichael 2001](#)), or even gene silencing ([Wang et al. 2005](#)).

The serotonin 5-HT<sub>2C</sub> receptor is a G protein-coupled receptor that has variants generated by A-to-I editing ([Burns et al. 1997](#)). 5-HT<sub>2C</sub> receptor transcripts can be edited at up to five sites, potentially generating 24 different receptor versions and hence a diverse receptor population. The RNA-edited 5-HT<sub>2C</sub> receptor affects ligand affinity and the efficacy of G protein coupling ([Berg et al. 2001](#); [Wang et al. 2000](#); [Yang et al. 2004](#)). The unedited form of the 5-HT<sub>2C</sub> receptor has the highest affinity to serotonin and exhibits constitutive activity independent of serotonin or serotonergic agonists. When RNA is edited, the basal activity of the 5-HT<sub>2C</sub> receptor is suppressed, and agonist potency and efficacy are modified.

# Non-Coding RNAs

About 2% of the human genome is transcribed into mature protein-coding RNAs, whereas the large majority, 70%–90%, is transcribed into non-protein-coding RNAs (ncRNAs). Classes of noncoding transcripts can be divided between housekeeping noncoding RNAs and regulatory noncoding RNAs. Housekeeping ncRNAs include rRNA, tRNA, snRNA, and small nucleolar RNAs and are usually expressed constitutively. Regulatory ncRNAs can be classified into miRNAs, Piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), promoter and enhancer RNAs, and long noncoding RNAs (lncRNAs) ([Kaikkonen et al. 2011](#); [Ponting et al. 2009](#)). The majority of the non-protein-coding transcripts belong to the group of lncRNAs, which are arbitrarily considered as >200 nucleotides in length ([Ponting et al. 2009](#)). However, many of these lncRNAs can also act as primary transcripts for the production of short RNAs, making the categorization of this group of ncRNAs ambiguous ([Kaikkonen et al. 2011](#)). The best-known ncRNAs are endogenous siRNAs. SiRNAs, together with miRNAs and piRNAs, play an instrumental regulatory and defensive role in organisms. These three classes of small RNAs show overlap with regard to their structure, synthesis, and biological role. Endogenous siRNAs are involved in gene regulation and transposon silencing, although the latter mechanism is still not understood.

## Modification of the Nascent Polypeptide Chain

Posttranslational modifications occur after translation is initiated. They may include removal of part of the translated sequence or the covalent addition of one or more chemical groups that are required for protein activity. Some of these modifications, such as glycosylation or prenylation, represent an obligatory step in the synthesis of the “finished” protein product. In addition, many proteins may be activated or inactivated by covalent attachment of a variety of chemical groups. Phosphorylation, glycosylation, hydroxylation, and prenylation are common types of covalent alterations in posttranslational modifications. A number of different enzymes coordinate these processes, and they represent a major portion of the events of cellular signaling.

---

## **Experimental Approaches to Determining and Manipulating Gene Expression**

---

Changes in gene expression within the central nervous system (CNS) have profound effects for all other aspects of the organism. Changes in gene expression are causally associated not only with the development of the CNS but also with the complex phenomena of brain function, such as memory formation, learning, cognition, and affective state. Changes in gene expression likely underlie the pathogenesis of many sporadic or inherited CNS-related disorders, such as Alzheimer’s disease, Huntington’s disease, depression, and schizophrenia. Thus, insight into and characterization of gene expression profiles are

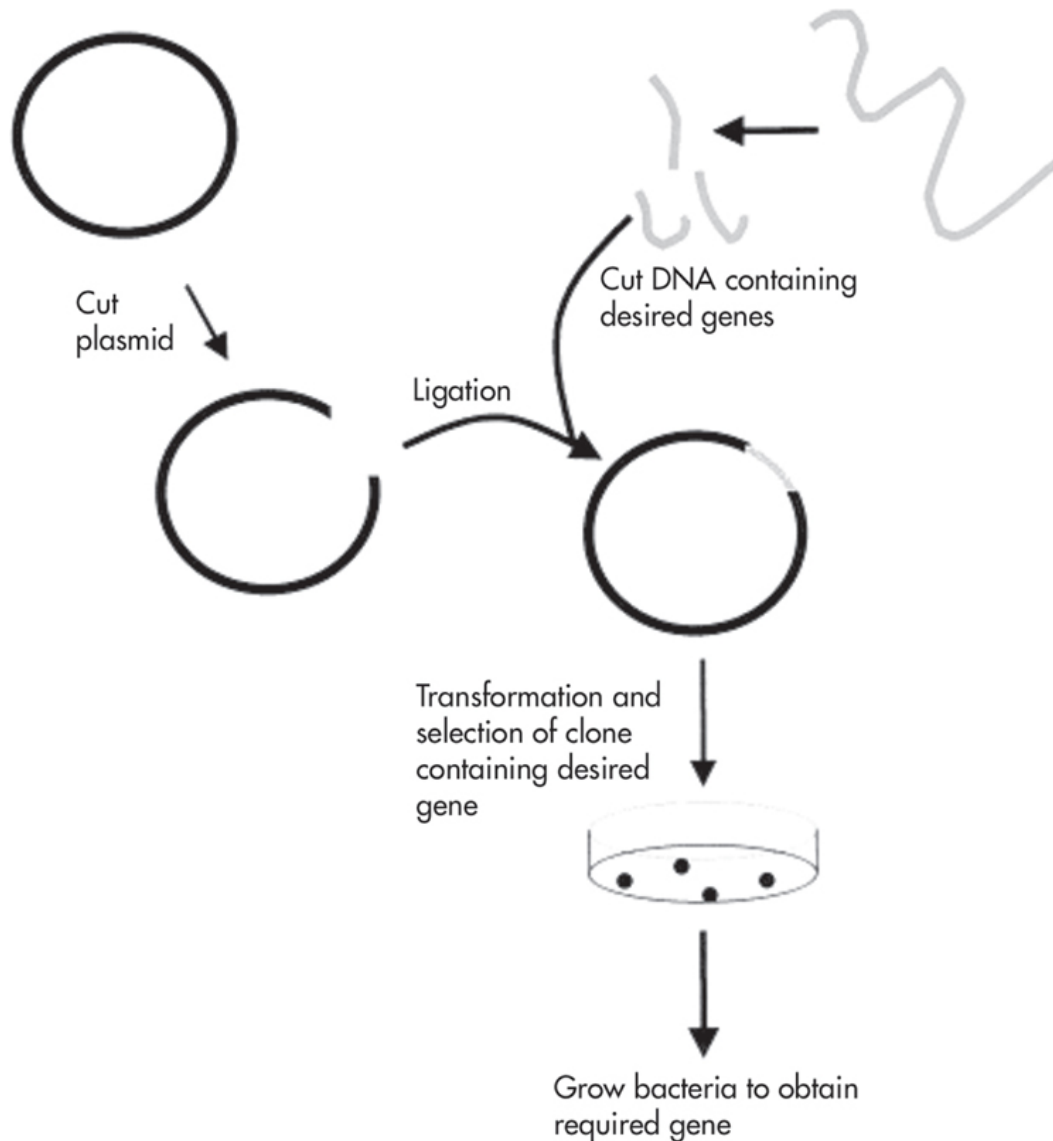
necessary steps for understanding how the brain functions at the molecular level and how malfunction will result in disease. Molecular biological and genomic technologies such as gene mapping and cloning, DNA libraries, gene transfection and expression, and gene knockout and gene targeting have provided numerous benefits to neuropsychopharmacology. Genomic methods applied to pedigree and population samples of patients with psychiatric disorders may soon make it possible to identify genes contributing to the etiology and pathogenesis of these diseases and to provide a potential basis for new therapies.

## Cloning of DNA

The cloning of DNA confers the ability to replicate and amplify individual pieces of genes. Cloning can be performed with genomic DNA or complementary DNA (cDNA). cDNA is synthesized artificially from mRNA in vitro with the aid of *reverse transcriptase*. Cloned genomic DNA may contain any stretch of DNA, either intron or exon, whereas cloned cDNA consists only of exons. For cloning ([Figure 1-5](#) outlines the process), the desired pieces of DNA (often called “inserts”) are connected with the DNA of genetically engineered vectors or plasmids and then introduced into hosts such as bacteria or mammalian cells. A DNA library is a collection of cloned restriction fragments of the DNA of an organism that consists of random pieces of genomic DNA (i.e., genomic library) or cDNA (i.e., cDNA library). Complete cDNA libraries contain all of the mRNA molecules expressed in a certain tissue. Sometimes cDNA libraries can be from a specific tissue in a distinct



circumstance. For example, a cDNA library could be made from cerebral cortex in rats with transient forebrain ischemia ([Abe et al. 1993](#)).



---

**FIGURE 1-5.** Outline of gene cloning.

See text for details.

The cloning of disease-related genes is an important step toward insight into the pathogenesis of diseases and development of new drugs against these diseases. If a

protein is suspected of involvement in pathogenesis, a nucleic acid sequence can be deduced from the partial amino acid sequence. cDNA libraries are screened with the partial sequence in order to fish out a complete clone of interest. The isolated cDNA molecules are used to infect bacteria, which amplify the cloned cDNA. Bacteria expressing these cDNA molecules will often make the protein of interest, which can be detected with antibody. A variation on the above technique uses antibodies against the purified proteins to screen a DNA library transfected into bacteriophages. The bacteriophages containing the “right” cDNA can be retrieved, and the sequence of cDNA can be analyzed.

## **Polymerase Chain Reaction**

*Polymerase chain reaction* (PCR) is a rapid procedure for in vitro enzymatic amplification of specific segments of DNA. Amplification of the genes of interest occurs by selecting and synthesizing “primers”—stretches of DNA that span the region of interest to be “filled in”—and heating DNA to make it single stranded, allowing polymerase and primers to bind. The polymerase then reads the “blank” stretch of DNA between the primers and synthesizes DNA corresponding to the region of interest. This is usually done in thermal cyclers that heat the DNA at regular intervals and allow “cycles” of PCR to amplify the genes repetitively. To avoid continual addition of polymerase, the DNA polymerase used is often from bacteria that inhabit hot springs or hot ocean vents. This polymerase is not denatured by heating and can support several cycles of PCR.

A variation on PCR is reverse transcriptase PCR (RT-PCR), in which the RNA is the template. Reverse transcriptase is

employed to synthesize cDNA from the RNA. Enzymatic amplification of this cDNA is then accomplished using PCR.

Real-time PCR is based on the method of RT-PCR, following the reverse transcription of RNA into cDNA. Real-time PCR requires suitable detection chemistries to report the presence of PCR products, as well as an instrument to monitor the amplification in real time. Generally, chemistries in PCR consist of fluorescent probes. Several probes exist, including DNA binding dyes such as ethidium bromide (EtBr) or SYBR green I, hydrolysis probes (5'-nuclease probes), and hybridization probes ([Valasek and Repa 2005](#)). Each type of probe has its own unique characteristics, but the strategy for each is to link a change in fluorescence to amplification of DNA ([Kubista et al. 2006](#)). The instrumentation to detect the production of PCR must be able to input energy for excitation of fluorescent chemistries at the desired wavelength and simultaneously detect a particular emission wavelength. Many instrument platforms are available for real-time PCR. The major differences among them are the excitation and emission wavelengths that are available, speed, and the number of reactions that can be run in parallel ([Kubista et al. 2006](#)).

## Positional Cloning

Disease genes can sometimes be isolated with the aid of *positional cloning*, a process also known as *reverse genetics* ([Collins 1995](#)). Positional cloning is the process used to identify a disease gene based only on knowledge of its chromosomal location, without any knowledge of the gene's biological function. Positional cloning requires a genetic map of unique DNA segments or genes (genetic markers), with known chromosomal locations, that exist in several alternative forms (alleles). These allelic variations

(polymorphisms) allow comparisons of the wild type as the “diseased” genotype.

Linkage analysis is a method of localizing one or more genes influencing a trait to specific chromosomal regions. This is performed by examining the cosegregation of the phenotype of interest with genetic markers. Relatives who are phenotypically alike will share common alleles at markers surrounding the genes influencing the phenotype, whereas relatives who are phenotypically dissimilar will not share these alleles. To carry out linkage analyses, investigators need, minimally, a set of families in which phenotypic individuals have known relationships to one another and the genotypes of these individuals, including one or more genetic markers.

Once the chromosomal location of the disease gene has been ascertained, the area of chromosomal DNA can be cloned. Until recently, the process of positional cloning involved laborious efforts to build a physical map and to sequence the region. (The sequencing of the human genome has obviated this step). Physical maps can be produced by isolating and linking together yeast and/or bacterial artificial chromosomes containing segments of human DNA from the region. These fragments are then sequenced and ordered, and from these data, the genomic DNA sequence for the region of the candidate gene is determined.

## Differential Display

The technique of differential display is designed to determine the complement of genes being expressed (mRNAs) by a tissue or organ at a given point in time. The

establishment of differential display is dependent on the random amplification and subsequent size separation of cDNA molecules ([Liang et al. 1992](#)). With RT-PCR amplification with specific oligo-T primers (one- or two-base anchored oligo-dT primers, such as oligo-T-XC, oligo-T-XG, oligo-T-XT, and oligo-T-XA; X=G/A/C), four separate cDNA synthesis reactions are performed. These cDNA synthesis reactions form the four pools of cDNA for one original mRNA population. The resulting cDNA molecules from each RT-PCR reaction are amplified, using the same primer of the reverse transcription step plus randomly chosen primers. Because the randomly chosen primers will anneal at various locations upstream of the oligo-T site, many individual cDNA fragments of different sizes are amplified in each PCR reaction. cDNA fragments derived from different original mRNA populations are sized and then separated on parallel gels to analyze the presence of unique bands. The differentially expressed cDNA fragments can be excised from gels, cloned, and further characterized by a variety of technologies based on different purposes, such as in situ hybridization, sequences, and Northern blot analysis.

Differential display is a useful tool for identifying region-specific mRNA transcripts in brain. The molecular markers for these regions can be found by screening for gene expression in specific brain regions or nuclei ([Mizushima et al. 2000](#); [Tochitani et al. 2001](#)). In addition, under different stimulation or behavioral conditions, the changes in gene expression can be explored by differential display ([Hong et al. 2002](#); [Liu et al. 2002](#); [Mello et al. 1997](#); [Tsai et al. 2002](#)). This technique has even been adapted to indicate the RNA expression profile of an individual neuron ([Eberwine et al. 1992](#)). Many genes related to ischemia or Alzheimer's disease in CNS have also been isolated using differential

display ([Doyu et al. 2001](#); [Imaizumi et al. 1997](#); [Tanaka et al. 2002](#)). Genes that are activated in response to chronic drug treatment (e.g., with opiates or antidepressants) can also be identified this way. Furthermore, as described later in this chapter, streamlined technologies are now available for this purpose.

## Gene Delivery Into Mammalian Cells

The introduction of recombinant DNA (including desired genes) into cells is an important strategy for understanding certain gene functions in neurons or glia. Gene function studies have benefited diagnosis and therapy for a variety of disorders that affect the CNS. The delivery of desired genes into cells or brain regions provides the technological base for insight into molecular mechanisms of brain function and, ultimately, for gene therapy in the CNS.

### Vectors and Delivery

For gene transfer, it is necessary to incorporate the desired cDNA into various vectors, such as appropriate plasmids or replication-deficient viruses. Vectors used for transfection generally possess two essentially independent functions: 1) carrying genes to the target cell and 2) expressing the genes properly in the target cell. There are currently many commercial mechanisms with different features from which to choose; the choice is dependent on the purpose of the experiments and on the characterizations of exogenous desired genes. In one form of transfection, *stable transfection*, cells expressing the gene of interest can be actively selected by a marker (e.g., neomycin resistance genes, *Neo*), and the cDNA or other type of foreign DNA is

stably integrated into the DNA of a chromosome. In *transient transfection*, however, cells express the gene of interest for a few days. Cells for hosting the foreign DNA can be either established cell lines or primary cultured neuronal cells. The desired cDNA delivered into cells may be native genes, fragments of the genes, mutant genes, or chimeric genes.

The main barrier to the delivery of DNA into cells is getting the foreign DNA through the cellular membrane. Various methods have been developed to convey the foreign DNA molecules into mammalian cells. These include chemical or physical techniques, such as calcium phosphate coprecipitation of DNA, liposome fusion, electroporation, microinjection, ballistic injection, and viral infection. At present, methods dependent on incorporation of DNA into cationic liposomes are used most widely (e.g., lipofectin). These methods of transfection are accessible to both cell lines and cultured primary neuronal cells. The ratio of DNA to liposomal suspension, cell density, and time duration of exposure to the DNA-liposomal complex must be optimized for each cell type in culture.

## **Viral Vectors**

Several viral vectors with low toxicity, high infection rate, and persistent expression have extended the methodology of delivery of genes to mammalian cells. These viruses include DNA viruses, such as adenoviruses and adeno-associated viruses, herpes simplex viruses, and RNA retroviruses. As a result of advances in genetic manipulation, adenoviruses and adeno-associated viruses are now more widely applied to gene transfer. The advantages of the adenoviruses are 1) the ability to carry large sequences of foreign DNA, 2) the ability to infect a

broad range of cell types, and 3) an almost 100% expression of the foreign genes in cells.

Human adenovirus is a large DNA virus (containing about 36 kilobase pairs) composed of early genes (from *E1* to *E4*) and later genes (from *L1* to *L5*). Wild-type adenovirus cannot be applied to gene transfer because it causes a lytic infection. Thus, recombinant adenoviruses with defects of some essential viral genes are used for gene delivery. These adenoviral expression systems are safe, have the capacity for large DNA inserts, and allow for relatively simple adenoviral production ([Harding et al. 1997](#); [He et al. 1998](#)).

The process of gene transfer into cells (cell lines and primary cells) via recombinant adenoviruses is simple, but the optimal viral titer, the time of exposure to virus, and the multiplicity of infection should be optimized for each cell type. Cell lines and a variety of primary neuronal cells have been infected by adenoviruses ([Barkats et al. 1996](#); [Chen and Lambert 2000](#); [Hughes et al. 2002](#); [Koshimizu et al. 2002](#); [Slack et al. 1996](#)). In addition, recombinant adenoviruses containing the desired genes can be delivered to neurons in vivo via intracerebral injection into particular brain areas ([Bemelmans et al. 1999](#); [Benraiss et al. 2001](#); [Berry et al. 2001](#); [Neve 1993](#)).

## Identification of Ectopic Gene Expression

After delivery of the desired genes into cells, identification of their proper expression is necessary. The general strategies for identification ([Chalfie et al. 1994](#); [Czysz et al. 2015](#); [Kohara et al. 2001](#); [Yu and Rasenick 2002](#)) include the following:

1. The measurement of some functional changes elicited by gene expression in targeted cells. If an enzyme is



expressed, this would involve measuring the activity of that enzyme.

2. The detection of the proteins coded by the desired genes via techniques relying on antibodies, such as western blot, immunoprecipitation, and immunocytochemistry. Expression of the desired genes tagged with some epitopes, such as HA, GST, and His-tag, can also be determined using antibodies directed against these epitopes.
3. The use of green fluorescent protein (GFP) as an indicator. GFP, a protein from the jellyfish *Aequorea victoria*, can be either cotransfected with the desired genes or fused with the desired genes before incorporation into cells. The fluorescence from GFP is easy to detect using fluorescent microscopy, and this allows the monitoring of gene expression in living cells. Furthermore, if GFP is fused with the gene of interest, the fluorescence from GFP provides a useful tool for studying the function and cellular localization of proteins coded by the genes of interest.

Several different “colors” have been developed through mutation of the initial GFP gene. Depending on the wavelengths of excitation, they can be used to localize multiple protein species, or fluorescence resonance energy transfer (FRET) can be used to demonstrate that two target proteins are in close (<10 nm) proximity. FRET uses two fluors with little spectral overlap and depends on the emission of one of the fluors exciting the other.

---

# Inhibition of Cellular Gene Expression

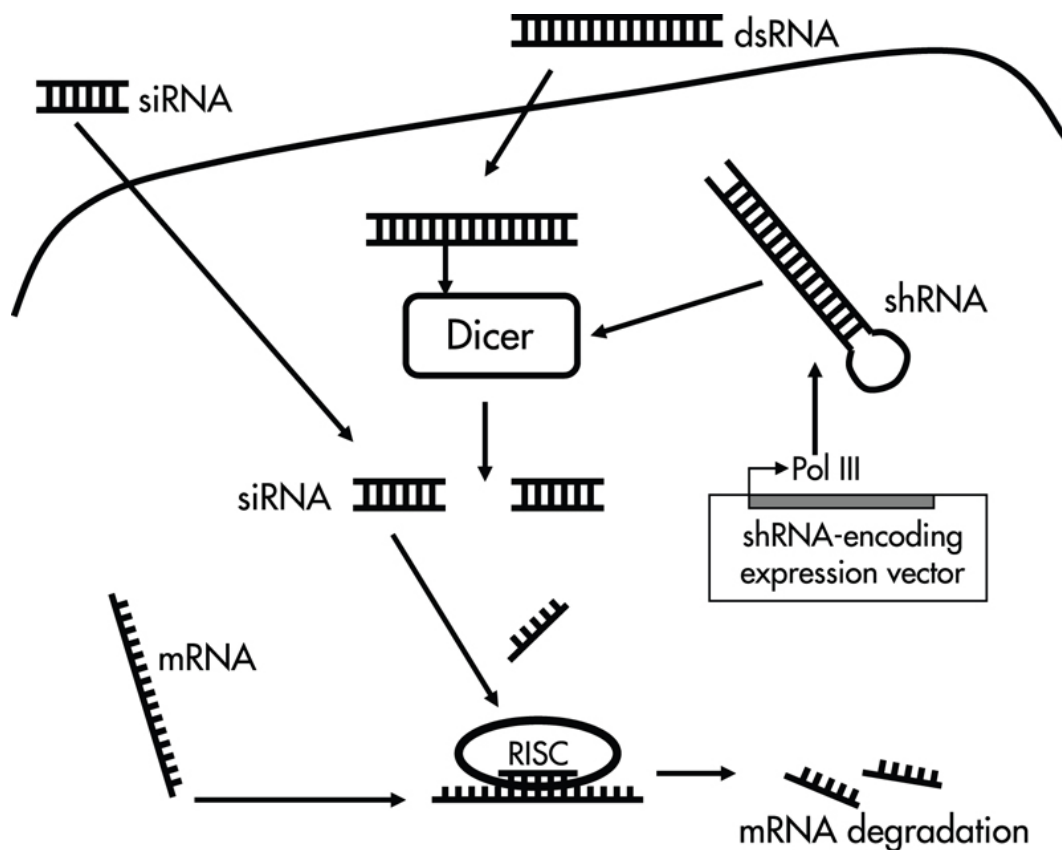
---

## RNA Interference

RNA interference (RNAi) is believed to be a biologically conserved function in a wide range of eukaryotic species. It may play a role in protection against dsRNA viruses ([Sijen et al. 2001](#)) and genome-invading transposable elements ([Provost et al. 2002](#); [Volpe et al. 2002](#)). Triggered by dsRNA, RNAi identifies and destroys the mRNA that shares homology with the dsRNA. Thus, the expression of a particular gene can be suppressed by introducing dsRNA whose antisense strand sequence matches the mRNA sequence. miRNA and siRNA are central to RNA interference.

[Fire et al. \(1998\)](#) first described RNAi in the nematode *Caenorhabditis elegans* as sequence-specific gene silencing in response to dsRNA. The mechanism of RNAi is partly understood, and key proteins involved in the pathway have been identified. In brief, the process of siRNA involves a series of steps. In a first initiation step, Dicer, an enzyme of the RNase III family, initiates ATP-dependent fragmentation of long dsRNA into 21- to 25-nucleotide double-stranded fragments, termed *small interfering RNAs* (siRNAs). These siRNAs are specifically characterized by overhanging 3' ends of two nucleotides and phosphorylated 5' ends. The siRNA duplexes bind with Dicer, which facilitates the formation of an siRNA/multiprotein complex called *RISC loading complex* (RLC). The siRNA duplex in RLC then unwinds (which requires the protein Ago2) to form an

active *RNA-induced silencing complex* (RISC) that contains a single-stranded RNA (called the *guide strand*). The RISC recognizes the target RNA through Watson-Crick base pairing with the guide strand and cleaves the target RNA. Finally, the RISC releases its cleaved product and goes on to catalyze a new cycle of target recognition and cleavage (Figure 1-6) (Tomari and Zamore 2005; Xia et al. 2005).



**FIGURE 1-6.** A schematic of the mechanism of RNA interference (RNAi) posttranscriptional knockdown of a gene product.

The procedure starts with introduction (transfection, electroporation, or injection) of double-stranded RNA (dsRNA) or small interfering RNA (siRNA) into cells, or expression of small hairpin RNA (shRNA) in cells with vectors encoding shRNAs. The

cellular ribonuclease (RNase) Dicer recognizes the long dsRNA molecules and shRNA. Subsequently, the dsRNA is cleaved, resulting in 21-nt RNA duplexes, the siRNAs. These siRNA molecules are then incorporated into the RNA-induced silencing complex (RISC) multiprotein complex, where they are unwound by an adenosine triphosphate (ATP)-dependent process, transforming the complex into an active state. Activated RISC uses one strand of the RNA as a bait to bind homologous RNA molecules. The target RNA is cleaved and degraded, resulting in gene silencing. mRNA=messenger RNA; pol III=RNA polymerase III.

miRNAs are formed in a similar manner, from longer RNA precursors, and are processed in the cytoplasm by Dicer before becoming part of RISC. However, siRNAs are the products of exogenous dsRNAs that are taken up by cells or that enter via vectors such as viruses. siRNAs bind to mRNA in the case of complete complementarity. miRNAs are products of endogenous ncRNA encoded from genes of the genome. They do not require full complementarity to bind with target mRNA (e.g., one type of miRNA may regulate many genes, and one gene may be regulated by several miRNAs) ([Carthew and Sontheimer 2009](#)).

## RNAi Knockdown of Gene Expression

Knockdown of gene expression is accomplished by designing siRNA sequences that target the coding and noncoding regions of the specified mRNAs with perfect complementarity. In mammalian cells, administration of siRNAs is effective in short-term investigations. Introduction of siRNA into cells is accomplished by transfection or electroporation of either the specific siRNA itself or small hairpin RNA (shRNA), in which the hair loop

is rapidly cleaved to produce siRNA. Most of the proposed applications of RNAi incorporate 21-nt siRNA duplexes that have 2-nt 3' overhangs, which allow large-scale and uniform production of siRNA molecules that can be chemically stabilized. In some siRNA-target combinations, the use of longer dsRNAs can increase the potency of RNAi ([Kim et al. 2005](#); [Siolas et al. 2005](#)).

For stable longer-term suppression, a gene construct coding for the shRNA with a Pol III or a Pol II promoter can be applied ([Brummelkamp et al. 2002](#); [Shi 2003](#)). RNA Pol II and III promoters are used to drive expression of shRNA constructs ([Amarzguoui et al. 2005](#)), depending on the type of expression required. Pol III promoters drive high levels of constitutive shRNA expression, and their transcription initiation points and termination signals are well defined. Pol II promoter-driven shRNAs can be expressed tissue-specifically ([Zeng et al. 2002](#)). Expressed shRNAs are incorporated into RISC, leading to a more potent inhibition of target gene expression. Generally, viral vectors such as adenovirus, lentivirus, and adeno-associated virus can carry the gene construct into cells to achieve adequate and prolonged expression for knockdown ([Kim and Rossi 2007](#)).

## RNAi Applications

RNAi is a straightforward method for inducing sequence-specific silencing of one or more genes of interest with the introduction of siRNAs. It has been a powerful tool for investigating gene function. Studies using RNAi have been performed in neuronal cells to examine the functional roles of individual genes in developing growth cones and neurite

outgrowth ([Eriksson et al. 2007](#); [Hengst et al. 2006](#); [Liu et al. 2007](#); [Schmitz et al. 2007](#); [Yanaka et al. 2007](#)), ion channels ([Geng et al. 2004](#); [Lauver et al. 2006](#); [Tahiliani et al. 2007](#)), apoptosis ([Yano et al. 2007](#); [Zhang et al. 2007](#)), and a variety of signaling pathways ([Meuer et al. 2007](#); [Sanada and Tsai 2005](#); [Shi et al. 2006](#); [Yamada et al. 2005](#)). Furthermore, RNAi is now being used for the knockdown of gene expression in animals. It appears to apply in virtually all mammalian species, as exemplified by its capability for silencing genes in mice, rats, and goats ([Peng et al. 2006](#); [Zhou et al. 2007](#)). Inducible RNAi based on the Cre-loxP system has also been developed in transgenic mice, enabling the investigator to control gene silencing both spatially and temporally ([Chang et al. 2004](#); [Coumoul et al. 2005](#); [Xia et al. 2006](#)).

The success of RNAi knockdown of specific genes suggests the possibility of using RNAi for therapeutic gene disruption. For example, RNAi-based therapies for age-related macular degeneration and respiratory syncytial virus have reached clinical trials. At this point in time, however, a number of concerns about both safety and efficacy need to be addressed.

RNAi has become a frequently used tool in a wide range of biomedical research. It provides a convenient method to study gene function via application of RNAi to cell lines, cultures, and embryonic stem cells. New uses for this tool are expected to be discovered.

## Chromatin Immunoprecipitation

The purpose of chromatin immunoprecipitation (ChIP) is to identify genomic sequence(s) associated with a protein of

interest ([Solomon et al. 1988](#)). ChIP has become the technique of choice to determine the genomic enrichment profiles of transcription factors, posttranslationally modified histones, histone variants, or chromatin-modifying enzymes. The method comprises three basic steps: 1) covalent cross-links between proteins and DNA are formed, typically by treating cells with formaldehyde or another chemical reagent; 2) an antibody specific to the protein of interest is used to coimmunoprecipitate the protein-bound DNA fragments that were covalently cross-linked; and 3) the immunoprecipitated protein-DNA links are reversed. DNA sequences associated with the precipitated protein can be identified by dot or slot blot, PCR, quantitative PCR (qPCR), labeling and hybridization to genomewide or tiling DNA microarrays (ChIP-Chip technique) ([Lee et al. 2006](#)), and sequencing technology ([Gogol-Döring and Chen 2012](#)).

---

## Genome-Editing Technologies

---

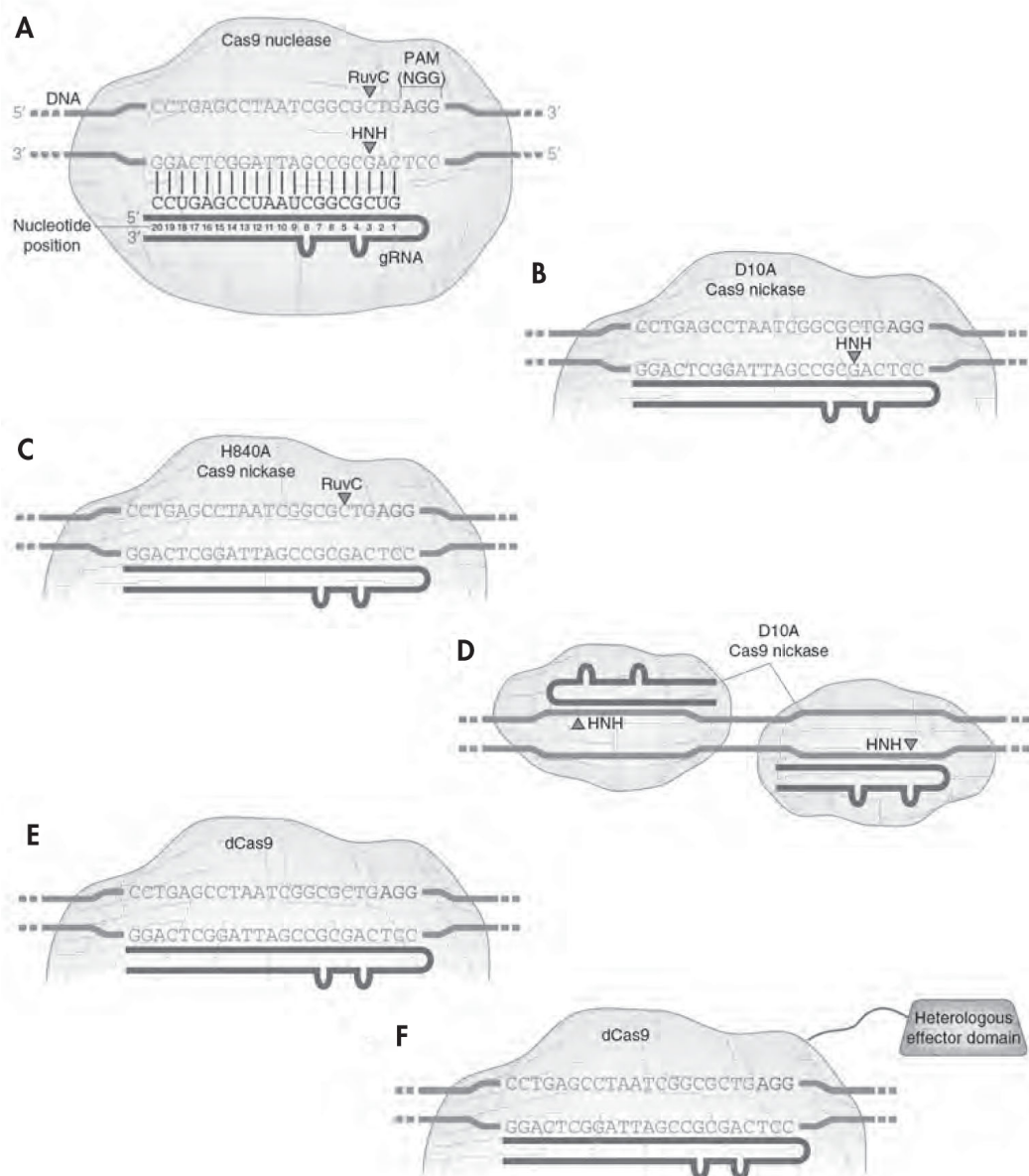
Genome-editing technologies based on site-specific DNA nucleases allow introduction of genetic modifications into almost any cell type and organism. To date, four major classes of customizable DNA binding proteins have been engineered for this purpose: meganucleases derived from microbial mobile genetic elements ([Smith et al. 2006](#)), zinc finger nucleases based on eukaryotic transcription factors ([Miller et al. 2007](#); [Urnov et al. 2005](#)), transcription activator-like effectors from *Xanthomonas* bacteria ([Christian et al. 2010](#); [Miller et al. 2011](#)), and the RNA-guided DNA endonuclease Cas9 (CRISPR-associated protein 9) from the type II bacterial adaptive immune

system CRISPR (clustered regularly interspaced short palindromic repeats) ([Cong et al. 2013](#); [Mali et al. 2013](#)). The most rapidly developing is the CRISPR/Cas9 system, which can be targeted to virtually any genomic location of choice via a short RNA guide. The CRISPR locus is typically composed of a clustered set of CRISPR-associated (Cas) genes and a series of repeat sequences interspaced by variable sequences (spacers) corresponding to sequences within foreign genetic elements (protospacers). A long pre-crRNA transcribed from the spacer-repeat CRISPR locus is processed into shorter CRISPR RNAs (crRNAs), which direct the nucleolytic activity of certain Cas enzymes to degrade target nucleic acids ([Brouns et al. 2008](#); [Hale et al. 2009](#)).

Prokaryotes have evolved diverse RNA-mediated systems that use short crRNAs and Cas proteins to detect and defend against viral DNA elements ([Bhaya et al. 2011](#); [Marraffini and Sontheimer 2008, 2010](#); [Wiedenheft et al. 2012](#)). The guide sequence within these crRNAs can be easily replaced by a sequence of interest to retarget the Cas9 nuclease. A simple two-component system—consisting of Cas9 from the bacterial species *Streptococcus pyogenes* ([Cong et al. 2013](#); [Mali et al. 2013](#)) or *Staphylococcus aureus* ([Ran et al. 2015](#)) and a fusion of the trans-activating crRNA-crRNA duplex to a single-guide RNA (sgRNA) ([Jinek et al. 2012](#))—has been engineered for expression in eukaryotic cells and can achieve DNA cleavage at any genomic locus of interest. Hence, Cas proteins can be targeted to specific DNA sequences simply by changing the short specificity-determining part of the guide RNA (gRNA), which can be easily achieved in one cloning step ([Heidenreich and Zhang 2016](#)).



Three variants of the Cas9 nuclease have been adopted to help genome editing. The first is wild-type Cas9, which can cleave double-stranded DNA at specific sites to form double-stranded breaks (DSBs). DSBs can be repaired by the cellular non-homologous end joining (NHEJ) or homology-directed recombination (HDR) pathway ([Burma et al. 2006](#); [Kass et al. 2013](#); [Maruyama et al. 2015](#)). If a donor template with homology to the targeted locus is supplied, the DSB may be repaired by HDR. If an exogenous homology repair template is absent, the DSBs can be repaired by inducing insertion or deletion mutations (indels) via the NHEJ repair pathway ([Bibikova et al. 2002](#)). The second variant of the Cas9 nuclease is a mutant form, known as Cas9D10A ([Cong et al. 2013](#)). It cleaves only one DNA strand and does not activate NHEJ. Instead, in the presence of a homologous repair template, DNA repairs are conducted via the HDR pathway only, resulting in reduced indel mutations ([Cong et al. 2013](#); [Jinek et al. 2012](#); [Qi et al. 2013](#)). The third variant is a nuclease-deficient Cas9 ([Qi et al. 2013](#)). Mutations inactivate cleavage activity but do not prevent DNA binding ([Gasiunas et al. 2012](#); [Jinek et al. 2012](#)). Therefore, this variant can be used either as a gene silencing or activation tool that “surgically” targets the desired region of the genome ([Gilbert et al. 2013](#); [Hu et al. 2014](#); [Maeder et al. 2013](#); [Perez-Pinera et al. 2013](#)). It can also be applied to visualize repetitive DNA sequences with a single sgRNA or nonrepetitive locus using multiple sgRNAs fused to enhanced green fluorescent protein ([Chen et al. 2013](#)). Alterations of gene sequence or expression induced by the CRISPR/Cas9 system are displayed in [Figure 1-7](#).



**FIGURE 1-7.** Cas9-based systems for altering gene sequence or expression.

*See Plate 1 to view this figure in color.*

**(A)** Cas9 nuclease creates double-strand breaks at DNA target sites with complementarity to the 5' end of a gRNA. **(B)** Cas9 nickase created by mutation of the RuvC nuclease domain with a D10A mutation. This nickase cleaves only the DNA strand that is complementary to and recognized by the gRNA. **(C)** Cas9 nickase

created by mutation of the HNH nuclease domain with an H840A mutation. This nickase cleaves only the DNA strand that does not interact with the small RNA. **(D)** Paired nickase strategy for improving Cas9 specificity. D10A Cas9 nickase directed by a pair of appropriately oriented gRNAs leads to induction of two nicks that, if introduced simultaneously, would be expected to generate a 5' overhang. **(E)** Catalytically inactive or "dead" Cas9 (dCas9) that can be recruited by a gRNA without cleaving the target DNA site. **(F)** Catalytically inactive dCas9-bearing dual D10A/H840A mutations fused to a heterologous effector domain. Cas9=CRISPR-associated protein 9 nuclease from *Streptococcus pyogenes*; CRISPR=clustered, regularly interspaced, short palindromic repeat; gRNA=guide RNA; PAM (NGG)=protospacer adjacent motif (sequence 5'-NGG-3', where "N" is any nucleobase followed by two guanine ("G") nucleobases).

*Source.* Reprinted from Sander JD, Joung JK: "CRISPR-Cas Systems for Editing, Regulating and Targeting Genomes." *Nature Biotechnology* 32(4):347-355, 2014. Copyright 2014, Nature Publishing Group. Used with permission.

The CRISPR/Cas9 system has achieved widespread use in targeting genes in many cell lines and organisms, including humans ([Mali et al. 2013](#)), bacteria ([Fabre et al. 2014](#)), zebrafish ([Gonzales and Yeh 2014](#)), *Caenorhabditis elegans* ([Hai et al. 2014](#)), plants ([Mali et al. 2013](#)), frogs ([Bhattacharya et al. 2015](#)), yeast ([Jacobs et al. 2014](#)), flies ([Li and Scott 2015](#)), monkeys ([Chen et al. 2015](#)), rabbits ([Yan et al. 2014](#)), pigs ([Hai et al. 2014](#)), rats ([Bao et al. 2015](#)), and mice ([Kalebic et al. 2016](#)). In neuroscience research, the benefits of using CRISPR/Cas9 systems to study the nervous system are highlighted by several successful applications studying synaptic and circuit function, neuronal development, and diseases ([Heidenreich](#)

and Zhang 2016). The delivery of Cas9 and sgRNA to target the methyl CpG binding protein 2 gene *Mecp2* in the adult mouse brain demonstrated phenotypes observed in classic *Mecp2*-mutant mouse models and patients with Rett syndrome (Swiech et al. 2015). Cas9-mediated deletion of common tumor-suppressor genes in the cerebellum and forebrain efficiently induced the formation of medulloblastoma and glioblastoma tumors, respectively (Zuckermann et al. 2015). Although NHEJ in postmitotic neurons has been demonstrated to be active, introduction of precise genetic mutations via HDR in the brain may remain challenging. It is commonly believed that HDR predominantly occurs in the S (synthesis) and G<sub>2</sub> (gap between DNA synthesis and mitosis) phases of the cell cycle, and HDR is therefore thought to be rare in nondividing cells, such as neurons (Heidenreich and Zhang 2016).

Not all manipulations of gene products are made at the gene level. It is possible to modify cell function by interfering directly with gene products. One mechanism for such manipulation involves adding peptides that correspond to the active regions of proteins. These peptides bind to the molecular targets of those proteins within the cell and block the downstream effects. Sometimes these peptides can mimic the effect of the larger peptide. For example, a peptide corresponding to the carboxyl-terminal region of a G protein (which interacts with G protein-coupled receptors) was used to block the interaction between receptors and G proteins while “mimicking” the G protein to shift the receptor into a “high-affinity” agonist-binding state (Rasenick et al. 1994). Although this strategy usually involves adding peptides to cells made permeable with a detergent or with electric current, it is also possible

to incorporate DNA plasmids encoding peptides into cells ([Gilchrist et al. 1999](#)).

Another proteomic strategy for manipulating cellular processes involves expression of “dominant-negative” proteins that are generated in a sufficient amount to block the activity of the native protein in the cell. This strategy usually involves the construction of a mutant protein that is similar to the protein of interest but deficient at some active site. This inactive mutant protein, expressed in considerable excess over the native protein, competes with the native protein for target sites and inhibits its activity ([Osawa and Johnson 1991](#)).

---

## **Transgenic and Gene-Targeting Techniques**

---

Over the past few decades, progress in the development of molecular genetic methods has enabled the manipulation of genes in intact organisms, such as mice. The technologies have provided a powerful and useful tool that allows the study of gene function and promotes understanding of the molecular mechanisms of disorders of the brain and mind. The mouse genome is by far the most accessible mammalian genome for manipulation. Many successful procedures for introducing new genes, expressing elevated levels of genes, and eliminating or altering the function of identified target genes have been reported. Many mouse models produced by manipulating genes may be used in a variety of fields relevant to neuroscience. It is noteworthy, however, that behavioral studies in mice differ from those in rats, let alone primates, and several factors induce

variability. As a result, interpretation of genetically induced behavioral alterations must be interpreted with caution ([Richter et al. 2009](#)).

Generally, transgenic mice are those expressing exogenous DNA because of the insertion of a gene into the mouse genome. Usually, that gene is randomly located within the mouse genome, often as several copies. The use of transgenic mice has represented a major strategy for the investigation of genetic questions since the feasibility and reproducibility of stably introducing DNA by microinjection into individual male mouse embryos were established ([Markert 1983](#)). In DNA constructs used for the generation of transgenic mice, the gene of interest is located 3' to promoter sequences to produce a desired distribution of gene expression. The selection of the promoter is the most important consideration in generating transgenic mice. Some promoters, such as platelet-derived growth factor (PDGF), thy1 (a cell surface glycosylphosphatidylinositol-linked glycoprotein), prin (PrP), neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP), have demonstrated the ability to direct high-level expression of exogenous genes in brain and/or in the neurons of mice ([Hsiao et al. 1996](#); [Nolte et al. 2001](#); [Sturchler-Pierrat et al. 1997](#); [Yang et al. 2004](#); [Zhu et al. 2001](#)). This level of expression can be modified by incorporation of a "tet-on" or "tet-off" vector into the desired inserted gene. Depending on the nature of the switch (on or off), the mouse will express the gene of interest when ingesting (or taken off) doxycycline.

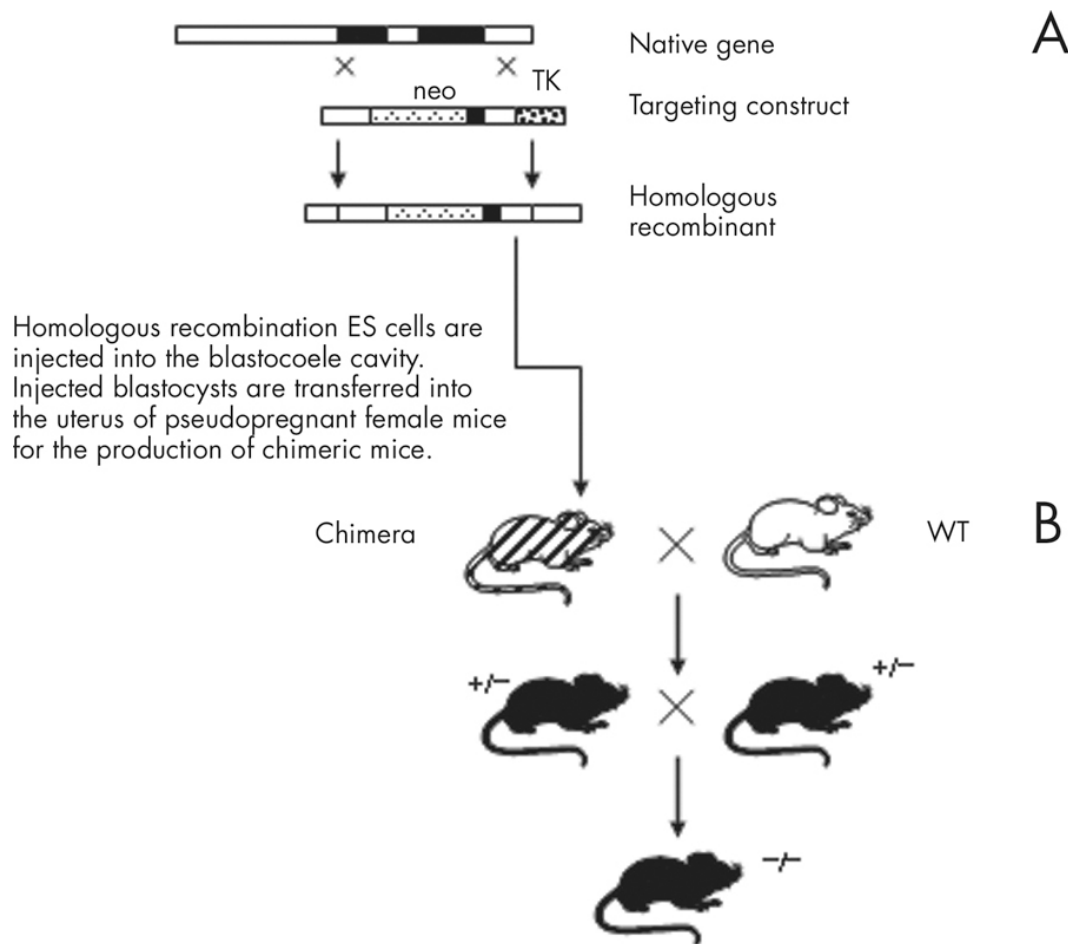
"Gene targeting" refers to the homologous recombination that occurs between a specifically designed targeting construct and the chromosomal target of interest, in which recombination at the target locus leads to replacement of

the native target sequence with a construct sequence. The method enables the precise introduction of a mutant into one of many murine genes and has proven invaluable in examining the roles of gene functions in complex biological processes. Most of the target constructs are used to disrupt a target and to eliminate gene function (conventional “knockout”). Generally, a gene-targeting construct that contains positive-negative selection markers is prepared such that the target gene is interrupted by the gene for neomycin resistance, which also serves as a positive selection marker, and a thymidine kinase (TK) gene is adjacent to either one or both ends of the homologous genomic sequence for negative selection ([Gusella et al. 1983](#)). The positive-negative deletion scheme is employed to enrich for homologous recombination.

The targeting construct is often introduced into mouse embryonic stem (ES) cells by electroporation. Cells that fail to integrate the targeting construct into the genome are killed by application of neomycin in the culture medium (positive selection). The majority of the remaining cells, in which the entire construct (including the TK gene) inserts randomly, will die as a result of the incorporation of ganciclovir or fialuridine (inactive thymidine analogs), either of which blocks DNA synthesis. Homologous recombinant clones that do not contain the TK gene are used to prepare chimeric mice. Cells from these clones are microinjected into the fluid-filled cavity of 3.5-day-old embryos at the blastocyst stage. The injected embryos are then surgically transferred into the uterus of pseudopregnant females. These animals will give birth to chimeric mice. Breeding can be used to generate mice that are heterozygous and homozygous for the mutation.



Homozygous mutants may express the gene of interest in any cell of the body (Figure 1-8).



**FIGURE 1-8.** Conventional gene disruption ("knockout").

**(A) Producing chimeric mice.** First, a mutant allele is produced by replacing the coding exons of the desired gene with a neomycin (neo) cassette and transferred into embryonic stem (ES) cells. Second, genetically altered ES cells are reintroduced into a developing blastocyst, where they contribute to the developing embryo. **(B) Breeding chimeric mice.** When the germ cells of the resulting chimeric mouse (chimera) are ES cell-derived (germ-line mutation), the heterozygotes ( $+/-$ ) can be produced by breeding. One-half of the offspring will be heterozygous. The heterozygous



animals may be bred to produce homozygous mice (-/-).  
TK=thymidine kinase; WT=wild type.

## Use of Mutant Mice in Studies of Brain Disease

Transgenic mice produced by this method are generally gain-of-function mutants, because the transgene is designed either to express a novel gene product or to disrupt a normal gene product by expressing a “dominant-negative” alternative. It is also possible to put a DNA fragment in the opposite direction and hence to produce transgenic mice expressing antisense RNA, which will reduce gene function ([Jouvenceau et al. 1999](#); [Katsuki et al. 1988](#)). Expression of mutant amyloid precursor protein (APP) or presenilin 1 (PS1) or mutant forms of tau in mice has generated many animal models that may be related to Alzheimer’s disease. These transgenic mice have facilitated studies of the pathogenesis, molecular mechanisms, and behavioral abnormalities of Alzheimer’s disease ([Bornemann and Staufenbiel 2000](#); [Janus et al. 2001](#)). Nevertheless, because the transgene integrates into the mouse genome randomly and often exists as several copies, the interpretation of studies with transgenic mice is difficult.

Experiments with knockout mice have provided novel insights into the functional roles of neuronal genes and, in some case, animal models relevant to brain disorders. The targeted mutants in a gene of interest, however, can sometimes lead to embryonic lethality in mice, thus obscuring the particular role of that gene in a target tissue or in the adult. Furthermore, in some instances, genes

related to the gene that was eliminated undergo increased expression in the knockout mice. In this case, the related gene compensates for the gene of interest and yields a phenotype that resembles the “normal” animal. This has been seen for the knockouts of the axonal microtubule-associated protein tau ([Takei et al. 2000](#)). In the remainder of this section, we use Huntington’s disease (HD) to exemplify the use of transgenic mice in the study of neurological and psychiatric disease.

HD is a genetic neurological disorder that is inherited in an autosomal dominant manner. The gradual atrophy of the striatum is its pathological hallmark. It occurs in 3–10 per 100,000 individuals in Western Europe and North America ([Gil and Rego 2008](#)). The first symptoms generally appear in middle age, and the disease is progressive and invariably fatal 15–20 years after its onset ([Ho et al. 2001](#)). HD is caused by an expansion of cytosine-adenine-guanine (CAG) repeats in exon 1 of the HD gene. The HD gene is located on the short arm of chromosome 4 (4p63) and encodes the protein huntingtin, composed of more than 3,100 amino acids with a polyglutamine tail, which is widely expressed throughout the body in both neuronal and non-neuronal cells.

The function of huntingtin has been revealed with different research approaches, especially those with transgenic mice. Engineered knockout mice that disrupt exon 4 or the promoter of mouse HD gene homology *hdh* showed embryonic lethality. A subsequent study using mutant human huntingtin to compensate for the absence of endogenous huntingtin rescued the embryonic lethality of mice homozygous for a targeted disruption of the *hdh* gene ([Zuccato et al. 2001](#)). These findings suggest that huntingtin has an essential role for normal embryonic

development. Another study indicated that huntingtin is also required throughout life, because adult knockout mice became sterile, developed a progressive motor phenotype, and had a short life span after the *hdh* gene was inactivated during adulthood ([Dragatsis et al. 2000](#)). Furthermore, in yeast artificial chromosome 18 (YAC18) transgenic mice (which express full-length human huntingtin containing a nonpathogenic number [18Q] of polyglutamine repeats), overexpression of wild-type huntingtin containing 12 glutamine residues conferred significant protection against apoptosis triggered by *N*-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity ([Leavitt et al. 2006](#)), suggesting that huntingtin may play a role in cellular apoptosis.

As mentioned, HD is a neurodegenerative disorder caused by uninterrupted CAG trinucleotide repeats located near the 5' end in exon 1. Consequently, mutant huntingtin bears a tract of consecutive glutamine residues in its NH<sub>2</sub>-terminal, 17 amino acids downstream of the initiator ([Gil and Rego 2008](#)). The length of glutamine residues in the NH<sub>2</sub>-terminal of mutant huntingtin is the primary and predominant determinant for severity of HD. To elucidate the mechanism of neurodegeneration in HD, multiple mouse models of HD have been established. These models vary in terms of the site of transgene incorporation, promoter used, gene expression levels, CAG repeat length, and background mouse strain used. These transgenic models have facilitated investigations into potential pathogenic mechanisms of HD ([Pouladi et al. 2013](#)). The following are mouse models commonly used in huntingtin research.

1. *Mice expressing exon-1 fragments of human huntingtin gene (HD) containing polyglutamine mutations (R6/1, R6/2, and R6/5).* This transgenic mouse carries exon 1 of the HD gene with 115–155 CAG repeats. The transgene protein contains the first 69 amino acids of huntingtin in addition to the number of residues encoded by the CAG repeat. Extensive neuropathological analysis has been performed on the brains in R6/2 mice. The mice display subtle motor and learning deficits at approximately 1 month and overt symptoms by 2 months, and they usually die at 3 or 4 months. The characteristic nuclear inclusions were first detected with antibodies against the *N*-terminal portion of huntingtin in R6/2 mice. R6/2 mice show measurable deficits in motor behavior that increase progressively until death. R6/2 mice are a model of HD to use for studying the severity of motor symptoms or the course of the disease. In R6/2 mice, many neurotransmitter receptors, such as NMDA, AMPA, group II metabotropic glutamate (mGluR2), dopamine D<sub>2</sub>, and  $\gamma$ -aminobutyric acid (GABA), display an abnormal response to their ligands ([Ali and Levine 2006](#); [Cepeda et al. 2004](#); [Dunah et al. 2002](#); [Starling et al. 2005](#)).
2. *Mice expressing the full-length human HD gene.* Yeast artificial chromosomes (YACs) were used to create a YAC transgenic mouse model of HD that expresses the full-length human HD gene. The transgenic mice express human transgenic huntingtin with 18, 46, 72, or 128 polyglutamine repeats. The YAC mice with 72 CAG repeats (YAC72 mice) develop a progressive motor phenotype, neuronal dysfunction, and selective striatal neurodegeneration similar to that seen in HD by 12 months of age. YAC mice with 128 CAG repeats (YAC128 mice) exhibit initial hyperactivity, followed by the onset of

a motor deficit and finally hypokinesia, which show phenotypic uniformity with low interanimal variability present. The motor deficit in the YAC128 mice is highly correlated with striatal neuronal loss, providing a structural correlate for the behavioral changes ([Hodgson et al. 1999](#); [Slow et al. 2003](#)). These lines of transgenic mice may be extremely useful for preclinical experimental therapeutics.

3. *Knock-in HD transgenic mice.* In knock-in mice, a mutated DNA sequence is exchanged for the endogenous sequence without any other disruption of the gene. To establish the line of knock-in HD mice, scientists replaced CAG repeats in the murine *hdh* gene with human mutant CAG repeats. Knock-in HD mice are characterized by a biphasic progression in behavioral anomalies, and the nuclear inclusions appear late and are preceded by nuclear staining for huntingtin, followed by the presence of microaggregates of the mutant protein in the nucleus and the neuropil ([Menalled and Chesselet 2002](#); [Menalled et al. 2003](#)). The knock-in mouse is considered to be an ideal genetic model of HD for evaluating the effectiveness of new therapies and to study the mechanisms involved in the neuropathology of HD.

These three mouse models illustrate the usefulness of manipulation of the mouse genome for the study of human neuropsychiatric disease.

## Tissue-Specific Gene Manipulation

A tissue-specific mechanism for gene targeting is the Cre-loxP system. Both the Cre (cyclization recombination) recombinase and loxP sequences are derived from the P1

bacteriophage, which uses this recombination system in its life cycle to maintain the phage genome as a unit copy plasmid in the lysogenic state. The Cre-loxP system enables the specific manipulation of DNA based on the direction and location of the two loxPs. As a member of the integrase superfamily of site-specific recombinases, the Cre recombinase does not require any host cofactors or accessory proteins to mediate loxP-specific recombination. In most cases, loxP sites are placed in the same chromosome in direct repeat positions so that the intervening DNA sequence can be deleted. The loxP sites can also be placed in different chromosomes to promote recombination between different chromosomes, or they can be placed in an inverted position in the same chromosome to create a switch to inactivate and activate genes of interest ([Bouabe and Okkenhaug 2013](#)).

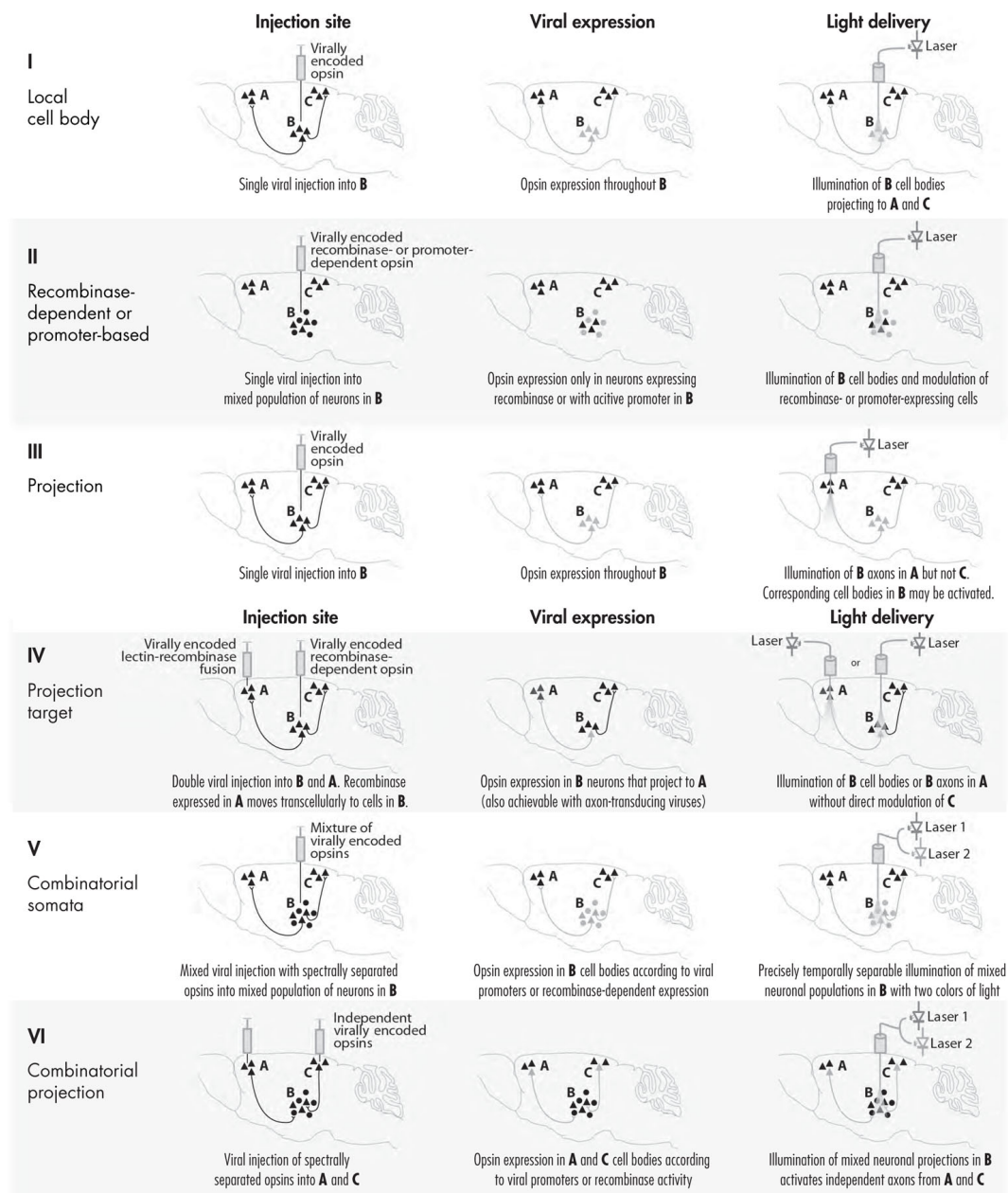
For conditional site-specific genome modification, two mouse lines are usually needed: 1) mice that have the DNA sequence of interest flanked by loxP sites (or “floxed”), which can be achieved by introducing loxP sites into the genomic locus of interest by homologous recombination as described in the previous paragraph, and 2) Cre recombinase transgenic mice, in which Cre is expressed under the control of a promoter that is active in specific cell types or tissues, or in which Cre is transiently expressed under the control of a promoter that is active at a particular developmental stage of tissues or cells. Cre expression can also be controlled temporally, by introducing an element into the promoter, which requires a ligand, such as a drug, for induction. When mice carrying such “floxed” genes are mated with transgenic mice expressing Cre recombinase, the target gene of the offspring is modified through Cre action in the cell types or tissues where Cre is expressed, or

in the cell or tissue when the mouse is treated with a drug, such as tamoxifen ([Bouabe and Okkenhaug 2013](#); [Friedel et al. 2011](#); [Liu et al. 2014](#)). Studies in which the NMDA receptor gene NR1 was deleted from specific hippocampal loci using Cre-loxP recombination technology reveal that a regional variation in NMDA receptor-dependent synaptic plasticity of postnatal excitatory neurons is required for specific aspects of hippocampal learning and memory ([McHugh et al. 2007](#); [Nakazawa et al. 2003](#)).

## Optogenetics

Optogenetics is a technique for parsing and manipulating specific neural circuits ([Figure 1-9](#)). Optogenetics was developed about 10 years ago and has been adapted both swiftly and broadly ([Deisseroth 2015](#)). Optogenetics makes use of microbial (bacterial and algal) opsins that have properties of both chromophores and ion channels. These molecules are unlike the metazoan rhodopsins, which convert light into an intracellular signal through a G protein-coupled receptor. Instead, these proteins (channelopsins and bacteriorhodopsin) form ion channels, and there are naturally occurring molecules that subserve both excitatory ( $\text{Na}^+$ ) and inhibitory ( $\text{Cl}^-$ ) functions, as activated by the channels.





**FIGURE 1-9.** Optogenetic manipulation of neural circuits.

*See **Plates 2 and 3** to view this figure in color.*

**(I)** Direct stimulation of neuronal cell bodies is achieved by injecting virus at the target region and then implanting a light-delivery device above the injected region. Even this simple experiment can provide specificity with viruses that will not



transduce afferent axons and fibers of passage. **(II)** Additional cell-type specificity is attained either by cell-type-specific promoters in the viral vector or via a recombinase-dependent virus, injected in a transgenic animal expressing a recombinase such as Cre in specific cells, leading to specific expression of the transgene only in defined cell types. **(III)** Projection (axonal) targeting is achieved by viral injection at the region harboring cell bodies, followed by implantation of a light-delivery device above the target region containing neuronal processes from the virally transduced region; in this way, cell types are targeted by virtue of their projections. **(IV)** Projection termination labeling is a more refined version of projection targeting, in which cells are targeted by virtue of synaptic connectivity to the target region, with likely exclusion of cells whose axons simply pass through the region. Transcellular labeling using a recombinase-dependent system is shown. Viruses expressing Cre fused to a transneuronal tracer (lectin) are delivered at the synaptic target site, and a Cre-dependent virus is injected into the region with cell bodies. Cells that project to the Cre-injected area express the Cre-dependent virus and become light sensitive. This can also be achieved with axon terminal-transducing viruses, although without control over the postsynaptic cell type. **(V)** Expression of two opsins with different characteristics in one brain region using a combination of promoter- or Cre-based approaches. Light delivery to the somata is performed using two different wavelengths designed to minimize cross-activation. **(VI)** Projections from two different brain regions are differentially stimulated with two wavelengths matched to the respective opsins expressed upstream.

*Source.* Reprinted from Yizhar O, Fenno LE, Davidson TJ, et al.: "Optogenetics in Neural Systems." *Neuron* 71(1):9-34, 2011. Copyright 2011, Elsevier, Inc. Used with permission.

The ingenious application that initially launched optogenetics toward worldwide adaptation was an engineered system that allowed both specificity of expression and specificity of excitation. This tool allowed an investigator to inject a virus encoding a channelrhodopsin activated by a specific wavelength of light and a targeting vector restricting expression to a certain class of cells (e.g., serotonergic) within a defined brain region. Introduction of a fiber-optic cable into the area of injection permitted the activation of the channelrhodopsin (and the subsequent activation or inhibition of the neuron containing that rhodopsin) by light. As the technique was further refined, channel opsins responsive to different wavelengths were expressed so that, depending on the wavelength used, different cells within a similar anatomic locus could be selectively activated or inhibited. The readout from such experiments could be anything from electrophysiological to behavioral. As optogenetics continues to be refined, the ability to translate from cells to circuits to behavior will increase in both complexity and resolution.

---

## **Proteomics and Beyond**

---

Shotgun proteomics takes its name from shotgun DNA sequencing, in which long DNA sequences are disassembled into shorter, easily readable components and reassembled. Shotgun proteomics works in much the same way, as the proteome of a cell is digested, subjected to analysis on mass spectrometry, and “reassembled” into proteins identified through a sophisticated bioinformatic analysis of the protein “fingerprint.” At first glance, such an approach

might seem problematic, because a tripeptide would have the same mass regardless of the order of the amino acids; however, ionization of the peptide reveals the order of the amino acids ([Filiou et al. 2011](#)).

Analysis if the proteome has the potential to yield much more information than simply the identity of the proteins being expressed in a given cell at a given time. Drugs that mimic, antagonize, or alter metabolism of neurotransmitters and neuromodulators make up the vast majority of the current psychiatric armamentarium. These drugs, often used chronically, have been shown to have long-term effects, altering second messenger systems. These second messengers (e.g., cAMP, inositol-1,4,5-triphosphate [IP<sub>3</sub>], cyclic guanosine monophosphate [cGMP]) activate or inhibit enzymes that modify proteins covalently. Phosphorylation, prenylation, and glycosylation are examples of these modifications, all of which can be determined in mass spectroscopic proteomic analysis.

In addition to—and in part due to—these modifications, molecules involved in neurotransmitter response and responsiveness move among cellular compartments in response to neurotransmitters, neuromodulators, and drugs that affect these. A simple example might be the agonist-induced depalmitoylation of the stimulatory G protein G<sub>s</sub>α that results in its translocation from the plasma membrane ([Wedegaertner and Bourne 1994](#)). This translocation, which can be either into the cytosol or into different membrane domains, can either amplify or attenuate signaling ([Allen et al. 2007](#)). A catalog of these protein shifts during disease or response to drug can thus be assembled.

G protein-coupled receptors comprise targets for the majority of drugs used in psychiatry. Curiously, many of

these drugs were thought to have a single site of action until a screening/informatics approach was applied. *Receptoromics* allows screening of compounds for their agonist or antagonist effects on receptors, measured through batteries of cells selectively expressing a single species of G protein-coupled receptor (or other receptor or transporter). Results from these studies have been both informative and surprising ([Strachan et al. 2006](#)). For example, atypical antipsychotics have been selected for their antagonist properties at the 5-HT<sub>2A</sub> receptor. Some of these drugs, such as olanzapine, have been associated with excessive weight gain, and this appears to be due to interaction with histamine H<sub>1</sub> receptors rather than being related to the therapeutic profile of the drug. Other effective antipsychotic drugs may owe their efficacy to actions at a panel of receptors that, when combined, contribute to a therapeutic whole ([Roth and Kroeze 2015](#)). The ability to screen libraries of compounds against a large number of receptor targets makes design and identification of new drugs an exciting possibility.

---

## Conclusion

---

Rapid advances in the identification of the human genome and in the methodology for genetic manipulation have combined to open a window into the brain. We are accumulating knowledge of human gene mutations and their connection to neurological and psychiatric diseases at a rapid pace. As genes are being identified, the proteins for which they code are also becoming known. This knowledge enables the pathogenic mechanism for some of these

diseases to become apparent. Understanding these maladies on the molecular level is likely to lead to new methods of diagnosis and novel approaches to therapy.

---

## References

---

- Abe K, Sato S, Kawagoe J, et al: Isolation and expression of an ischaemia-induced gene from gerbil cerebral cortex by subtractive hybridization. *Neurol Res* 15(1):23-28, 1993 8098848
- Ali NJ, Levine MS: Changes in expression of N-methyl-D-aspartate receptor subunits occur early in the R6/2 mouse model of Huntington's disease. *Dev Neurosci* 28(3):230-238, 2006 16679770
- Allen JA, Halverson-Tamboli RA, Rasenick MM: Lipid raft microdomains and neurotransmitter signalling. *Nat Rev Neurosci* 8(2):128-140, 2007 17195035
- Amarzguioui M, Rossi JJ, Kim D: Approaches for chemically synthesized siRNA and vector-mediated RNAi. *FEBS Lett* 579(26):5974-5981, 2005 16199038
- Ballestar E, Esteller M: The impact of chromatin in human cancer: linking DNA methylation to gene silencing. *Carcinogenesis* 23(7):1103-1109, 2002 12117766
- Bao D, Ma Y, Zhang X, et al: Preliminary characterization of a leptin receptor knockout rat created by CRISPR/Cas9 system. *Sci Rep* 5:15942, 2015 26537785
- Barkats M, Bemelmans AP, Geoffroy MC, et al: An adenovirus encoding CuZnSOD protects cultured striatal neurones against glutamate toxicity. *Neuroreport* 7(2):497-501, 1996 8730814
- Barski A, Cuddapah S, Cui K, et al: High-resolution profiling of histone methylations in the human genome. *Cell* 129(4):823-837, 2007 17512414

- Bass BL: RNA editing and hypermutation by adenosine deamination. *Trends Biochem Sci* 22(5):157-162, 1997 9175473
- Bass BL: RNA editing by adenosine deaminases that act on RNA. *Annu Rev Biochem* 71:817-846, 2002 12045112
- Bemelmans AP, Horellou P, Pradier L, et al: Brain-derived neurotrophic factor-mediated protection of striatal neurons in an excitotoxic rat model of Huntington's disease, as demonstrated by adenoviral gene transfer. *Hum Gene Ther* 10(18):2987-2997, 1999 10609659
- Benraiss A, Chmielnicki E, Lerner K, et al: Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *J Neurosci* 21(17):6718-6731, 2001 11517261
- Berg KA, Cropper JD, Niswender CM, et al: RNA-editing of the 5-HT(2C) receptor alters agonist-receptor-effector coupling specificity. *Br J Pharmacol* 134(2):386-392, 2001 11564657
- Berry M, Barrett L, Seymour L, et al: Gene therapy for central nervous system repair. *Curr Opin Mol Ther* 3(4):338-349, 2001 11525557
- Bhattacharya D, Marfo CA, Li D, et al: CRISPR/Cas9: an inexpensive, efficient loss of function tool to screen human disease genes in *Xenopus*. *Dev Biol* 408(2):196-204, 2015 26546975
- Bhaya D, Davison M, Barrangou R: CRISPR-Cas systems in bacteria and archaea: versatile small RNAs for adaptive defense and regulation. *Annu Rev Genet* 45:273-297, 2011 22060043
- Bibikova M, Golic M, Golic KG, et al: Targeted chromosomal cleavage and mutagenesis in *Drosophila* using zinc-finger nucleases. *Genetics* 161(3):1169-1175, 2002 12136019
- Bornemann KD, Staufenbiel M: Transgenic mouse models of Alzheimer's disease. *Ann N Y Acad Sci* 908:260-266,

2000 10911965

- Bouabe H, Okkenhaug K: Gene targeting in mice: a review. *Methods Mol Biol* 1064:315–336, 2013 23996268
- Brouns SJ, Jore MM, Lundgren M, et al: Small CRISPR RNAs guide antiviral defense in prokaryotes. *Science* 321(5891):960–964, 2008 18703739
- Brummelkamp TR, Bernards R, Agami R: A system for stable expression of short interfering RNAs in mammalian cells. *Science* 296(5567):550–553, 2002 11910072
- Burma S, Chen BP, Chen DJ: Role of non-homologous end joining (NHEJ) in maintaining genomic integrity. *DNA Repair (Amst)* 5(9–10):1042–1048, 2006 16822724
- Burns CM, Chu H, Rueter SM, et al: Regulation of serotonin-2C receptor G-protein coupling by RNA editing. *Nature* 387(6630): 303–308, 1997 9153397
- Carthew RW, Sontheimer EJ: Origins and mechanisms of miRNAs and siRNAs. *Cell* 136(4):642–655, 2009 19239886
- Cedar H, Bergman Y: Linking DNA methylation and histone modification: patterns and paradigms. *Nat Rev Genet* 10(5):295–304, 2009 19308066
- Cepeda C, Starling AJ, Wu N, et al: Increased GABAergic function in mouse models of Huntington's disease: reversal by BDNF. *J Neurosci Res* 78(6):855–867, 2004 15505789
- Chalfie M, Tu Y, Euskirchen G, et al: Green fluorescent protein as a marker for gene expression. *Science* 263(5148):802–805, 1994 8303295
- Chang HS, Lin CH, Chen YC, et al: Using siRNA technique to generate transgenic animals with spatiotemporal and conditional gene knockdown. *Am J Pathol* 165(5):1535–1541, 2004 15509524
- Chen B, Gilbert LA, Cimini BA, et al: Dynamic imaging of genomic loci in living human cells by an optimized

- CRISPR/Cas system. *Cell* 155(7):1479–1491, 2013 24360272
- Chen H, Lambert NA: Endogenous regulators of G protein signaling proteins regulate presynaptic inhibition at rat hippocampal synapses. *Proc Natl Acad Sci U S A* 97(23):12810–12815, 2000 11050179
- Chen Y, Zheng Y, Kang Y, et al: Functional disruption of the dystrophin gene in rhesus monkey using CRISPR/Cas9. *Hum Mol Genet* 24(13):3764–3774, 2015 25859012
- Christian M, Cermak T, Doyle EL, et al: Targeting DNA double-strand breaks with TAL effector nucleases. *Genetics* 186(2):757–761, 2010 20660643
- Collins FS: Positional cloning moves from perdditional to traditional. *Nat Genet* 9(4):347–350, 1995 7795639
- Cong L, Ran FA, Cox D, et al: Multiplex genome engineering using CRISPR/Cas systems. *Science* 339(6121):819–823, 2013 23287718
- Coumoul X, Shukla V, Li C, et al: Conditional knockdown of Fgfr2 in mice using Cre-LoxP induced RNA interference. *Nucleic Acids Res* 33(11):e102, 2005 15987787
- Czysz AH, Schappi JM, Rasenick MM: Lateral diffusion of Gas in the plasma membrane is decreased after chronic but not acute antidepressant treatment: role of lipid raft and non-raft membrane microdomains. *Neuropsychopharmacology* 40(3):766–773, 2015 25249058
- DeCerbo J, Carmichael GG: SINEs point to abundant editing in the human genome. *Genome Biol* 6(4):216, 2005 15833131
- Deisseroth K: Optogenetics: 10 years of microbial opsins in neuroscience. *Nat Neurosci* 18(9):1213–1225, 2015 26308982
- Dindot SV, Person R, Strivens M, et al: Epigenetic profiling at mouse imprinted gene clusters reveals novel epigenetic and genetic features at differentially



- methyated regions. *Genome Res* 19(8):1374-1383, 2009 19542493
- Doyu M, Sawada K, Mitsuma N, et al: Gene expression profile in Alzheimer's brain screened by molecular indexing. *Brain Res Mol Brain Res* 87(1):1-11, 2001 11223154
- Dragatsis I, Dietrich P, Zeitlin S: Expression of the Huntingtin-associated protein 1 gene in the developing and adult mouse. *Neurosci Lett* 282(1-2):37-40, 2000 10713390
- Dunah AW, Jeong H, Griffin A, et al: Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. *Science* 296(5576):2238-2243, 2002 11988536
- Eberwine J, Yeh H, Miyashiro K, et al: Analysis of gene expression in single live neurons. *Proc Natl Acad Sci U S A* 89(7):3010-3014, 1992 1557406
- Eriksson M, Taskinen M, Leppä S: Mitogen activated protein kinase-dependent activation of c-Jun and c-Fos is required for neuronal differentiation but not for growth and stress response in PC12 cells. *J Cell Physiol* 210(2):538-548, 2007 17111371
- Fabre L, Le Hello S, Roux C, et al: CRISPR is an optimal target for the design of specific PCR assays for salmonella enterica serotypes Typhi and Paratyphi A. *PLoS Negl Trop Dis* 8(1):e2671, 2014 24498453
- Filiou MD, Turck CW, Martins-de-Souza D: Quantitative proteomics for investigating psychiatric disorders. *Proteomics Clin Appl* 5(1-2):38-49, 2011 21280236
- Fire A, Xu S, Montgomery MK, et al: Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* 391(6669):806-811, 1998 9486653
- Friedel RH, Wurst W, Wefers B, et al: Generating conditional knockout mice. *Methods Mol Biol* 693:205-231, 2011 21080282

- Gasiunas G, Barrangou R, Horvath P, et al: Cas9-crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria. *Proc Natl Acad Sci U S A* 109(39):E2579–E2586, 2012 22949671
- Geng C, Pellegrino A, Bowman J, et al: Complete RNAi rescue of neuronal degeneration in a constitutively active *Drosophila* TRP channel mutant. *Biochim Biophys Acta* 1674(1):91–97, 2004 15342118
- Gil JM, Rego AC: Mechanisms of neurodegeneration in Huntington's disease. *Eur J Neurosci* 27(11):2803–2820, 2008 18588526
- Gilbert LA, Larson MH, Morsut L, et al: CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes. *Cell* 154(2):442–451, 2013 23849981
- Gilchrist A, Bünemann M, Li A, et al: A dominant-negative strategy for studying roles of G proteins in vivo. *J Biol Chem* 274(10):6610–6616, 1999 10037756
- Gogol-Döring A, Chen W: An overview of the analysis of next generation sequencing data. *Methods Mol Biol* 802:249–257, 2012 22130885
- Gonzales AP, Yeh JR: Cas9-based genome editing in zebrafish. *Methods Enzymol* 546:377–413, 2014 25398350
- Graves L, Dalvi A, Lucki I, et al: Behavioral analysis of CREB alphas delta mutation on a B6/129 F1 hybrid background. *Hippocampus* 12(1):18–26, 2002 11918283
- Grosjean H, Auxilien S, Constantinesco F, et al: Enzymatic conversion of adenosine to inosine and to N1-methylinosine in transfer RNAs: a review. *Biochimie* 78(6):488–501, 1996 8915538
- Guenther MG, Levine SS, Boyer LA, et al: A chromatin landmark and transcription initiation at most promoters in human cells. *Cell* 130(1):77–88, 2007 17632057
- Gusella JF, Wexler NS, Conneally PM, et al: A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 306(5940):234–238, 1983 6316146

- Hai T, Teng F, Guo R, et al: One-step generation of knockout pigs by zygote injection of CRISPR/Cas system. *Cell Res* 24(3):372-375, 2014 24481528
- Hale CR, Zhao P, Olson S, et al: RNA-guided RNA cleavage by a CRISPR RNA-Cas protein complex. *Cell* 139(5):945-956, 2009 19945378
- Halliday KR, Stein PJ, Chernoff N, et al: Limited trypsin proteolysis of photoreceptor GTP-binding protein: light- and GTP-induced conformational changes. *J Biol Chem* 259(1):516-525, 1984 6323413
- Harding TC, Geddes BJ, Noel JD, et al: Tetracycline-regulated transgene expression in hippocampal neurones following transfection with adenoviral vectors. *J Neurochem* 69(6):2620-2623, 1997 9375698
- He TC, Zhou S, da Costa LT, et al: A simplified system for generating recombinant adenoviruses. *Proc Natl Acad Sci U S A* 95(5):2509-2514, 1998 9482916
- Heidenreich M, Zhang F: Applications of CRISPR-Cas systems in neuroscience. *Nat Rev Neurosci* 17(1):36-44, 2016 26656253
- Heintzman ND, Stuart RK, Hon G, et al: Distinct and predictive chromatin signatures of transcriptional promoters and enhancers in the human genome. *Nat Genet* 39(3):311-318, 2007 17277777
- Hengst U, Cox LJ, Macosko EZ, et al: Functional and selective RNA interference in developing axons and growth cones. *J Neurosci* 26(21):5727-5732, 2006 16723529
- Ho LW, Carmichael J, Swartz J, et al: The molecular biology of Huntington's disease. *Psychol Med* 31(1):3-14, 2001 11200958
- Hodgson JG, Agopyan N, Gutekunst CA, et al: A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. *Neuron* 23(1):181-192, 1999 10402204

- Hong J, Yoshida K, Rosner MR: Characterization of a cysteine proteinase inhibitor induced during neuronal cell differentiation. *J Neurochem* 81(5):922-934, 2002 12065604
- Hsiao K, Chapman P, Nilsen S, et al: Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science* 274(5284):99-102, 1996 8810256
- Hu J, Lei Y, Wong WK, et al: Direct activation of human and mouse Oct4 genes using engineered TALE and Cas9 transcription factors. *Nucleic Acids Res* 42(7):4375-4390, 2014 24500196
- Hughes SM, Moussavi-Harami F, Sauter SL, et al: Viral-mediated gene transfer to mouse primary neural progenitor cells. *Mol Ther* 5(1):16-24, 2002 11786041
- Imaizumi K, Tsuda M, Imai Y, et al: Molecular cloning of a novel polypeptide, DP5, induced during programmed neuronal death. *J Biol Chem* 272(30):18842-18848, 1997 9228060
- Jacobs JZ, Ciccaglione KM, Tournier V, et al: Implementation of the CRISPR-Cas9 system in fission yeast. *Nat Commun* 5:5344, 2014 25352017
- Janus C, Phinney AL, Chishti MA, et al: New developments in animal models of Alzheimer's disease. *Curr Neurol Neurosci Rep* 1(5):451-457, 2001 11898556
- Jenuwein T, Allis CD: Translating the histone code. *Science* 293(5532):1074-1080, 2001 11498575
- Jinek M, Chylinski K, Fonfara I, et al: A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 337(6096):816-821, 2012 22745249
- Jones PA: Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat Rev Genet* 13(7):484-492, 2012 22641018
- Jouvenneau A, Potier B, Battini R, et al: Glutamatergic synaptic responses and long-term potentiation are impaired in the CA1 hippocampal area of calbindin

- D(28k)-deficient mice. *Synapse* 33(3):172–180, 1999 10420165
- Kable ML, Heidmann S, Stuart KD: RNA editing: getting U into RNA. *Trends Biochem Sci* 22(5):162–166, 1997 9175474
- Kaikkonen MU, Lam MT, Glass CK: Non-coding RNAs as regulators of gene expression and epigenetics. *Cardiovasc Res* 90(3):430–440, 2011 21558279
- Kalebic N, Taverna E, Tavano S, et al: CRISPR/Cas9-induced disruption of gene expression in mouse embryonic brain and single neural stem cells in vivo. *EMBO Rep* 17(3):338–348, 2016 26758805
- Kandel ER: The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. *Mol Brain* 5:14, 2012 22583753
- Kass EM, Helgadottir HR, Chen CC, et al: Double-strand break repair by homologous recombination in primary mouse somatic cells requires BRCA1 but not the ATM kinase. *Proc Natl Acad Sci U S A* 110(14):5564–5569, 2013 23509290
- Katsuki M, Sato M, Kimura M, et al: Conversion of normal behavior to shiverer by myelin basic protein antisense cDNA in transgenic mice. *Science* 241(4865):593–595, 1988 2456614
- Kaziro Y, Itoh H, Kozasa T, et al: Structure and function of signal-transducing GTP-binding proteins. *Annu Rev Biochem* 60:349–400, 1991 1909108
- Keshet I, Lieman-Hurwitz J, Cedar H: DNA methylation affects the formation of active chromatin. *Cell* 44(4):535–543, 1986 3456276
- Kim DH, Rossi JJ: Strategies for silencing human disease using RNA interference. *Nat Rev Genet* 8(3):173–184, 2007 17304245
- Kim DH, Behlke MA, Rose SD, et al: Synthetic dsRNA Dicer substrates enhance RNAi potency and efficacy. *Nat Biotechnol* 23(2):222–226, 2005 15619617

- Klengel T, Binder EB: Epigenetics of stress-related psychiatric disorders and gene  $\times$  environment interactions. *Neuron* 86(6): 1343–1357, 2015 26087162
- Kohara K, Kitamura A, Morishima M, et al: Activity-dependent transfer of brain-derived neurotrophic factor to postsynaptic neurons. *Science* 291(5512):2419–2423, 2001 11264540
- Kornberg RD, Lorch Y: Twenty-five years of the nucleosome, fundamental particle of the eukaryote chromosome. *Cell* 98(3): 285–294, 1999 10458604
- Koshimizu H, Araki T, Takai S, et al: Expression of CD47/integrin-associated protein induces death of cultured cerebral cortical neurons. *J Neurochem* 82(2):249–257, 2002 12124426
- Kouzarides T: Histone acetylases and deacetylases in cell proliferation. *Curr Opin Genet Dev* 9(1):40–48, 1999 10072350
- Kubista M, Andrade JM, Bengtsson M, et al: The real-time polymerase chain reaction. *Mol Aspects Med* 27(2–3):95–125, 2006 16460794
- Lander ES, Linton LM, Birren B, et al; International Human Genome Sequencing Consortium: Initial sequencing and analysis of the human genome. *Nature* 409(6822):860–921, 2001 11237011
- Lauver A, Yuan LL, Jeromin A, et al: Manipulating Kv4.2 identifies a specific component of hippocampal pyramidal neuron A-current that depends upon Kv4.2 expression. *J Neurochem* 99(4):1207–1223, 2006 17026528
- Leavitt BR, van Raamsdonk JM, Shehadeh J, et al: Wild-type huntingtin protects neurons from excitotoxicity *J Neurochem* 96(4):1121–1129, 2006 16417581
- Lee TI, Johnstone SE, Young RA: Chromatin immunoprecipitation and microarray-based analysis of protein location. *Nat Protoc* 1(2):729–748, 2006 17406303

- Li F, Scott MJ: CRISPR/Cas9-mediated mutagenesis of the white and Sex lethal loci in the invasive pest, *Drosophila suzukii*. *Biochem Biophys Res Commun* 469(4):911–916, 2015 26721433
- Liang P, Averboukh L, Keyomarsi K, et al: Differential display and cloning of messenger RNAs from human breast cancer versus mammary epithelial cells. *Cancer Res* 52(24):6966–6968, 1992 1458489
- Liu J, Lamb D, Chou MM, et al: Nerve growth factor-mediated neurite outgrowth via regulation of Rab5. *Mol Biol Cell* 18(4):1375–1384, 2007 17267689
- Liu J, Deutsch U, Fung I, Lobe CG: Conditional and inducible transgene expression in endothelial and hematopoietic cells using Cre/loxP and tetracycline-off systems. *Exp Ther Med* 8(5):1351–1356, 2014 25289022
- Liu QR, Zhang PW, Zhen Q, et al: KEPI, a PKC-dependent protein phosphatase 1 inhibitor regulated by morphine. *J Biol Chem* 277(15):13312–13320, 2002 11812771
- Maeder ML, Linder SJ, Cascio VM, et al: CRISPR RNA-guided activation of endogenous human genes. *Nat Methods* 10(10):977–979, 2013 23892898
- Mali P, Esvelt KM, Church GM: Cas9 as a versatile tool for engineering biology. *Nat Methods* 10(10):957–963, 2013 24076990
- Markert CL: Fertilization of mammalian eggs by sperm injection. *J Exp Zool* 228(2):195–201, 1983 6663257
- Marraffini LA, Sontheimer EJ: CRISPR interference limits horizontal gene transfer in staphylococci by targeting DNA. *Science* 322(5909):1843–1845, 2008 19095942
- Marraffini LA, Sontheimer EJ: Self versus non-self discrimination during CRISPR RNA-directed immunity. *Nature* 463(7280):568–571, 2010 20072129
- Maruyama T, Dougan SK, Truttmann MC, et al: Increasing the efficiency of precise genome editing with CRISPR-Cas9 by inhibition of nonhomologous end joining. *Nat Biotechnol* 33(5):538–542, 2015 25798939

- McHugh TJ, Jones MW, Quinn JJ, et al: Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. *Science* 317(5834):94-99, 2007 17556551
- Mello CV, Jarvis ED, Denisenko N, et al: Isolation of song-regulated genes in the brain of songbirds. *Methods Mol Biol* 85:205-217, 1997 9276326
- Menalled LB, Chesselet MF: Mouse models of Huntington's disease. *Trends Pharmacol Sci* 23(1):32-39, 2002 11804649
- Menalled LB, Sison JD, Dragatsis I, et al: Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. *J Comp Neurol* 465(1):11-26, 2003 12926013
- Meuer K, Suppanz IE, Lingor P, et al: Cyclin-dependent kinase 5 is an upstream regulator of mitochondrial fission during neuronal apoptosis. *Cell Death Differ* 14(4):651-661, 2007 17218957
- Mikkelsen TS, Ku M, Jaffe DB, et al: Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. *Nature* 448(7153):553-560, 2007 17603471
- Miller JC, Holmes MC, Wang J, et al: An improved zinc-finger nuclease architecture for highly specific genome editing. *Nat Biotechnol* 25(7):778-785, 2007 17603475
- Miller JC, Tan S, Qiao G, et al: A TALE nuclease architecture for efficient genome editing. *Nat Biotechnol* 29(2):143-148, 2011 21179091
- Mizushima K, Miyamoto Y, Tsukahara F, et al: A novel G-protein-coupled receptor gene expressed in striatum. *Genomics* 69(3):314-321, 2000 11056049
- Murata T, Kurokawa R, Krones A, et al: Defect of histone acetyltransferase activity of the nuclear transcriptional coactivator CBP in Rubinstein-Taybi syndrome. *Hum Mol Genet* 10(10):1071-1076, 2001 11331617
- Nakazawa K, Sun LD, Quirk MC, et al: Hippocampal CA3 NMDA receptors are crucial for memory acquisition of



- one-time experience. *Neuron* 38(2):305–315, 2003 12718863
- Neve RL: Adenovirus vectors enter the brain. *Trends Neurosci* 16(7):251–253, 1993 7689766
- Nolte C, Matyash M, Pivneva T, et al: GFAP promoter-controlled EGFP-expressing transgenic mice: a tool to visualize astrocytes and astrogliosis in living brain tissue. *Glia* 33(1):72–86, 2001 11169793
- Oike Y, Hata A, Mamiya T, et al: Truncated CBP protein leads to classical Rubinstein-Taybi syndrome phenotypes in mice: implications for a dominant-negative mechanism. *Hum Mol Genet* 8(3):387–396, 1999 9949198
- Osawa S, Johnson GL: A dominant negative G alpha s mutant is rescued by secondary mutation of the alpha chain amino terminus. *J Biol Chem* 266(8):4673–4676, 1991 1848223
- Peng S, York JP, Zhang P: A transgenic approach for RNA interference-based genetic screening in mice. *Proc Natl Acad Sci U S A* 103(7):2252–2256, 2006 16461920
- Perez-Pinera P, Kocak DD, Vockley CM, et al: RNA-guided gene activation by CRISPR-Cas9-based transcription factors. *Nat Methods* 10(10):973–976, 2013 23892895
- Petrij F, Giles RH, Dauwerse HG, et al: Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. *Nature* 376(6538):348–351, 1995 7630403
- Ponting CP, Oliver PL, Reik W: Evolution and functions of long noncoding RNAs. *Cell* 136(4):629–641, 2009 19239885
- Pouladi MA, Morton AJ, Hayden MR: Choosing an animal model for the study of Huntington's disease. *Nat Rev Neurosci* 14(10):708–721, 2013 24052178
- Provost P, Silverstein RA, Dishart D, et al: Dicer is required for chromosome segregation and gene silencing in

- fission yeast cells. *Proc Natl Acad Sci U S A* 99(26):16648–16653, 2002 12482946
- Qi LS, Larson MH, Gilbert LA, et al: Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. *Cell* 152(5):1173–1183, 2013 23452860
- Ran FA, Cong L, Yan WX, et al: In vivo genome editing using *Staphylococcus aureus* Cas9. *Nature* 520(7546):186–191, 2015 25830891
- Rasenick MM, Watanabe M, Lazarevic MB, et al: Synthetic peptides as probes for G protein function: carboxyl-terminal G alpha s peptides mimic Gs and evoke high affinity agonist binding to beta-adrenergic receptors. *J Biol Chem* 269(34):21519–21525, 1994 8063788
- Richter FM, Hsiao HH, Plessmann U, et al: Enrichment of protein-RNA crosslinks from crude UV-irradiated mixtures for MS analysis by on-line chromatography using titanium dioxide columns. *Biopolymers* 91(4):297–309, 2009 19140157
- Roll-Mecak A, Cao C, Dever TE, et al: X-ray structures of the universal translation initiation factor IF2/eIF5B: conformational changes on GDP and GTP binding. *Cell* 103(5):781–792, 2000 11114334
- Roth BL, Kroeze WK: Integrated approaches for genome-wide interrogation of the druggable non-olfactory G protein-coupled receptor superfamily. *J Biol Chem* 290(32):19471–19477, 2015 26100629
- Ruthenburg AJ, Li H, Patel DJ, et al: Multivalent engagement of chromatin modifications by linked binding modules. *Nat Rev Mol Cell Biol* 8(12):983–994, 2007 18037899
- Sanada K, Tsai LH: G protein betagamma subunits and AGS3 control spindle orientation and asymmetric cell fate of cerebral cortical progenitors. *Cell* 122(1):119–131, 2005 16009138

- Sander JD, Joung JK: CRISPR-Cas systems for editing, regulating and targeting genomes. *Nat Biotechnol* 32(4):347-355, 2014 24584096
- Scadden AD, Smith CW: Specific cleavage of hyper-edited dsRNAs. *EMBO J* 20(15): 4243-4252, 2001 11483527
- Schmitz C, Kinge P, Hutter H: Axon guidance genes identified in a large-scale RNAi screen using the RNAi-hypersensitive *Caenorhabditis elegans* strain nre-1(hd20) lin-15b(hd126). *Proc Natl Acad Sci U S A* 104(3):834-839, 2007 17213328
- Seeburg PH, Hartner J: Regulation of ion channel/neurotransmitter receptor function by RNA editing. *Curr Opin Neurobiol* 13(3):279-283, 2003 12850211
- Setou M, Nakagawa T, Seog DH, et al: Kinesin superfamily motor protein KIF17 and mLin-10 in NMDA receptor-containing vesicle transport. *Science* 288(5472):1796-1802, 2000 10846156
- Shi GX, Rehmann H, Andres DA: A novel cyclic AMP-dependent Epac-Rit signaling pathway contributes to PACAP38-mediated neuronal differentiation. *Mol Cell Biol* 26(23):9136-9147, 2006 17000774
- Shi Y: Mammalian RNAi for the masses. *Trends Genet* 19(1):9-12, 2003 12493242
- Sijen T, Fleenor J, Simmer F, et al: On the role of RNA amplification in dsRNA-triggered gene silencing. *Cell* 107(4):465-476, 2001 11719187
- Simpson L, Emeson RB: RNA editing. *Annu Rev Neurosci* 19:27-52, 1996 8833435
- Siolas D, Lerner C, Burchard J, et al: Synthetic shRNAs as potent RNAi triggers. *Nat Biotechnol* 23(2):227-231, 2005 15619616
- Slack RS, Belliveau DJ, Rosenberg M, et al: Adenovirus-mediated gene transfer of the tumor suppressor, p53, induces apoptosis in postmitotic neurons. *J Cell Biol* 135(4):1085-1096, 1996 8922388

- Slow EJ, van Raamsdonk J, Rogers D, et al: Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. *Hum Mol Genet* 12(13):1555-1567, 2003 12812983
- Smith J, Grizot S, Arnould S, et al: A combinatorial approach to create artificial homing endonucleases cleaving chosen sequences. *Nucleic Acids Res* 34(22):e149, 2006 17130168
- Solomon MJ, Larsen PL, Varshavsky A: Mapping protein-DNA interactions in vivo with formaldehyde: evidence that histone H4 is retained on a highly transcribed gene. *Cell* 53(6):937-947, 1988 2454748
- Starling AJ, André VM, Cepeda C, et al: Alterations in N-methyl-D-aspartate receptor sensitivity and magnesium blockade occur early in development in the R6/2 mouse model of Huntington's disease. *J Neurosci Res* 82(3):377-386, 2005 16211559
- Steger DJ, Lefterova MI, Ying L, et al: DOT1L/KMT4 recruitment and H3K79 methylation are ubiquitously coupled with gene transcription in mammalian cells. *Mol Cell Biol* 28(8):2825-2839, 2008 18285465
- Steward O, Wallace CS: mRNA distribution within dendrites: relationship to afferent innervation. *J Neurobiol* 26(3):447-449, 1995 7775977
- Strachan RT, Ferrara G, Roth BL: Screening the receptorome: an efficient approach for drug discovery and target validation. *Drug Discov Today* 11(15-16):708-716, 2006 16846798
- Strahl BD, Allis CD: The language of covalent histone modifications. *Nature* 403(6765): 41-45, 2000 10638745
- Stuart K, Panigrahi AK: RNA editing: complexity and complications. *Mol Microbiol* 45(3):591-596, 2002 12139607
- Sturchler-Pierrat C, Abramowski D, Duke M, et al: Two amyloid precursor protein transgenic mouse models with

- Alzheimer disease-like pathology. *Proc Natl Acad Sci U S A* 94(24):13287-13292, 1997 9371838
- Swiech L, Heidenreich M, Banerjee A, et al: In vivo interrogation of gene function in the mammalian brain using CRISPR-Cas9. *Nat Biotechnol* 33(1):102-106, 2015 25326897
- Tahiliani M, Mei P, Fang R, et al: The histone H3K4 demethylase SMCX links REST target genes to X-linked mental retardation. *Nature* 447(7144):601-605, 2007 17468742
- Takei Y, Teng J, Harada A, et al: Defects in axonal elongation and neuronal migration in mice with disrupted tau and map1b genes. *J Cell Biol* 150(5):989-1000, 2000 10973990
- Tanaka S, Kitagawa K, Ohtsuki T, et al: Synergistic induction of HSP40 and HSC70 in the mouse hippocampal neurons after cerebral ischemia and ischemic tolerance in gerbil hippocampus. *J Neurosci Res* 67(1):37-47, 2002 11754079
- Tochitani S, Liang F, Watakabe A, et al: The occ1 gene is preferentially expressed in the primary visual cortex in an activity-dependent manner: a pattern of gene expression related to the cytoarchitectonic area in adult macaque neocortex. *Eur J Neurosci* 13(2):297-307, 2001 11168534
- Tomari Y, Zamore PD: Perspective: machines for RNAi. *Genes Dev* 19(5):517-529, 2005 15741316
- Tsai KJ, Chen SK, Ma YL, et al: sgk, a primary glucocorticoid-induced gene, facilitates memory consolidation of spatial learning in rats. *Proc Natl Acad Sci U S A* 99(6):3990-3995, 2002 11891330
- Urnov FD, Miller JC, Lee YL, et al: Highly efficient endogenous human gene correction using designed zinc-finger nucleases. *Nature* 435(7042):646-651, 2005 15806097

- Vakoc CR, Sachdeva MM, Wang H, et al: Profile of histone lysine methylation across transcribed mammalian chromatin. *Mol Cell Biol* 26(24):9185-9195, 2006 17030614
- Valasek MA, Repa JJ: The power of real-time PCR. *Adv Physiol Educ* 29(3):151-159, 2005 16109794
- Venter JC, Adams MD, Myers EW, et al: The sequence of the human genome. *Science* 291(5507):1304-1351, 2001 11181995
- Volpe TA, Kidner C, Hall IM, et al: Regulation of heterochromatic silencing and histone H3 lysine-9 methylation by RNAi. *Science* 297(5588):1833-1837, 2002 12193640
- Wang Q, O'Brien PJ, Chen CX, et al: Altered G protein-coupling functions of RNA editing isoform and splicing variant serotonin<sub>2C</sub> receptors. *J Neurochem* 74(3):1290-1300, 2000 10693963
- Wang Q, Zhang Z, Blackwell K, et al: Vigilins bind to promiscuously A-to-I-edited RNAs and are involved in the formation of heterochromatin. *Curr Biol* 15(4):384-391, 2005 15723802
- Wedegaertner PB, Bourne HR: Activation and depalmitoylation of Gs  $\alpha$ . *Cell* 77(7):1063-1070, 1994 7912657
- Wieden HJ, Gromadski K, Rodnin D, et al: Mechanism of elongation factor (EF)-Ts-catalyzed nucleotide exchange in EF-Tu. Contribution of contacts at the guanine base. *J Biol Chem* 277(8):6032-6036, 2002 11744709
- Wiedenheft B, Sternberg SH, Doudna JA: RNA-guided genetic silencing systems in bacteria and archaea. *Nature* 482(7385): 331-338, 2012 22337052
- Xia X, Zhou H, Huang Y, Xu Z: Allele-specific RNAi selectively silences mutant SOD1 and achieves significant therapeutic benefit in vivo. *Neurobiol Dis* 23(3):578-586, 2006 16857362

- Xia XG, Zhou H, Xu Z: Promises and challenges in developing RNAi as a research tool and therapy for neurodegenerative diseases. *Neurodegener Dis* 2(3-4):220-231, 2005 16909029
- Yamada T, Sakisaka T, Hisata S, et al: RA-RhoGAP, Rap-activated Rho GTPase-activating protein implicated in neurite outgrowth through Rho. *J Biol Chem* 280(38):33026-33034, 2005 16014623
- Yan Q, Zhang Q, Yang H, et al: Generation of multi-gene knockout rabbits using the Cas9/gRNA system. *Cell Regen (Lond)* 3(1):12, 2014 25408890
- Yanaka N, Nogusa Y, Fujioka Y, et al: Involvement of membrane protein GDE2 in retinoic acid-induced neurite formation in Neuro2A cells. *FEBS Lett* 581(4):712-718, 2007 17275818
- Yang W, Wang Q, Kaness SJ, et al: Altered RNA editing of serotonin 5-HT<sub>2C</sub> receptor induced by interferon: implications for depression associated with cytokine therapy. *Brain Res Mol Brain Res* 124(1):70-78, 2004 15093687
- Yano M, Nakamura S, Shiota M, et al: Gatekeeper role of 14-3-3 $\tau$  protein in HIV-1 gp120-mediated apoptosis of human endothelial cells by inactivation of Bad. *AIDS* 21(8):911-920, 2007 17457084
- Yizhar O, Fenno LE, Davidson TJ, et al: Optogenetics in neural systems. *Neuron* 71(1):9-34, 2011 21745635
- Yu JZ, Rasenick MM: Real-time visualization of a fluorescent G( $\alpha$ )(s): dissociation of the activated G protein from plasma membrane. *Mol Pharmacol* 61(2):352-359, 2002 11809860
- Zeng Y, Wagner EJ, Cullen BR: Both natural and designed micro RNAs can inhibit the expression of cognate mRNAs when expressed in human cells. *Mol Cell* 9(6):1327-1333, 2002 12086629
- Zhang Z, Carmichael GG: The fate of dsRNA in the nucleus: a p54(nrb)-containing complex mediates the nuclear

- retention of promiscuously A-to-I edited RNAs. *Cell* 106(4):465–475, 2001 11525732
- Zhang Z, Yang X, Zhang S, et al: BNIP3 upregulation and EndoG translocation in delayed neuronal death in stroke and in hypoxia. *Stroke* 38(5):1606–1613, 2007 17379825
- Zhou H, Falkenburger BH, Schulz JB, et al: Silencing of the Pink1 gene expression by conditional RNAi does not induce dopaminergic neuron death in mice. *Int J Biol Sci* 3(4):242–250, 2007 17389931
- Zhu H, Bilgin M, Bangham R, et al: Global analysis of protein activities using proteome chips. *Science* 293(5537):2101–2105, 2001 11474067
- Zuccato C, Ciammola A, Rigamonti D, et al: Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* 293(5529):493–498, 2001 11408619
- Zuckermann M, Hovestadt V, Knobbe-Thomsen CB, et al: Somatic CRISPR/Cas9-mediated tumour suppressor disruption enables versatile brain tumour modelling. *Nat Commun* 6:7391, 2015 26067104



## CHAPTER 2

# Neurotransmitters and Receptors in Psychiatric Disorders

Carolyn M. Drazinic, M.D., Ph.D.

Steven T. Szabo, M.D., Ph.D.

Todd D. Gould, M.D.

Husseini K. Manji, M.D., F.R.C.P.C.

This chapter serves as a primer on the recent advances in our understanding of neural function both in health and in disease. It is beyond the scope of this chapter to cover these important areas in extensive detail, and readers are referred to outstanding textbooks that are entirely devoted to the topic ([Kandel 2013](#); [Nestler et al. 2015](#); [Squire 2013](#)). Here, we focus on the principles of neurotransmission that are critical for an understanding of the biological bases of major psychiatric disorders, as well as the mechanisms by which effective treatments may exert

their beneficial effects. In particular, our goal is to lay the groundwork for the subsequent chapters in this volume that focus on individual disorders and their treatments.

Although this chapter is intended to provide a general overview on neurotransmitter function, whenever possible, we emphasize the neuropsychiatric relevance of specific observations. We outline principles that are of fundamental importance to the study and practice of psychopharmacology. The figure legends contain additional details for the interested reader.

---

## What Are Neurotransmitters?

---

Several criteria have been established for a neurotransmitter, including that 1) it is synthesized and released from neurons; 2) it is released from nerve terminals in a chemically or pharmacologically identifiable form; 3) it interacts with postsynaptic receptors and brings about the same effects as are seen with stimulation of the presynaptic neuron; 4) its interaction with the postsynaptic receptor displays a specific pharmacology; and 5) its actions are terminated by active processes ([Kandel 2013](#); [Nestler et al. 2015](#); [Squire 2013](#)). However, our growing appreciation of the complexity of the central nervous system (CNS) and of the existence of numerous molecules that exert *neuromodulatory* and *neurohormonal* effects has blurred the classical definition of neurotransmitters somewhat, and even well-known neurotransmitters do not meet all these criteria under certain situations ([Cooper et al. 2003](#)).

Most neuroactive compounds are small polar molecules that are synthesized in the CNS via local machinery or are able to permeate the blood-brain barrier. To date, more than 50 endogenous substances have been found to be present in the brain that appear to be capable of functioning as neurotransmitters. There are many plausible explanations for why the brain would need so many transmitters and receptor subtypes to transmit messages. Perhaps the simplest explanation is that the sheer complexity of the CNS results in many afferent nerve terminals impinging onto a single neuron. This requires a neuron to be able to distinguish the multiple information-conveying inputs. Although this can be accomplished partially by spatial segregation, it is accomplished in large part by chemical coding of the inputs—that is, different chemicals convey different information. Moreover, as we discuss in detail later, the evolution of multiple receptors for a single neurotransmitter means that the same chemical can convey different messages depending on the receptor subtypes it acts on. Additionally, the firing pattern of neurons is a means of conveying information; thus, the firing activities of neurons in the brain differ widely, and a single neuron firing at different frequencies can even release different neuroactive compounds depending on the firing rate (e.g., the release of peptides often occurs at higher firing rates than that which is required to release monoamines). These multiple mechanisms to enhance the diversity of responses—chemical coding, spatial coding, frequency coding—are undoubtedly critical in endowing the CNS with its complex repertoire of physiological and behavioral responses ([Kandel 2013](#); [Nestler et al. 2015](#)). Finally, the existence of multiple neuroactive compounds also provides built-in safeguards to ensure that vital brain

circuits are able to partially compensate for loss of function of particular neurotransmitters.

---

## Receptors

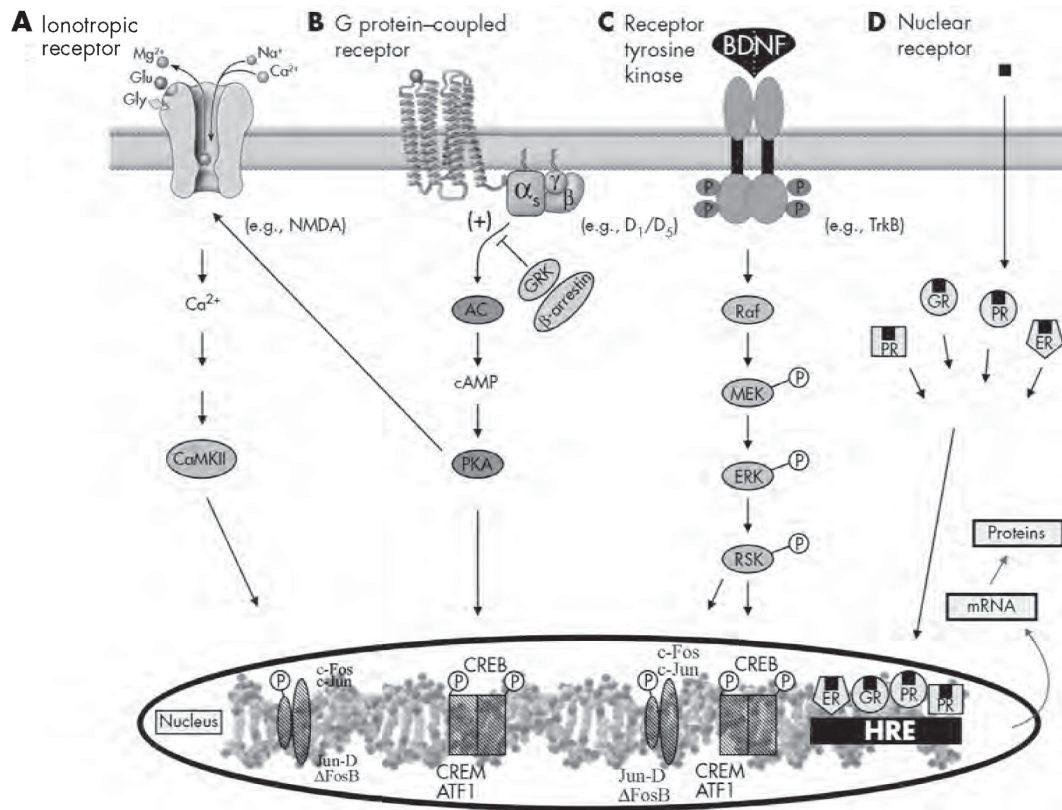
---

An essential property of any living cell is its ability to recognize and respond to external stimuli. Cell surface receptors have two major functions: recognition of specific molecules (neurotransmitters, hormones, growth factors, and even sensory signals) and activation of “effectors.” Binding of the appropriate agonist (i.e., neurotransmitter or hormone) externally to the receptor alters the conformation (shape) of the protein. Cell surface receptors use a variety of membrane-transducing mechanisms to transform an agonist’s message into cellular responses. In neuronal systems, the most typical responses ultimately (in some cases rapidly, in others more slowly) involve changes in transmembrane voltage and hence neuronal changes in excitability. Collectively, the processes are referred to as *transmembrane signaling* or *signal transduction mechanisms*. This process is not restricted to neurons. For instance, astrocytes were once thought to be uninvolved in neurotransmission, but they have since been shown to possess volume-regulated Cl<sup>-</sup> anion channels, which work together with gap junction/hemichannels to permit efflux of amino acids such as taurine, glutamate, and aspartate in response to swelling due to brain injury ([Mulligan and MacVicar 2006](#); [Ye et al. 2009](#)).

Interestingly, although increasing numbers of potential neuroactive compounds and receptors continue to be identified, it has become clear that translation of the

extracellular signals (into a form that can be interpreted by the complex intracellular enzymatic machinery) is achieved through a relatively small number of cellular mechanisms. Generally speaking, these transmembrane signaling systems, and the receptors that use them, can be divided into four major groups ([Figure 2-1](#)):

1. Those that are relatively self-contained in structure and whose message takes the form of transmembrane ion fluxes (**ionotropic receptors**)
2. Those that are multicomponent in nature and generate intracellular second messengers (**G protein-coupled receptors**)
3. Those that contain intrinsic enzymatic activity (**receptor tyrosine kinases and phosphatases**)
4. Those that are cytoplasmic and translocate to the nucleus to directly regulate transcription (gene expression) after they are activated by lipophilic molecules (often hormones) that enter the cell (**nuclear receptors**)



**FIGURE 2-1.** Major receptor subtypes in the central nervous system.

See [Plate 4](#) to view this figure in color.

This figure depicts the four major classes of receptors in the CNS. **(A) Ionotropic receptors.** These receptors comprise multiple protein subunits that are combined in such a way as to create a central membrane pore through this complex, allowing the flow of ions. This type of receptor has a very rapid response time (milliseconds). The consequences of receptor stimulation (i.e., excitatory or inhibitory) depend on the types of ions that the receptor specifically allows to enter the cell. Thus, for example, Na<sup>+</sup> entry through the NMDA (*N*-methyl-D-aspartate) receptor depolarizes the neuron and brings about an excitatory response, whereas Cl<sup>-</sup> efflux through the  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptor hyperpolarizes the neuron and brings about an inhibitory response. Illustrated here is the NMDA receptor regulating a channel permeable to Ca<sup>2+</sup>, Na<sup>+</sup>,

and  $K^+$  ions. The NMDA receptors also have binding sites for glycine,  $Zn^{2+}$ , phencyclidine, MK801/ketamine, and  $Mg^{2+}$ ; these molecules are able to regulate the function of this receptor. **(B) *G protein-coupled receptors*** (GPCRs). The majority of neurotransmitters, hormones, and even sensory signals mediate their effects via seven transmembrane domain-spanning receptors that are G protein-coupled. The amino terminus of the G protein is on the outside of the cell and plays an important role in the recognition of specific ligands; the third intracellular loop and carboxy terminus of the receptor play an important role in coupling to G proteins and are sites of regulation of receptor function (e.g., by phosphorylation). All G proteins are heterotrimers (consisting of  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits). The G proteins are attached to the membrane by isoprenoid moieties (fatty acid) via their  $\gamma$  subunits. Compared with the ionotropic receptors, GPCRs mediate a slower response (on the order of seconds). Detailed depiction of the activation of G protein-coupled receptors is given in [Figure 2-2](#). Here we depict a receptor coupled to the G protein  $G_s$  (the s stands for stimulatory to the enzyme adenylyl cyclase [AC]). Activation of such a receptor produces activation of AC and increases in cyclic adenosine monophosphate (cAMP) levels. G protein-coupled pathways exhibit major amplification properties, and, for example, in model systems researchers have demonstrated a 10,000-fold amplification of the original signal. The effects of cAMP are mediated largely by activation of protein kinase A (PKA). One major downstream target of PKA is CREB (cAMP response element-binding protein), which may be important to the mechanism of action of antidepressants. **(C) *Receptor tyrosine kinases***. These receptors are activated by neurotrophic factors and are able to bring about acute changes in synaptic function, as well as long-term effects on neuronal growth and survival. These receptors contain intrinsic tyrosine kinase activity. Binding of the ligand triggers receptor dimerization and transphosphorylation of tyrosine residues in its cytoplasmic domain,

which then recruits cytoplasmic signaling and scaffolding proteins. The recruitment of effector molecules generally occurs via interaction of proteins with modular binding domains SH2 and SH3 (named after homology to the src oncogenes–src homology domains); SH2 domains are a stretch of about 100 amino acids that allow high-affinity interactions with certain phosphotyrosine motifs. The ability of multiple effectors to interact with phosphotyrosines is undoubtedly one of the keys to the pleiotropic effects that neurotrophins can exert. Shown here is a tyrosine kinase receptor type B (TrkB), which upon activation produces effects on the Raf, MEK (mitogen-activated protein kinase/ERK), extracellular response kinase (ERK), and ribosomal S6 kinase (RSK) signaling pathway. Some major downstream effects of RSK are CREB and stimulation of factors that bind to the AP-1 site (c-Fos and c-Jun). **(D) Nuclear receptors.** These receptors are transcription factors that regulate the expression of target genes in response to steroid hormones and other ligands. Many hormones (including glucocorticoids, gonadal steroids, and thyroid hormones) are able to rapidly penetrate into the lipid bilayer membrane, because of their lipophilic composition, and thereby directly interact with these cytoplasmic receptors inside the cell. Upon activation by a hormone, the nuclear receptor–ligand complex translocates to the nucleus, where it binds to specific DNA sequences, referred to as *hormone responsive elements* (HREs), and regulates gene transcription. Nuclear receptors often interact with a variety of coregulators that promote transcriptional activation when recruited (coactivators) and those that attenuate promoter activity (corepressors). However, nongenomic effects of neuroactive steroids have also been documented, with the majority of evidence suggesting modulation of ionotropic receptors. This figure illustrates both the genomic and the nongenomic effects. ATF1=activation transcription factor 1; BDNF=brain-derived neurotrophic factor; CaMKII=Ca<sup>2+</sup>/calmodulin-dependent protein kinase II;



CREM=cyclic adenosine 5'-monophosphate response element modulator; D<sub>1</sub>=dopamine<sub>1</sub> receptor; D<sub>5</sub>=dopamine<sub>5</sub> receptor; ER=estrogen receptor; GR=glucocorticoid receptor; GRK=G protein-coupled receptor kinase; P=phosphorylation; PR=progesterone receptor.

A more extensive and continuously updated synopsis of these and many other receptors and ligands can be found at the International Union of Basic and Clinical Pharmacology/British Pharmacological Society Guide to Pharmacology Web site ([www.guidetopharmacology.org](http://www.guidetopharmacology.org)) and associated publications (Alexander et al. 2013a, 2013b, 2013c, 2013d, 2013e, 2013f). We review the four major groups in the following subsections.

## Ionotropic Receptors

The first class of receptors contains in their molecular complex an intrinsic *ion channel*. Receptors of this class include those for several amino acids, including glutamate (e.g., the NMDA [*N*-methyl-D-aspartate] receptor), GABA ( $\gamma$ -aminobutyric acid via the GABA<sub>A</sub> receptor), and the nicotinic acetylcholine (nACh) receptor and the serotonin type 3 (5-HT<sub>3</sub>) receptor. Ion channels are integral membrane proteins that are directly responsible for the electrical activity of the nervous system by virtue of their regulation of the movement of ions across membranes. Receptors containing intrinsic ion channels have been called *ionotropic* and are generally composed of four or five subunits that open transiently when a neurotransmitter binds, allowing ions to flow into (e.g., Na<sup>+</sup>, Ca<sup>2+</sup>, Cl<sup>-</sup>) or out

of (e.g.,  $K^+$ ) the neuron, thereby generating synaptic potential (see [Figure 2-1](#)).

Often, the ionotropic receptors are composed of different combinations of various subunits, thereby providing the system with considerable flexibility. For example, there is extensive research into the potential development of an anxiolytic that is devoid of sedative effects by targeting GABA<sub>A</sub> receptor subunits present in selected brain regions ([Salerno et al. 2012](#); [Taliani et al. 2009](#)). In general, neurotransmission that is mediated by ionotropic receptors is very fast, with ion channels opening and closing within milliseconds, and these receptors regulate much of the tonic excitatory (e.g., glutamate-mediated) and inhibitory (e.g., GABA-mediated) activity in the CNS; as we discuss in the “Neurotransmitter and Neuropeptide Systems” section later in this chapter, many of the classic neurotransmitters (e.g., monoamines) exert their effects on a slower time scale and are therefore often considered to be modulatory in their effects.

## G Protein–Coupled Receptors

Most receptors in the CNS do not have intrinsic ionic conductance channels within their structure but instead regulate cellular activity by the generation of various “second messengers.” Receptors of this class generally do not interact directly with the various second-messenger-generating enzymes but transmit information to the appropriate “effector” by the activation of interposed coupling proteins. These are the G protein-coupled receptor families, and they provide a slower onset, but longer duration of signaling, compared with ionotropic

receptors ([Squire 2013](#)). The *G protein-coupled receptors* (GPCRs, which constitute more than 80% of all known receptors in the body and number about 800 in humans) all span the plasma membrane seven times and have three intracellular loops and three extracellular loops (see [Figure 2-1](#)) ([Alexander et al. 2013b](#)). G proteins are so named because of their ability to bind the guanine nucleotides guanosine triphosphate and guanosine diphosphate. Receptors coupled to G proteins include those for dopamine, serotonin, acetylcholine, various peptides, and even sensory signals such as light and odorants.

GPCRs have increasingly become the focus of extensive research in psychiatry ([Catapano and Manji 2007](#)). The amino terminus is on the outside of the cell and plays a critical role in recognition of the ligand, which can be a small molecule, peptide, or large protein; the carboxy terminus and third intracellular loop are inside the cell and regulate coupling to different G proteins, “cross-talk” between receptors, and desensitization (see [Figure 2-1](#)) ([Alexander et al. 2013b](#)). Although the bimodal model of ligands switching the GPCR “on” or “off” is appealing, an individual GPCR can actually assume many different conformations, which influences the nature of the ligand-receptor interaction and the predominant complex signal generated in a particular cell type; this concept is called ligand-induced selective signaling ([Millar and Newton 2010](#)). Differential oligomerization, differential phosphorylation, signaling through molecules other than G proteins, and second-messenger independent signaling together add even more complexity for future GPCR research ([Kandel 2013](#); [Millar and Newton 2010](#)).

In conclusion, many classes and subtypes of G proteins exist, playing key roles in amplifying and integrating

signals.

## Autoreceptors and Heteroreceptors

*Autoreceptors* are receptors located on neurons that produce the endogenous ligand for that particular receptor (e.g., a serotonergic receptor on a serotonergic neuron). By contrast, *heteroreceptors* are receptor subtypes that are present on neurons that do not contain an endogenous ligand for that particular receptor subtype (e.g., a serotonergic receptor located on a dopaminergic neuron).

Two major classes of autoreceptors play very important roles in fine-tuning neuronal activity. *Somatodendritic autoreceptors* are present on cell bodies and dendrites and exert critical roles in regulating the firing rate of neurons. In general, activation of somatodendritic autoreceptors (e.g.,  $\alpha_2$ -adrenergic receptors for noradrenergic neurons, 5-HT<sub>1A</sub> receptors for serotonergic neurons, or dopamine type 2 [D<sub>2</sub>] receptors for dopaminergic neurons) inhibits the firing rate of the neurons by opening K<sup>+</sup> channels and by reducing cyclic adenosine monophosphate (cAMP) levels, both of which may be important in psychiatric disease. For instance, TREK-1 is a background K<sup>+</sup> channel regulator protein important in serotonin transmission and potentially in moodlike behavior regulation in mice ([Heurteaux et al. 2006](#)). This exemplifies how fundamental mechanisms of neuronal transmission such as K<sup>+</sup> channels, which regulate membrane potentials, may relate to global alterations in brain functioning relevant to psychiatry.

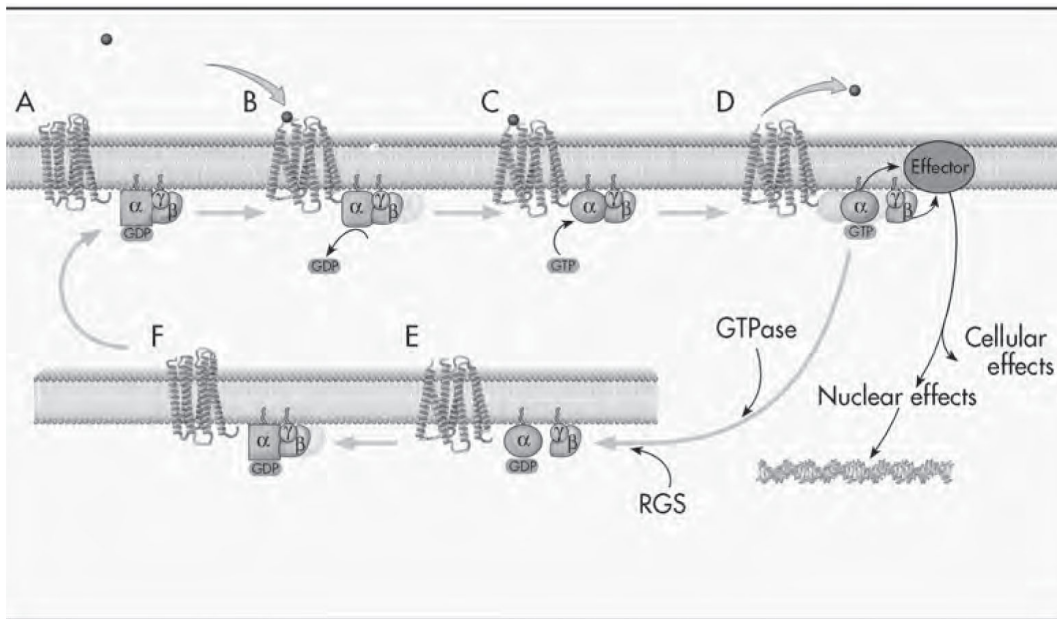
The second major class of autoreceptors, *nerve terminal autoreceptors*, play an important role in regulating the amount of neurotransmitter released per nerve impulse, generally by closing nerve terminal Ca<sup>2+</sup> channels. Both of

these types of autoreceptors are typically members of the GPCR family. Neurotransmitter release is known to be triggered by influx and alterations of intracellular calcium, with functioning of three types of SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein [SNAP] receptor) proteins mediating a critical role. The distinct kinetics of neurotransmitter release modulators, such as botulinum and tetanus neurotoxins, induce prominent alterations in synaptobrevin and syntaxin, leading to calcium-independent mechanisms of neurotransmitter regulation ([Sakaba et al. 2005](#)). Most synapses are dependent on influx of  $\text{Ca}^{2+}$  through voltage-gated calcium channels for presynaptic neurotransmitter release; however, in the retina, this influx of calcium occurs via glutamatergic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors ([Chávez et al. 2006](#)). Beyond the receptor level, presynaptic SAD (synapses of amphids defective, originally identified as a regulator of neuronal polarity in the *Caenorhabditis elegans* worm model), an intracellular serine threonine kinase, is associated with the active zone cytomatrix that regulates neurotransmitter release, and SAD kinases in presynaptic neurons also control the maturation and arborization of synapses in the central and peripheral nervous systems ([Inoue et al. 2006](#); [Lilley et al. 2014](#)). These data further exemplify the dynamic nature of basic processes involved in neurotransmitter regulation that may possibly aid in advancing treatment of psychopathology.

## **GPC Receptor Regulation and Trafficking**

The mechanism by which GPCRs translate extracellular signals into cellular changes was once envisioned as a simple linear model. It is now known, however, that the

activity of GPCRs is subject to at least three additional principal modes of regulation: desensitization, downregulation, and trafficking (Carman and Benovic 1998) (Figure 2-2). *Desensitization*, the process by which cells rapidly adapt to stimulation by agonists, is generally believed to occur by two major mechanisms: homologous and heterologous.



**FIGURE 2-2.** G protein-coupled receptors and G protein activation.

*See Plate 5 to view this figure in color.*

All G proteins are heterotrimers consisting of  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits. The receptor shuttles between a low-affinity form that is not coupled to a G protein and a high-affinity form that is coupled to a G protein. **(A)** At rest, G proteins are largely in their inactive state, namely, as  $\alpha\beta\gamma$  heterotrimers, which have GDP (guanosine diphosphate) bound to the  $\alpha$  subunit. **(B)** When a receptor is activated by a neurotransmitter, it undergoes a conformational (shape) change, forming a transient state referred to as a *high-affinity ternary complex*, comprising the agonist, the receptor in a

high-affinity state, and the G protein. A consequence of the receptor interaction with the G protein is that the GDP comes off the G protein  $\alpha$  subunit, leaving a very transient empty guanine nucleotide binding domain. **(C)** Guanine nucleotides (generally GTP) quickly bind to this nucleotide binding domain; thus, one of the major consequences of active receptor-G protein interaction is to facilitate guanine nucleotide exchange—this is basically the “on switch” for the G protein cycle. **(D)** A family of GTPase-activating proteins for G protein-coupled receptors has been identified, and they are called regulators of G protein signaling (RGS) proteins. Since activating GTPase activity facilitates the “turn off” reaction, these RGS proteins are involved in dampening the signal. Binding of GTP to the  $\alpha$  subunit of G proteins results in subunit dissociation, whereby the  $\alpha$ -GTP dissociates from the  $\beta\gamma$  subunits. Although not covalently bound, the  $\beta$  and  $\gamma$  subunits remain tightly associated and generally function as dimers. The  $\alpha$ -GTP and  $\beta\gamma$  subunits are now able to activate multiple diverse effectors, thereby propagating the signal. While they are in their active states, the G protein subunits can activate multiple effector molecules in a “hit and run” manner; this results in major signal amplification (i.e., one active G protein subunit can activate multiple effector molecules). The activated G protein subunits also dissociate from the receptor, converting the receptor to a low-affinity conformation and facilitating the dissociation of the agonist from the receptor. The agonist can now activate another receptor, and this also results in signal amplification. Together, these processes have been estimated to produce a 10,000-fold amplification of the signal in certain models. **(E)** Interestingly, the  $\alpha$  subunit has intrinsic GTPase activity, which cleaves the third phosphate group from GTP (G-P-P-P) to GDP (G-P-P). Since  $\alpha$ -GDP is an inactive state, the GTPase activity serves as a built-in timing mechanism, and this is the “turn off” reaction. **(F)** The reassociation of  $\alpha$ -GDP with  $\beta\gamma$  is

thermodynamically favored, and the reformation of the inactive heterotrimer ( $\alpha\beta\gamma$ ) completes the G protein cycle.

*Homologous desensitization* is receptor specific; that is, only the receptor actively being stimulated becomes desensitized. This form of desensitization occurs via a family of kinases known as G protein-coupled kinases. When a receptor activates a G protein and causes dissociation of the  $\alpha$  subunit from the  $\beta\gamma$  subunits, the  $\beta\gamma$  subunits are able to provide an “anchoring surface” for the G protein-coupled kinases to allow them to come into the proximity of the activated receptor and phosphorylate it. This phosphorylation then recruits another family of proteins known as *arrestins*, which physically interfere with the coupling of the phosphorylated receptor and the G protein, thereby dampening the signal. This form of desensitization is very rapid and usually transient (i.e., the receptors get dephosphorylated and return to the baseline state). However, if the stimulation of the receptor is excessive and prolonged, it leads to an internalization of the receptor, and often its degradation, a process referred to as *downregulation*.

*Heterologous desensitization* is not receptor specific and is mediated by second-messenger kinases such as protein kinase A (PKA) and protein kinase C (PKC). Thus, when a receptor activates PKA, the activated PKA is capable of phosphorylating (and thereby desensitizing) not only that particular receptor but also other receptors that are present in proximity and have the correct phosphorylation motif, thereby producing heterologous desensitization.

After prolonged or repeated activation of receptors by agonist ligands, the process of receptor *downregulation* is observed. Downregulation is associated with a reduced



number of receptors detected in cells or tissues, thereby leading to attenuation of cellular responses ([Carman and Benovic 1998](#)). The process of GPCR sequestration is mediated by a well-characterized endocytic pathway involving the concentration of receptors in clathrin-coated pits and subsequent internalization and recycling back to the plasma membrane ([Tsao and von Zastrow 2000](#)). Endocytosis can thus clearly serve as a primary mechanism to attenuate signaling by rapidly and reversibly removing receptors from the cell surface. However, endocytosis and receptor trafficking also mediate GPCR signaling by way of certain effector pathways, most notably mitogen-activated protein (MAP) kinase cascades. Evidence also indicates that endocytosis of GPCRs may be required for certain signal transduction pathways leading to the nucleus ([Tsao and von Zastrow 2000](#)). These diverse functions of GPCR endocytosis and trafficking lead to unexpected insights into the biochemical and functional properties of endocytic vesicles. Indeed, there is considerable excitement about our growing understanding of the diverse molecular mechanisms for signaling specificity and receptor trafficking and the possibility that this knowledge could lead to new selective therapeutics.

## Receptor Tyrosine Kinases

The receptor tyrosine kinases, as their name implies, contain intrinsic tyrosine kinase activity and are generally used by growth factors, such as neurotrophic factors, and cytokines. Binding of an agonist initiates receptor dimerization and transphosphorylation of tyrosine residues in its cytoplasmic domain ([Patapoutian and Reichardt 2001](#))

(see [Figure 2-1](#)). The phosphotyrosine residues of the receptor function as binding sites for recruiting specific cytoplasmic signaling and scaffolding proteins. The ability of multiple effectors to interact with phosphotyrosines is undoubtedly one of the keys to the pleiotropic effects that neurotrophins can exert. These pleiotropic and yet distinct effects of growth factors are mediated by varying degrees of activation of three major signaling pathways: the MAP kinase pathway, the phosphoinositide-3 (PI<sub>3</sub>) kinase pathway, and the phospholipase C (PLC)- $\gamma$ 1 pathway. These pathways are part of complex secondary messaging systems of the cell, which are beyond the scope of this chapter.

## Nuclear Receptors

Nuclear receptors are transcription factors that regulate the expression of target genes in response to steroid hormones and other ligands. Many hormones (including glucocorticoids, gonadal steroids, and thyroid hormones) are able to rapidly penetrate into the lipid bilayer membrane because of their lipophilic composition, and thereby directly interact with these cytoplasmic receptors inside the cell (see [Figure 2-1](#)). On activation by a hormone, the nuclear receptor-ligand complex translocates to the nucleus, where it binds to specific DNA sequences referred to as *hormone-responsive elements*, and subsequently regulates gene transcription ([Mangelsdorf et al. 1995](#); [Truss and Beato 1993](#)). Nuclear receptors often interact with a variety of coregulators that promote transcriptional activation when recruited (*coactivators*) and those that attenuate promoter activity (*corepressors*). Numerous

nuclear receptors have been identified, as reviewed elsewhere ([Alexander et al. 2013e](#)).

With this broad overview of neurotransmitters and receptor subtypes, we now turn to a discussion of selected individual neurotransmitters and their receptors.

---

## Neurotransmitter and Neuropeptide Systems

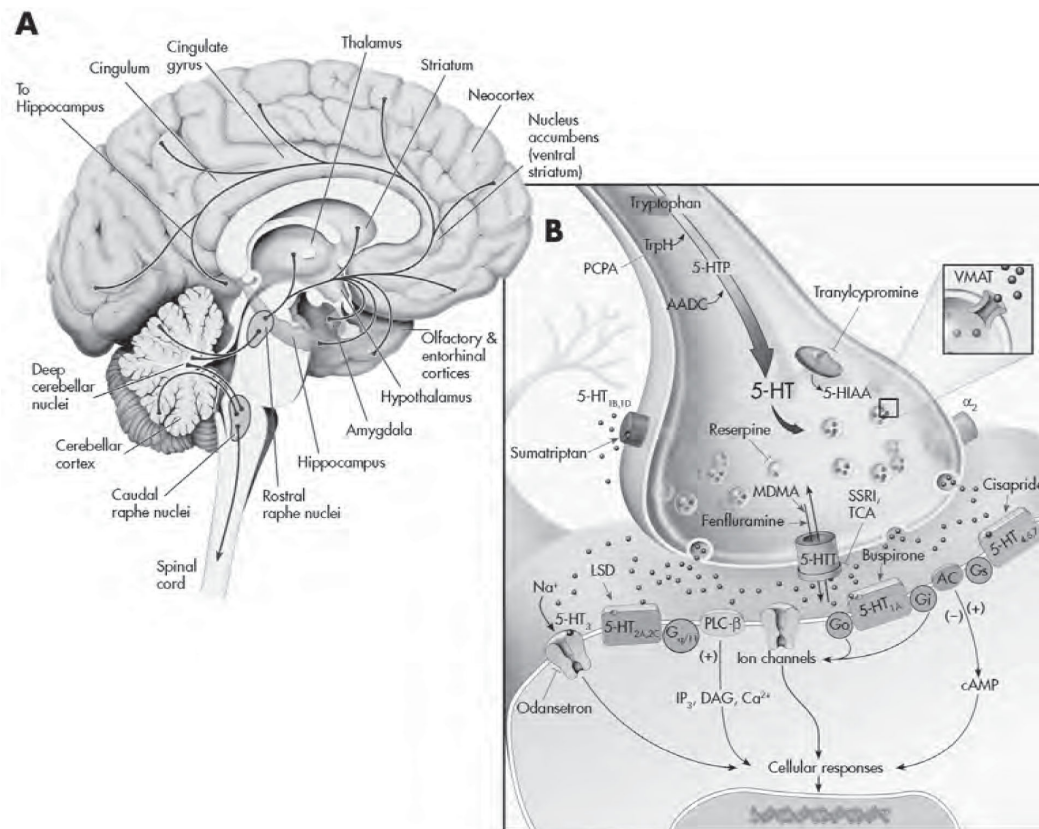
---

### Serotonergic System

Largely on the basis of the observation that most effective antidepressants and antipsychotics target these systems, the monoaminergic systems (e.g., serotonin, norepinephrine, dopamine) have been extensively studied. Serotonin was given that name because of its activity as an endogenous vasoconstrictor in blood serum ([Rapport et al. 1948](#)). It was later acknowledged as being the same molecule (secretine) that is found in the intestinal mucosa and that is “secreted” by chromaffin cells ([Brodie 1900](#)). Following these findings, serotonin later was characterized as a neurotransmitter in the CNS ([Bogdanski et al. 1956](#)).

Serotonin-producing cell bodies in the brain are localized to the central gray, in the surrounding reticular formation, and in cell clusters located in the center, and thus the name *raphe* (from Latin, meaning “midline”) was adopted ([Figure 2-3A](#)). The dorsal raphe, the largest brain stem serotonin nucleus, contains approximately 50% of the total serotonin neurons in the mammalian CNS; in contrast, the medial raphe comprises 5% ([Descarries et al. 1982](#); [Wiklund and](#)

[Björklund 1980](#)). Serotonergic neurons project widely throughout the CNS rather than to discrete anatomical locations (as the dopaminergic neurons appear to do; see [Figure 2-4A](#) later in this chapter), leading to the suggestion that serotonin exerts a major *modulatory* role throughout the CNS ([Reader 1980](#)). Interestingly, evidence suggests that infralimbic and prelimbic regions of the ventromedial prefrontal cortex (vmPFC) in rats are responsible for detecting whether a stressor is under the organism's control. When a stressor is controllable, stress-induced activation of the dorsal raphe nucleus is inhibited by the vmPFC, and the behavioral sequelae of the uncontrollable stress response are blocked ([Amat et al. 2005](#)). The ability to regulate serotonin neuron activity and function has been a major ongoing focus of psychiatric disorder research and treatments. Lysergic acid diethylamide, a hallucinogen, has a chemical structure similar to that of serotonin, and monoamine oxidase (MAO) inhibitors (MAOIs), which are classic antidepressants, increase the levels of monoamines such as serotonin in the synapse ([Squire 2013](#)).



**FIGURE 2-3.** The serotonergic system.

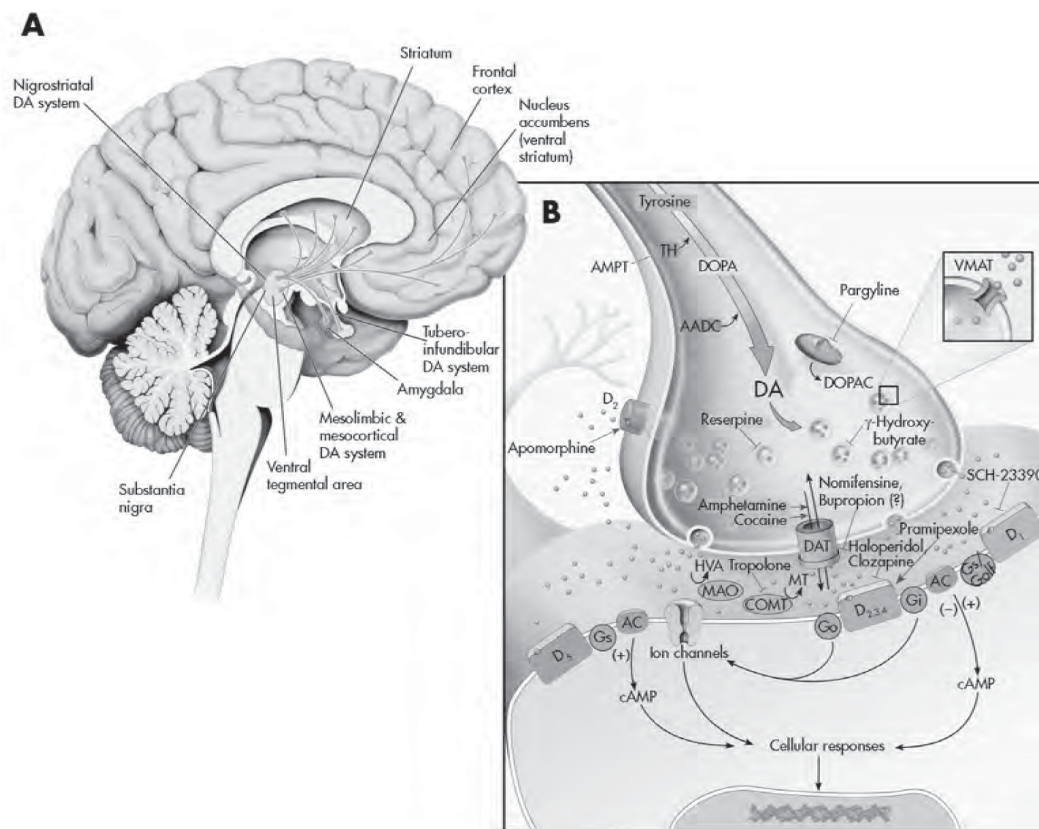
*See Plate 6 to view this figure in color.*

This figure depicts the location of the major serotonin (5-HT)-producing cells (raphe nuclei) innervating brain structures **(A)**, and various cellular regulatory processes involved in serotonergic neurotransmission **(B)**. 5-HT neurons project widely throughout the CNS and innervate virtually every part of the neuroaxis. L-Tryptophan, an amino acid actively transported into presynaptic 5-HT-containing terminals, is the precursor for 5-HT. It is converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme tryptophan hydroxylase (TrpH). This enzyme is effectively inhibited by the drug *p*-chlorophenylalanine (PCPA). Aromatic amino acid decarboxylase (AADC) converts 5-HTP to 5-HT. Once released from the presynaptic terminal, 5-HT can interact with a variety (15 different types) of presynaptic and postsynaptic receptors.

Presynaptic regulation of 5-HT neuron firing activity and release occurs through somatodendritic 5-HT<sub>1A</sub> (not shown) and 5-HT<sub>1B,1D</sub> autoreceptors, respectively, located on nerve terminals. Sumatriptan is a 5-HT<sub>1B,1D</sub> receptor agonist. (The antimigraine effects of this agent are likely mediated by local activation of this receptor subtype on blood vessels, which results in their constriction.) Buspirone is a partial 5-HT<sub>1A</sub> receptor agonist that activates both pre- and postsynaptic receptors. Cisapride is a preferential 5-HT<sub>4</sub> receptor agonist that is used to treat irritable bowel syndrome as well as nausea associated with antidepressants. The binding of 5-HT to G protein receptors (G<sub>o</sub>, G<sub>i</sub>, etc.) that are coupled to adenylyl cyclase (AC) and phospholipase C-β (PLC-β) will result in the production of a cascade of second-messenger and cellular effects. Lysergic acid diethylamide (LSD) likely interacts with numerous 5-HT receptors to mediate its effects. Pharmacologically this ligand is often used as a 5-HT<sub>2</sub> receptor agonist in receptor-binding experiments. Ondansetron is a 5-HT<sub>3</sub> receptor antagonist that is marketed as an antiemetic agent for chemotherapy patients but is also given to counteract side effects produced by antidepressants in some patients. 5-HT has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron through 5-HT transporters (5-HTTs). Once inside the neuron, it can either be repackaged into vesicles for reuse or undergo enzymatic catabolism. The selective 5-HT reuptake inhibitors (SSRIs) and older-generation tricyclic antidepressants (TCAs) are able to interfere/block the reuptake of 5-HT. 5-HT is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase (MAO), located on the outer membrane of mitochondria or sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). Reserpine causes a depletion of 5-HT in vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported with this agent). Tranylcypromine is an MAO inhibitor (MAOI) and an effective antidepressant.

Fenfluramine (an anorectic agent) and 3,4-methylenedioxymethamphetamine (MDMA; “Ecstasy”) are able to facilitate 5-HT release by altering 5-HTT function. cAMP=cyclic adenosine monophosphate; DAG=diacylglycerol; IP<sub>3</sub>=inositol-1,4,5-triphosphate.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Modified from Nestler et al. 2001.



**FIGURE 2-4.** The dopaminergic system.

*See Plate 7 to view this figure in color.*

This figure depicts the dopaminergic projections throughout the brain **(A)** and various regulatory processes involved in

dopaminergic neurotransmission **(B)**. The amino acid L-tyrosine is actively transported into presynaptic dopamine (DA) nerve terminals, where it is ultimately converted into DA. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase (TH).  $\alpha$ -Methyl-*p*-tyrosine (AMPT) is a competitive inhibitor of tyrosine hydroxylase and has been used to assess the impact of reduced catecholaminergic function in clinical studies. The production of DA requires that L-aromatic amino acid decarboxylase (AADC) act on L-dopa. Thus, the administration of L-dopa to patients with Parkinson's disease bypasses the rate-limiting step and is able to produce DA quite readily. DA has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron through DA transporters (DATs). DA is then metabolized to dihydroxyphenylalanine (DOPAC) by intraneuronal monoamine oxidase (MAO; preferentially by the MAO-B subtype) located on the outer membrane of mitochondria, or is sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). Reserpine causes a depletion of DA in vesicles by interfering and irreversibly damaging uptake and storage mechanisms.  $\gamma$ -Hydroxybutyrate inhibits the release of DA by blocking impulse propagation in DA neurons. Pargyline inhibits MAO and may have efficacy in treating parkinsonian symptoms by augmenting DA levels through inhibition of DA catabolism. Other clinically used inhibitors of MAO are nonselective and thus likely elevate the levels of DA, norepinephrine, and serotonin. Once released from the presynaptic terminal (because of an action potential and calcium influx), DA can interact with five different G protein-coupled receptors (D<sub>1</sub>-D<sub>5</sub>), which belong to either the D<sub>1</sub> or D<sub>2</sub> receptor family. Presynaptic regulation of DA neuron firing activity and release occurs through somatodendritic (not shown) and nerve terminal D<sub>2</sub> autoreceptors, respectively. Pramipexole is a D<sub>2</sub>/D<sub>3</sub> receptor agonist and has been documented to have efficacy as an



augmentation strategy in cases of treatment-resistant depression and in the management of Parkinson's disease. The binding of DA to G protein receptors ( $G_o$ ,  $G_i$ , etc.) positively or negatively coupled to adenylyl cyclase (AC) results in the activation or inhibition of this enzyme, respectively, and the production of a cascade of second-messenger and cellular effects (see diagram). Apomorphine is a  $D_1/D_2$  receptor agonist that has been used clinically to aid in the treatment of Parkinson's disease. (SKF-82958 is a pharmacologically selective  $D_1$  receptor agonist.) SCH-23390 is a  $D_1/D_5$  receptor antagonist. There are likely physiological differences between  $D_1$  and  $D_5$  receptors, but the current unavailability of selective pharmacological agents has precluded an adequate differentiation thus far. Haloperidol is a  $D_2$  receptor antagonist, and clozapine is a nonspecific  $D_2/D_4$  receptor antagonist (both are effective antipsychotic agents). Once inside the neuron, DA can either be repackaged into vesicles for reuse or undergo enzymatic catabolism. Nomifensine is able to interfere/block the reuptake of DA. The antidepressant bupropion has affinity for the dopaminergic system, but it is not known whether this agent mediates its effects through DA or possibly by augmenting other monoamines. DA can be degraded to homovanillic acid (HVA) through the sequential action of catechol-*O*-methyltransferase (COMT) and MAO. Tropolone is an inhibitor of COMT. Evidence suggests that the COMT gene may be linked to schizophrenia ([Akil et al. 2003](#)). cAMP=cyclic adenosine monophosphate; DOPA=dihydroxyphenylalanine; MT=methoxytyramine;

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

The precursor for serotonin synthesis is L-tryptophan, an amino acid that comes primarily from the diet and crosses the blood-brain barrier through a carrier for large neutral amino acids. Tryptophan hydroxylase is the rate-limiting enzyme in serotonin biosynthesis ([Figure 2-3B](#)), and polymorphisms in this enzyme have been extensively investigated in psychiatric disorders, with equivocal results. A more fruitful research strategy in humans has been tryptophan depletion via dietary restriction to study the role of serotonin in the pathophysiology and treatment of psychiatric disorders ([Bell et al. 2001](#); [van Donkelaar et al. 2011](#)). These studies have indicated that acute tryptophan depletion (ATD) produces a rapid depressive relapse in patients taking selective serotonin reuptake inhibitors (SSRIs) but not in those taking norepinephrine reuptake inhibitors; the data suggesting induction of depressive symptoms in remitted patients or individuals with family histories of mood disorders are more equivocal ([Bell et al. 2001](#)). Findings similar to those from ATD depression studies also have been identified in numerous studies of panic disorder, whereby healthy subjects with no history of panic disorder, or patients with panic disorder in remission, were not very sensitive to ATD, but patients with unremitted panic disorder were extremely sensitive to carbon dioxide challenges ([Sobczak and Schruers 2014](#)). Some of the inconsistencies of the ATD findings in the literature may have been due to the various formulations of the tryptophan depletion amino acid cocktails used, but more surprising are suggestions that the classic ATD cocktails may not have been depleting extracellular synaptic serotonin levels after all but may have been working through other molecular mechanisms as described elsewhere ([Sobczak and Schruers 2014](#); [van Donkelaar et](#)

al. 2011). Nevertheless, numerous studies in the literature suggest that, in general, low levels of serotonin in the plasma and/or cerebrospinal fluid (CSF) correlate with depression, impulsivity, aggression, alcohol dependence, suicide attempts, completed suicides, and violent suicides (Bortolato et al. 2013; Moberg et al. 2011; Oo et al. 2016; Purselle and Nemeroff 2003; Ruljancic et al. 2011, 2013; Spreux-Varoquaux et al. 2001). Serotonin dysfunction-related endophenotypes that could predict patients at risk for suicide are being explored, including fenfluramine challenges leading to poor prolactin release, increased time spent in rapid eye movement (REM) sleep stages, increased loudness-dependent auditory evoked potentials, and increased frontal cortex P300 (Lee and Kim 2011). Furthermore, postmortem studies in depressed bipolar patients who completed suicide found lower serotonin and norepinephrine activity (Wiste et al. 2008).

More sophisticated molecular approaches targeting individual serotonin receptors and transporters are described in the following subsections.

## Serotonin Transporters

As is the case for many classic neurotransmitters, termination of the effects of serotonin in the synaptic cleft is brought about in large part by an active reuptake process mediated by the serotonin transporter (5-HTT). Serotonin is taken up into the presynaptic terminals, where it is metabolized by the enzyme MAO or sequestered into secretory vesicles by the vesicle monoamine transporter (see Figure 2-3B). This presumably underlies the mechanism by which MAOIs initiate their therapeutic effects; that is, the blockade of monoamine breakdown results in an increase in the available pool for release when

an action potential invades the nerve terminal. It is now well established that many tricyclic antidepressants and SSRIs exert their initial primary pharmacological effects by binding to the 5-HTT and blocking serotonin reuptake, thereby increasing the intrasynaptic levels of serotonin, which initiates a cascade of downstream effects (see [Figure 2-3B](#) for details). It has been hypothesized that the first step in serotonin transport involves the binding of serotonin to the 5-HTT and then a cotransport with  $\text{Na}^+$ , and the second step involves the translocation of  $\text{K}^+$  across the membrane to the outside of the cell. SSRIs bind to the same site on the transporter as serotonin itself. Elegant biochemical and mutagenesis experiments have elucidated a leucine transporter from bacterial species, providing information that helped unravel the mechanism by which mammalian transporters couple ions and substrates to mediate neurotransmitter clearance. The crystal structure for sodium- and chloride-dependent neurotransmitter transporters (including transporters for serotonin [SERT], dopamine [DAT], norepinephrine [NET], glycine [GlyT1b], and GABA [GAT1]) with the L-leucine binding sites for  $\text{Na}^+$  ions also has been elucidated ([Henry et al. 2006](#); [Yamashita et al. 2005](#)).

In the brain, 5-HTTs have been radiolabeled with [ $^3\text{H}$ ]-imipramine ([Hrdina et al. 1985](#); [Langer et al. 1980](#)) and with SSRIs such as [ $^3\text{H}$ ]cyanoimipramine ([Wolf and Bobik 1988](#)), [ $^3\text{H}$ ]paroxetine ([Habert et al. 1985](#)), and [ $^3\text{H}$ ]citalopram ([D'Amato et al. 1987](#)). The regional distribution of 5-HTT corresponds to discrete regions of rat brain known to contain cell bodies of serotonin neurons and synaptic axon terminals, most notably the cerebral cortex, neostriatum, thalamus, and limbic areas ([Cooper et al.](#)

2003; Hrdina et al. 1985; Madden 2002). The specific cellular localization of 5-HTT in the CNS also has been accomplished by using site-specific antibodies (Lawrence et al. 1995a). Immunohistochemical studies that used antibodies against the serotonin carrier have reported both neuronal and glial staining in areas of the rat brain containing serotonin somata and terminals (i.e., dorsal raphe and hippocampus) (Lawrence et al. 1995b). Experimental alterations of 5-HTT in young mice for a brief period during early development indicate abnormal emotional behavior in the same mice later in life, similar to the phenotype in mice in which 5-HTT is deficient throughout life (Ansorge et al. 2004). This suggests the necessity of serotonin early in emotional development and provides a possible mechanism by which genetic changes in the 5-HTT system may lead to susceptibility to develop psychiatric diseases such as depression (Caspi et al. 2003). Furthermore, serotonin uptake ability has been documented in primary astrocyte cultures (Kimelberg and Katz 1985) and has been postulated to account for considerable serotonin uptake in the frontal cortex and periventricular region (Ravid et al. 1992).

Because 5-HTT is transcribed from a single copy gene, abnormalities in platelet 5-HTT are thought to reflect CNS abnormalities (Owens and Nemeroff 1998). Several studies on platelet 5-HTT density have been undertaken using [<sup>3</sup>H]imipramine binding or [<sup>3</sup>H]paroxetine binding in mood disorders. Although the results of these studies are not entirely consistent, in total the results suggest that the receptor density value for platelet serotonin density is significantly lower in depressed subjects compared with healthy control subjects (Owens and Nemeroff 1998). The distribution of SERT (5-HTT) in the postmortem human

brain was found to be highest in the thalamus, amygdala, putamen, globus pallidus externa, lateral geniculate body, hippocampus, and caudate, with the lowest amounts in the cerebral cortex and minimal levels in the cerebellum and white matter ([Kish et al. 2005](#)).

Numerous studies have examined suicide risk related to individual genetic polymorphisms in SERT. For example, the serotonin-transporter-linked polymorphic region (5-HTTLPR) short S allele, which decreases presynaptic 5-HTT expression and thereby decreases serotonin reuptake and has an interaction with childhood abuse to increase lifetime depression risk, has nevertheless yielded contradictory results related to suicide risk, likely because of other confounding polymorphisms ([Purselle and Nemeroff 2003](#); [Ressler et al. 2010](#)). In patients with major depressive disorder (MDD) who attempted suicide, positron emission tomographic (PET) scanning with the [ $^{11}\text{C}$ ]N,N-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine ([ $^{11}\text{C}$ ]DASB) ligand indicated that SERT (5-HTT) levels were lower in the midbrain regions ([Miller et al. 2013](#)). In bipolar I patients with depression who completed suicide, a nearly 50% decrease in serotonin and norepinephrine activity was observed related to the locus coeruleus in postmortem brain studies, as compared with unipolar depressed patients who completed suicide and matched control subjects ([Wiste et al. 2008](#)). Three different antidepressants, sertraline (SSRI), citalopram (SSRI), and venlafaxine (serotonin-norepinephrine reuptake inhibitor), at clinical dosages in living patients were shown with PET ligand [ $^{11}\text{C}$ ]DASB to have 85% occupancy of SERT, effectively blocking SERT-mediated reuptake of free serotonin in the synapse and increasing serotonin synaptic levels ([Voineskos et al. 2007](#)). In summary, multiple

mechanisms can lead to insufficient levels of serotonin in neuronal synapses, which contributes significantly to the risk for depression and for suicide.

## Serotonin Receptors

In 1957, the existence of two separate serotonin receptors was first proposed, primarily because of the opposing phenomenon this neurotransmitter produces, in reference to cholinergic mediation of smooth muscle contraction ([Gaddum and Picarelli 1957](#)). Through the use of more precise molecular cloning and pharmacological and biochemical studies, seven distinct serotonin receptor families have been identified (5-HT<sub>1-7</sub>), many of which contain several subtypes. With the exception of the 5-HT<sub>3</sub> receptor, which is an excitatory ionotropic receptor, all the other serotonin receptors are GPCRs. The 5-HT<sub>1A,B,D,E,F</sub> receptors are negatively coupled to adenylyl cyclase; the 5-HT<sub>2A,B,C</sub> subtypes are positively coupled to PLC; and the 5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> subtypes are positively coupled to adenylyl cyclase (see [Figure 2-3B](#)) ([Humphrey et al. 1993](#); [Nestler et al. 2015](#)). When all types and subtypes are counted, 13 serotonin receptors are identified in humans ([Nestler et al. 2015](#)).

**5-HT<sub>1</sub> receptors.** 5-HT<sub>1A</sub> receptors are found in particularly high density in several limbic structures, including the hippocampus, septum, amygdala, and entorhinal cortex, as well as on serotonergic neuron cell bodies, where they serve as autoreceptors regulating serotonin neuronal firing rates ([Blier et al. 1998](#); [Cooper et al. 2003](#); [Pazos et al. 1985](#)). The highest density of labeling is found in the dorsal raphe, with lower densities observed

in the remaining raphe nuclei ([Pazos et al. 1985](#)). The density and messenger RNA (mRNA) expression of 5-HT<sub>1A</sub> receptors appear insensitive to reductions in serotonin transmission associated with lesioning the raphe or administering the serotonin-depleting agent *p*-chlorophenylalanine. Similarly, elevation of serotonin transmission, resulting from chronic administration of an SSRI or MAOI, does not consistently alter 5-HT<sub>1A</sub> receptor density or mRNA in the cortex, hippocampus, amygdala, or hypothalamus. In contrast to the insensitivity to serotonin, 5-HT<sub>1A</sub> receptor density is downregulated by adrenal steroids. Postsynaptic 5-HT<sub>1A</sub> receptor gene expression is under tonic inhibition by adrenal steroids in the hippocampus and some other regions. Thus, in rodents, hippocampal 5-HT<sub>1A</sub> receptor mRNA expression is increased by adrenalectomy and decreased by corticosterone administration or chronic stress. The stress-induced downregulation of 5-HT<sub>1A</sub> receptor expression is prevented by adrenalectomy. Mineralocorticoid receptor stimulation has the most potent effect on downregulating 5-HT<sub>1A</sub> receptors, although glucocorticoid receptor stimulation also contributes to this effect.

In addition to being expressed on neurons, postsynaptic 5-HT<sub>1A</sub> receptors are also abundantly expressed by astrocytes and some other glia ([Whitaker-Azmitia et al. 1990](#)) (see [Figure 2-7](#) later in this chapter). Stimulation of astrocyte-based 5-HT<sub>1A</sub> sites causes astrocytes to acquire a more mature morphology and to release the trophic factor S-100 $\beta$ , which promotes growth and arborization of serotonergic axons. Administration of 5-HT<sub>1A</sub> receptor antagonists, antibodies to S-100 $\beta$ , or agents that deplete serotonin produces similar losses of dendrites, spines,



and/or synapses in adult and developing animals—effects that are blocked by administration of 5-HT<sub>1A</sub> receptor agonists or SSRIs. These observations have led to the hypothesis that a reduction of 5-HT<sub>1A</sub> receptor function may play an important role in mood disorders that are known to be associated with glial reductions ([Manji et al. 2001](#)). The use of conditional knockouts of the 5-HT<sub>1A</sub> receptor, in which gene expression is altered only in particular anatomical regions and/or during particular times, has illustrated the caution necessary in attributing complex behaviors to simple “too much” or “too little” neurotransmitter or receptor hypotheses. One report used a knockout/rescue approach with regional and temporal specificity to show that the anxiety-related effect of the 5-HT<sub>1A</sub> receptor knockout was actually developmental. Specifically, expression limited to the hippocampus and cortex during early postnatal development was sufficient to counteract the anxious phenotype of the mutant, even though the receptor was still absent in adulthood ([Gross et al. 2002](#)). As is discussed in the chapters on antidepressants (see [Chapters 8–23](#)), there is interest in the observation that antidepressants enhance hippocampal neurogenesis ([Duman 2002](#); [Malberg et al. 2000](#)). It is noteworthy that data suggest that 5-HT<sub>1A</sub> receptor activation is required for SSRI-induced hippocampal neurogenesis in mice ([Jacobs et al. 2000](#)). Altering serotonin levels with the SSRI fluoxetine does not affect division of stem cells in the dentate gyrus, but rather increases symmetric divisions of an early progenitor cell class that exists after stem-cell division ([Encinas et al. 2006](#)).

5-HT<sub>1A</sub> receptors are now known to use a variety of signaling mechanisms to bring about their effects in distinct

brain areas. Thus, somatodendritic 5-HT<sub>1A</sub> receptors appear to inhibit the firing of serotonergic neurons by opening a K<sup>+</sup> channel through a pertussis toxin-sensitive G protein (likely G<sub>o</sub>, discussed later in the section on G proteins) ([Andrade et al. 1986](#)), as well as by reducing cAMP levels. Postsynaptic 5-HT<sub>1A</sub> receptors appear to exert many of their effects by inhibiting adenylyl cyclase via G<sub>i</sub> ([De Vivo and Maayani 1990](#)) but also have been found to potentiate the activity of certain adenylyl cyclases ([Bourne and Nicoll 1993](#)) and to stimulate inositol-1,4,5-triphosphate (IP<sub>3</sub>) production and activate PKC ([Liu and Albert 1991](#)). Structurally, the 5-HT<sub>1A</sub> receptors are more related to D<sub>2</sub> receptors than to other serotonin receptors ([Squire 2013](#)). Functional polymorphisms in the promotor of 5-HT<sub>1A</sub> receptors influencing 5-HT<sub>1A</sub> receptor expression did not lead to changes in binding of 5-HT<sub>1A</sub> receptor antagonists in healthy subjects based on two PET studies, suggesting that there are compensatory mechanisms in the brains of healthy living human subjects ([Bortolato et al. 2013](#); [David et al. 2005](#); [Lothe et al. 2010](#)). PET studies also reported that 5-HT<sub>1A</sub> receptors decrease with advancing age in men, which may potentially explain the increased risk of suicide in this population ([Moses-Kolko et al. 2011](#)). A functional promoter polymorphism, rs6295, for which the G allele causes decreased transcription of 5-HT<sub>1A</sub>, may have a role in increasing risk for depression and suicide, because it is overrepresented in patients with depression, although the mechanism is not clear, because postmortem brain samples from depressed individuals who committed suicide showed more equal expression of the G allele with the C allele ([Donaldson et al. 2016](#); [Savitz et al. 2009](#)). Buspirone

is a 5-HT<sub>1A</sub> receptor agonist indicated for treating generalized anxiety disorder (Nestler et al. 2015).

5-HT<sub>1D</sub> receptors are virtually absent in rodents but have been detected in guinea pigs and humans (Bruinvels et al. 1993). On the basis of an approximately 74% sequence homology, it has been proposed that 5-HT<sub>1B</sub> receptors are the rodent homologue of 5-HT<sub>1D</sub> receptors (Saxena et al. 1998). Furthermore, the distribution of the 5-HT<sub>1D</sub> receptors in guinea pigs and humans is approximately equivalent to that of the 5-HT<sub>1B</sub> receptors in rats (Bruinvels et al. 1993). Both 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors have been proposed to represent the major nerve terminal autoreceptors regulating the amount of serotonin released per nerve impulse (Piñeyro and Blier 1999) (see Figure 2-3B). Like 5-HT<sub>1A</sub> receptors, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors inhibit cAMP formation and stimulate IP<sub>3</sub> production and activate PKC (Schoeffer and Bobirnac 1995). This appears to be the case for many receptors coupled to G<sub>i</sub> and G<sub>o</sub> (Table 2-1). The  $\alpha$  subunits of the G protein ( $\alpha_i$  and  $\alpha_o$ ) inhibit adenylyl cyclase and regulate ion channels, respectively, whereas the  $\beta\gamma$  subunits activate PLC isozymes to stimulate IP<sub>3</sub> production and activate PKC. Examples of 5-HT<sub>1B/1D</sub> receptor agonists include the triptan family of medications used to treat migraines, which are incidentally contraindicated in patients who have comorbid coronary artery disease because of the presence of 5-HT<sub>1B</sub> receptors causing constriction of coronary arteries (Lambert 2005; Nestler et al. 2015). 5-HT<sub>1B</sub> receptor agonists have shown promise for decreasing reactive aggression and alcohol intake in animal models, but human polymorphism studies searching for a relationship between *HTR1B*

polymorphisms and aggression or suicide risk have yielded inconsistent results ([Bortolato et al. 2013](#)).

**TABLE 2-1. Key features of G protein subunits**

<b>G protein class</b>	<b>Members</b>	<b>Effector(s)/functions</b>	<b>Examples of receptors</b>
$\alpha_i$	$G\alpha_{i1-3}$ , $G\alpha_o$	AC (+)	$\alpha_2$ , $D_2$ , $A_1$ , $\mu$ , $M_2$ , $5-HT_{1A}$
		Ligand-type $Ca^{2+}$ channels (+)	Olfactory signals
	$G\alpha_z$ , $G\alpha_{t1-2}$	K <sup>+</sup> channels (+)	
		$Ca^{2+}$ channels (–) <sup>a</sup> cGMP	GABA <sub>B</sub> Retinal rods, cones (rhodopsins)
		Phosphodiesterase (+) ( $G\alpha_{t1-2}$ )	
$\alpha_q$	$G\alpha_q$ , $G\alpha_{11}$ , $G\alpha_{14}$ , $G\alpha_{15}$ , $G\alpha_{16}$	PLC- $\beta$ (+)	TxA <sub>2</sub> , $5-HT_{2C}$ , $M_1$ , $M_3$ , $M_5$ , $\alpha_1$
$\alpha_{12}$	$G\alpha_{12}$ , $G\alpha_{13}$	RGS domain-containing rho exchange factors	TxA <sub>2</sub> , thrombin

**G****protein****class****Members****Effector(s)/functions****Examples of****receptors**

$\beta_b$	$\beta (\times 5)$	AC type I (–); AC types II, IV (potentiation) PLC (+) Receptor kinases (+) Inactivates $\alpha_s$
$\gamma$	$\gamma (\times 12)$	$\beta \gamma$ subunits required for interaction of $\alpha$ subunit with receptor

*Note.* AC=adenylyl cyclase;  $A_1$ ,  $A_2$ =adenosine receptor subtypes;  $\beta_1$ ,  $\alpha_1$ ,  $\alpha_2$ =adrenergic receptor subtypes; cGMP=cyclic guanosine monophosphate;  $D_1$ ,  $D_2$ =dopamine receptor subtypes;  $G\alpha_o$ =olfactory, but also found in limbic areas;  $G\alpha_t$ =transducin;  $GABA_B$ = $\gamma$ -amino-butyric acid receptor subtype;  $5-HT_{1A}$ ,  $5-HT_{2C}$ =serotonin receptor subtypes;  $M_1$ ,  $M_2$ ,  $M_3$ ,  $M_5$ =muscarinic receptor subtypes;  $\mu$ =opioid  $\mu$  receptor; PLC=phospholipase C; RGS=regulators of G protein signaling;  $TxA_2$ =thromboxane  $A_2$  receptor.

<sup>a</sup>Although regulation of  $Na^+/H^+$  exchange and  $Ca^{2+}$  channels by  $G\alpha_{1-2}$  and  $G\alpha_{1-3}$  has been demonstrated in artificial systems in vitro, these findings await definitive confirmation.

<sup>b</sup>Effectors are regulated by  $\beta \gamma$  subunits as a dimer.

The 5-HT<sub>1C</sub> receptors have structural and transductional similarities to the 5-HT<sub>2</sub> receptor class ([Hoyer et al. 1986](#)).

**5-HT<sub>2</sub> receptors.** The three subtypes of 5-HT<sub>2</sub> receptors are 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub>. The highest level of 5-HT<sub>2A</sub> binding sites and mRNA for these receptors exists in the cortex, and these receptors have been implicated in the psychotomimetic effects of agents such as lysergic acid diethylamide, as reviewed by [Aghajanian and Marek \(1999\)](#). In addition, lesioning serotonin neurons with 5,7-DHT does not reduce the 5-HT<sub>2</sub> receptor density reported in brain regions ([Hoyer et al. 1986](#)), indicating that these receptors are primarily (if not exclusively) postsynaptic. Autoradiography performed with the potent and selective radioligand [<sup>3</sup>H]MDL 100,907 has localized 5-HT<sub>2A</sub> receptors to many similar brain regions in the rat and primate brain ([López-Giménez et al. 1997](#)). Hallucinogenesis is likely a result of cortical 5-HT<sub>2A</sub> receptor activation, because experiments in mice expressing 5-HT<sub>2A</sub> receptors in the cortex only incur receptor signaling and behavior changes to hallucinogenic drugs similar to that of genetically unaltered mice ([González-Maeso et al. 2007](#)). Competition studies with other radioligands ([Westphal and Sanders-Bush 1994](#)) and their mRNA distribution indicate that 5-HT<sub>2C</sub> receptors are considerably widespread throughout the CNS, with the highest density in the choroid plexus ([Hoffman and Mezey 1989](#)). 5-HT<sub>2B</sub> receptors are detected sparingly in the brain and are more prominently located in the fundus, gut, kidney, lungs, and heart ([Hoyer et al. 1986](#)).

Evidence from animal experiments in which cortical 5-HT<sub>2A</sub> receptors are disrupted indicates a specific role of

these receptors in modulation of conflict anxiety without affecting fear conditioning and depression-like behaviors (Weisstaub et al. 2006). Furthermore, chronic administration of many antidepressants downregulates 5-HT<sub>2</sub> receptors, suggesting that this effect may be important for their efficacy (Scott and Crews 1986). However, chronic electroconvulsive shock appears to upregulate 5-HT<sub>2</sub> expression, precluding a simple mechanism for antidepressant efficacy. The obesity seen in 5-HT<sub>2C</sub> knockout animals suggests that in addition to histamine receptor blockade, 5-HT<sub>2C</sub> receptor blockade may play a role in the weight gain observed with certain psychotropic agents; this is an area of considerable research. In keeping, evidence suggests that the weight gain “orexigenic” properties of atypical antipsychotics are likely due to potent activation of hypothalamic AMP-kinase through histamine type 1 (H<sub>1</sub>) receptors (Kim et al. 2007). Aggressive and impulsive behaviors are also linked to the serotonin system, in which a neuropeptide Y (NPY) and serotonin interaction from studies in NPY knockout mice detected circuits responsible for aggressive behavior linked to feeding (Emeson and Morabito 2005). The regulation of 5-HT<sub>2</sub> receptors is intriguing, as not only is it important in psychiatric disorders and therapeutic benefit, but also both agonists and antagonists appear to cause an internalization of the receptor. Moreover, data suggest that mRNA editing may play an important role in regulating the levels and activity of this receptor subtype (Niswender et al. 1998). All of the 5-HT<sub>2</sub> receptor subtypes are linked to the phosphoinositide signaling system, and their activation produces IP<sub>3</sub> and diacylglycerol (DAG), via PLC activation (Conn and Sanders-Bush 1987) (see Figure 2-3B).

A pharmacogenetic study searched for genetic predictors of treatment outcome in 1,953 patients with MDD who received the antidepressant citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study and were prospectively assessed ([McMahon et al. 2006](#)). In a split-sample design, a selection of 68 candidate genes was genotyped with 768 single-nucleotide-polymorphism markers chosen to detect common genetic variation. A significant and reproducible association was found between treatment outcome and a marker in *HTR2A* ( $P=1\times 10^{-6}$  to  $3.7\times 10^{-5}$  in the total sample). The “A” allele (associated with better outcome) was six times more frequent in white than in black participants, for whom treatment was also less effective in this sample ([McMahon et al. 2006](#)). The A allele thus may contribute to racial differences in outcomes of antidepressant treatment. Taken together with prior neurobiological findings, these genetic data make a compelling case for a key role of *HTR2A* in the mechanism of antidepressant action.

A leading hypothesis for the mechanism of action of atypical antipsychotic agents suggests that the ratio of D<sub>2</sub>-to-5-HT<sub>2</sub> blockade confers “atypicality” properties of many currently available antipsychotic agents ([Meltzer 2002](#)). Several antidepressants (e.g., mianserin, mirtazapine) and atypical antipsychotics (e.g., clozapine, risperidone, olanzapine) are antagonists of 5-HT<sub>2A</sub> receptors, raising the possibility that blockade of 5-HT<sub>2</sub> receptors may play an important role in the therapeutic efficacy of these agents ([Nestler et al. 2015](#)). Studies comparing the various compounds and the state of 5-HT<sub>2A/2C</sub> receptors based on psychiatric phenotype would be enhanced by the development of a highly specific PET ligand, [<sup>18</sup>F]FECIMBI-



36, which was confirmed in postmortem human brain tissue sections to bind at high levels to the prefrontal cortex (PFC), temporal cortex, and hippocampus for 5-HT<sub>2A</sub> receptors and to the choroid plexus for 5-HT<sub>2C</sub> receptors (Prabhakaran et al. 2015).

5-HT<sub>2C</sub> receptors are expressed on pro-opiomelanocortin (POMC) neurons of the arcuate nucleus of the hypothalamus (Nestler et al. 2015). The selective 5-HT<sub>2C</sub> receptor agonist lorcaserin is used for the treatment of obesity (Nestler et al. 2015). Many second-generation antipsychotic drugs cause weight gain through 5-HT<sub>2C</sub> receptor antagonism (Nestler et al. 2015).

**5-HT<sub>3-7</sub> receptors.** Unlike the other serotonin receptors, 5-HT<sub>3</sub> receptors are ligand-gated ion channels capable of mediating fast synaptic responses, although the opening of the channel is relatively slower compared with other ligand-gated ion channels (see Figure 2-3B) (Squire 2013; Yun and Rhim 2011). The *cis-trans* isomerization and molecular rearrangement at proline 8 is the structural mechanism that opens the 5-HT<sub>3</sub> receptor protein pore (Lummis et al. 2005). 5-HT<sub>3</sub> receptors are present in multiple brain areas, including the hippocampus, dorsal motor nucleus of the solitary tract, and area postrema (Laporte et al. 1992). The 5-HT<sub>3</sub> receptor, located mostly in the peripheral nervous system, is effectively modulated by a variety of compounds, such as alcohols and anesthetics, and antagonists of this receptor are used as effective antiemetics in patients who are undergoing chemotherapy (e.g., ondansetron) (Squire 2013).

5-HT<sub>4</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> are GPCRs that are preferentially coupled to G<sub>s</sub> and activate adenylyl cyclases

(see [Figure 2-3B](#)). 5-HT<sub>4</sub> receptors are able to modulate the release of monoamines and GABA in the brain, appear to improve memory and learning in mice, and mediate pituitary prolactin release in the presence of estrogen ([Darcet et al. 2016](#); [Papageorgiou and Denef 2007](#)). 5-HT<sub>4</sub> receptor subtypes include 5-HT<sub>4A</sub>, 5-HT<sub>4B</sub>, 5-HT<sub>4C</sub>, 5-HT<sub>4D</sub>, 5-HT<sub>4E</sub>, 5-HT<sub>4F</sub>, 5-HT<sub>4G</sub>, 5-HT<sub>4H</sub>, and 5-HT<sub>4HB</sub> ([Yun and Rhim 2011](#)). 5-HT<sub>5</sub> receptors are located in the hypothalamus, hippocampus, corpus callosum, fibra, cerebral ventricles, and glia ([Hoyer et al. 2002](#)). The 5-HT<sub>5A</sub> receptor is negatively coupled to adenylyl cyclase, whereas the 5-HT<sub>5B</sub> receptor is not functional because of stop codons ([Grailhe et al. 2001](#)). 5-HT<sub>6</sub> receptors are located in the striatum, amygdala, nucleus accumbens, hippocampus, cortex, and olfactory tubercle ([Hoyer et al. 2002](#)). Of interest, many antipsychotic agents and antidepressants are high-affinity antagonists of 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors, and 5-HT<sub>6</sub> receptor antagonism is being specifically investigated for its ability to improve cognition in patients with Alzheimer's disease ([Parker et al. 2015](#); [Roth et al. 1994](#); [Yun and Rhim 2011](#)). 5-HT<sub>7</sub> receptors, made up of subtypes 5-HT<sub>7A</sub>, 5-HT<sub>7B</sub>, 5-HT<sub>7C</sub>, and 5-HT<sub>7D</sub>, have been localized to the cerebral cortex, medial thalamic nuclei, substantia nigra, central gray, and dorsal raphe nucleus ([Hoyer et al. 2002](#); [Yun and Rhim 2011](#)). Chronic treatment with antidepressants downregulates 5-HT<sub>7</sub> receptors, whereas acute stress has been reported to increase 5-HT<sub>7</sub> expression ([Sleight et al. 1995](#); [Yau et al. 2001](#)). Lurasidone and vortioxetine, agents used to treat schizophrenia and depression, respectively, are also nonselective 5-HT<sub>7</sub> receptor antagonists that work through increased AMPA-

mediated neurotransmission ([Andreetta et al. 2016](#); [Fountoulakis et al. 2015](#); [Sanchez et al. 2015](#)).

In the future, the subtle differences between the different serotonin receptors and their subtypes will be elucidated as specific PET ligands, genotype-phenotype correlations, and receptor-selective medications are developed ([Kumar and Mann 2014](#)).

## Dopaminergic System

Dopamine was originally thought to be simply a precursor of norepinephrine and epinephrine synthesis, but the demonstration that its distribution in the brain was quite distinct from that of norepinephrine led to extensive research establishing its role as a critical, unique neurotransmitter. Dopamine synthesis requires transport of the amino acid L-tyrosine across the blood-brain barrier and into the cell. Once tyrosine enters the neuron, the rate-limiting step for dopamine synthesis is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase; L-dopa is readily converted to dopamine and, hence, is used as a precursor strategy to correct a dopamine deficiency in the treatment of Parkinson's disease ([Figure 2-4B](#)). The activity of tyrosine hydroxylase can be regulated by many factors, including the activity of catecholamine neurons; furthermore, catecholamines function as end-product inhibitors of tyrosine hydroxylase by competing with a tetrahydrobiopterin cofactor ([Cooper et al. 2003](#)).

In contrast to the widespread serotonin and norepinephrine projections, dopamine neurons form more discrete circuits, with the nigrostriatal, mesolimbic,

tuberoinfundibular, and tuberohypophysial pathways constituting the major CNS dopaminergic circuits ([Figure 2-4A](#)). The nigrostriatal circuit is composed of dopamine neurons from the mesencephalic reticular formation (region A8) and the pars compacta region of the substantia nigra (region A9) of the mesencephalon. These neurons give rise to axons that travel via the medial forebrain bundle to innervate the caudate nucleus and putamen ([Andén et al. 1964](#); [Ungerstedt 1971](#)). The dopamine neurons that make up the nigrostriatal circuit have been assumed to be critical for maintaining normal motor control, because destruction of these neurons is associated with Parkinson's disease; however, it is now clear that these projections subserve a variety of additional functions. For instance, evidence from human brain imaging studies indicates that drugs that modulate striatal dopamine receptor activation correlate with the subject's ability to choose gradations of rewarding actions during instrumental learning tasks. This further implies that the dopamine reward pathway in the brain is likely convergent on many discrete brain circuits and neurotransmitter alterations and shows that striatal activity can also account for how the human brain proceeds toward making future decisions based on reward prediction ([Pessiglione et al. 2006](#)).

The mesolimbic dopamine circuit consists of dopamine neurons located in the midbrain just medial to the A9 cells in an area termed the *ventral tegmental area* (VTA) ([Cooper et al. 2003](#); [Nestler et al. 2015](#); [Squire 2013](#)). This circuit shares some similarities to the nigrostriatal circuit in that it is a parallel circuit consisting of axons that make up the medial forebrain bundle. However, these axons ascend through the lateral hypothalamus and project to the nucleus accumbens; olfactory tubercle; bed nucleus of the

stria terminalis; lateral septum; and frontal, cingulate, and entorhinal regions of the cerebral cortex ([Cooper et al. 2003](#)). This circuit innervates many limbic structures known to play critical roles in motivational, motor, and reward pathways and has therefore been implicated in a variety of clinical conditions, including psychosis and drug abuse ([Cooper et al. 2003](#)). Data also suggest a potential role of dopamine—and, in particular, mesolimbic pathways—in the pathophysiology of bipolar mania, as well as bipolar and unipolar depression ([Beaulieu et al. 2004](#); [Dunlop and Nemeroff 2007](#); [Goodwin et al. 2007](#); [Roybal et al. 2007](#)). It is perhaps surprising that the role of the dopaminergic system in the pathophysiology of mood disorders has not received greater study, because it represents a prime candidate on several theoretical grounds. The motoric changes in bipolar disorder are perhaps the most defining characteristics of the illness, ranging from near catatonic immobility to the hyperactivity of manic states. Similarly, loss of motivation is one of the central features of depression, whereas anhedonia and “hyperhedonic states” are among the most defining characteristics of bipolar depression and mania, respectively. In this context, it is noteworthy that the midbrain dopaminergic system is known to play a critical role in regulating not only motoric activity but also motivational and reward circuits. It is clear that motivation and motor function are closely linked and that motivational variables can influence motor output both qualitatively and quantitatively. Furthermore, considerable evidence indicates that the mesolimbic dopaminergic pathway plays a crucial role in the selection and orchestration of goal-directed behaviors, particularly those elicited by incentive stimuli ([Goodwin et al. 2007](#)).

The firing pattern of mesolimbic dopamine neurons appears to be an important regulatory mechanism; thus, in rats, electrical or glutamatergic stimulation of medial PFC elicits a burst firing pattern of dopaminergic cells in the VTA and increases dopamine release in the nucleus accumbens (Murase et al. 1993; Taber and Fibiger 1993). The burst firing of dopamine cell activity elicits more terminal dopamine release per action potential than the nonbursting, pacemaker firing pattern (Roth et al. 1987). The phasic, burst firing of dopamine neurons and accompanying rise in dopamine release normally occur in response to primary rewards (until they become fully predicted) and reward-predicting stimuli. Such a role also has been postulated to provide a neural mechanism by which PFC dysfunction could alter hedonic perceptions and motivated behavior in mood disorders (Drevets et al. 2002). Studies indicate that the amygdala has importance in the learning of new cocaine drug-seeking responses and its habit-forming properties (Lee et al. 2005). The supraphysiological levels of dopamine induced by cocaine and other drugs of abuse lead to powerful reinforcement of drug-seeking behavior, by co-opting the dopamine reward circuit of the brain, as reviewed elsewhere (Volkow and Morales 2015).

## Dopamine Transporters

As with serotonin, the dopamine signal in the synaptic cleft is terminated primarily by reuptake into the presynaptic terminal. The DAT comprises 12 transmembrane domains and is located somatodendritically as well as on dopamine nerve terminals (see Figure 2-4B). Like other monoamine transporters, the DAT functions as a Na<sup>+</sup>/K<sup>+</sup> pump to clear dopamine from the synaptic cleft on its release. However,

data suggest that many drugs of abuse are capable of altering the function of these transporters. Thus, the amphetamines are thought to mediate their effects, in part, by reversing the direction of the transporter so that it *releases* dopamine. Cocaine is capable of blocking the reuptake of DAT, leading to an increase in dopamine in the synaptic cleft. Of interest, altered neuronal long-term potentiation in the VTA in response to chronic cocaine exposure has been linked to drug-associated memory and likely contributes to the powerful addictive potential of this drug of abuse ([Liu et al. 2005](#)). Dopamine in the medial frontal cortex is taken up predominantly by the norepinephrine transporter, which goes against the dogma of transporters being able to selectively take up only their respective neurotransmitter. Furthermore, this provides a mechanism by which norepinephrine reuptake-inhibiting antidepressants also may increase synaptic levels of dopamine in the frontal cortex, an effect that may be therapeutically very important. Interestingly, a meta-analysis of single photon emission computed tomography (SPECT) scans examining the DAT gene *SLC6A3* variable-number tandem repeat (VNTR) polymorphism did not find significant changes in the levels of the dopamine transporters in the brains of patients with schizophrenia, attention-deficit/hyperactivity disorder (ADHD), and even Parkinson's disease ([Costa et al. 2011](#)). However, another DAT polymorphism of note, a VNTR in the nontranslated 3' end of exon 15, causes a 25% decreased density of DAT in humans with a VNTR of 9 repeats instead of the more common 10 repeats ([Lacerda-Pinheiro et al. 2014](#)). SPECT scanning of the brain with the presynaptic DAT radioligand is now being used to distinguish Parkinson's disease syndromes from other causes of parkinsonism such as

antipsychotic-induced parkinsonism, the latter of which does not show a deficit in DAT binding in the caudate and putamen ([Tatsch and Poepperl 2013](#)).

In patients with MDD and bipolar disorder, SPECT studies showed that DAT availability is higher—and, by inference, synaptic dopamine is lower—in patients with depression ([Camardese et al. 2014a, 2014b](#)). PET studies identified decreased binding potential of the DAT PET ligand to the dopamine transporter in the striatum in MDD patients and more specifically in the caudate in bipolar patients ([Anand et al. 2011](#); [Meyer et al. 2001](#); [Savitz and Drevets 2013](#)). Postmortem studies in patients with MDD showed lower DAT levels in the amygdala and higher D<sub>2</sub> and D<sub>3</sub> receptor levels (no change in D<sub>1</sub> receptors), consistent with similar observations in rats with dopamine depletion ([Klimek et al. 2002](#)).

To treat refractory depression, the new triple transporter reuptake inhibitor compound BMS-820836, reported by PET studies to specifically inhibit monoamine transporters DAT, SERT, and NET, was developed for the goal of increasing synaptic levels of the respective monoamines dopamine, serotonin, and norepinephrine and thereby decreasing depressive symptoms ([Risinger et al. 2014](#)). Moderate to severe MDD or atypical MDD (with reversed neurovegetative symptoms) was found by PET studies to be associated with higher levels of MAO-A, an enzyme that catabolizes and thus decreases synaptic dopamine, serotonin, and norepinephrine, presumably increasing depressive symptoms ([Chiuccariello et al. 2014](#)). Classic MAOIs increase all three monoamines in the synapse by blocking the catabolizing enzyme MAO (both A and B enzyme subtypes).



Bupropion is widely believed to increase synaptic dopamine by blocking the DAT-mediated reuptake, but a PET study showed that it has at most only 22% occupancy of the DAT ([Meyer et al. 2002](#)). Given the observation of a decreased binding potential of 15% of DAT in patients with MDD, it remains unknown whether bupropion occupies the same binding site on DAT as the PET ligand, whether 22% occupancy of DAT is sufficient for bupropion to work (as compared with 80% binding to SERT for SSRIs), and whether bupropion works by another uncharacterized mechanism to achieve its antidepressant properties ([Meyer et al. 2001, 2002](#)).

## Dopaminergic Receptors

The existence of two subtypes of dopamine receptors, D<sub>1</sub> and D<sub>2</sub>, was initially established with classic pharmacological techniques in the 1970s ([Stoof and Kebabian 1984](#)). Subsequent molecular biological studies have shown that the D<sub>1</sub> family contains both the D<sub>1</sub> and the D<sub>5</sub> receptors, whereas the D<sub>2</sub> family contains the D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors ([Cooper et al. 2003](#)). D<sub>1</sub> receptor family members were originally defined solely on the ability to stimulate adenylyl cyclase, whereas the D<sub>2</sub> family inhibited the enzyme. Interestingly, dopamine receptors complexed with subunits from other subclasses of dopamine receptors within a receptor family are able to form distinct hetero-oligomeric receptors also termed *kissing cousin receptors*. Notably, hetero-oligomeric D<sub>1</sub>-D<sub>2</sub> receptor complexes in the brain require binding to active sites of both receptor subtypes to induce activation of the hetero-oligomeric receptor complex. These receptors have been shown to use traditional D<sub>1</sub> receptor intracellular signaling components

of  $G_{q/11}$  and  $Ca^{2+}$ /calmodulin-dependent protein kinase II (CaMKII) second-messenger activation as seen in the nucleus accumbens ([Rashid et al. 2007](#)). This opens up possibilities for the brain to use different receptor subunit proportions to further fine-tune brain neurophysiology. Similar to the *DAT* exon 15 VNTR, the  $D_2$  dopamine receptor gene (*DRD2*) has a TaqIA polymorphism (allele A1+) in the 3' nontranslated region that reduces  $D_2$  receptor density ([Lacerda-Pinheiro et al. 2014](#)).

**$D_1$  and  $D_5$  receptors.** The  $D_1$  and  $D_5$  receptors stimulate adenylyl cyclase activity via the activation of  $G_s$  or  $G_{olf}$  (a G protein originally thought to be present exclusively in olfactory tissue but now known to be abundantly present in limbic areas) (see [Figure 2-4B](#)). Other second-messenger pathways also have been reported to be activated by  $D_1$  receptors, an effect that may play a role in the reported  $D_1$ - $D_2$  cross-talk ([Clark and White 1987](#)). The frontal cortex contains almost exclusively  $D_1$  receptors ([Clark and White 1987](#)), suggesting that this receptor may play an important role in higher cognitive function and perhaps in the actions of medications such as methylphenidate. A  $D_1/D_5$  receptor agonist, dihydrexidine, has been developed and tested for its ability to improve cognition and working memory in patients with schizophrenia but was prematurely terminated because of hypotension and potentially increased seizure risk ([Arnsten et al. 2017](#)). Although the  $D_5$  receptor is a neuron-specific receptor located primarily in limbic areas of the brain, no compounds have been developed so far that pharmacologically distinguish it from the homologous  $D_1$  receptor ([Arnsten et al. 2017](#)). Drugs

such as cocaine and methylphenidate cause peak dopamine activation of D<sub>1</sub> receptors on striatal GABAergic medium spiny neurons, which plays a key role in the direct striatal pathway mediating expectations of reward ([Volkow and Morales 2015](#)).

**D<sub>2</sub> receptors.** Four types of D<sub>2</sub> receptors have been identified: two subtypes of D<sub>2</sub> receptors (the short and long splice variants, D<sub>2S</sub> and D<sub>2L</sub>, respectively) and D<sub>3</sub> and D<sub>4</sub> receptors. Although a seemingly identical pharmacological profile for these receptors exists, there are undoubtedly physiological differences between the two subtypes. D<sub>2</sub> receptors mediate their cellular effects via the G<sub>i</sub>/G<sub>o</sub> proteins and thereby several effectors (see [Figure 2-4B](#)). In addition to the well-characterized inhibition of adenylyl cyclase, D<sub>2</sub> receptors in different brain areas also regulate PLC, bring changes in K<sup>+</sup> and Ca<sup>2+</sup> currents, and possibly regulate phospholipase A<sub>2</sub>. D<sub>2</sub> receptors are located on cell bodies and nerve terminals of dopamine neurons and function as autoreceptors. Thus, activation of somatodendritic D<sub>2</sub> receptors reduces dopamine neuron firing activity, likely via the opening of K<sup>+</sup> channels, whereas activation of nerve-terminal D<sub>2</sub> autoreceptors reduces the amount of dopamine released per nerve impulse, in large part by closing voltage-gated Ca<sup>2+</sup> channels. As discussed extensively elsewhere in this volume (see [Chapter 24, “Classic Antipsychotic Medications,” by Nasrallah and Tandon](#)), D<sub>2</sub> receptors have long been implicated in the pathophysiology and treatment of schizophrenia. In one study, transgenic mice overexpressing D<sub>2</sub> receptors in the striatum had many

phenotypic hallmarks of schizophrenia ([Kellendonk et al. 2006](#)). However, the potential role of D<sub>2</sub> receptors in contributing to depression is a comparatively more recent recognition, confirmed by the observation that D<sub>2</sub> receptor binding is increased by PET ligand [<sup>11</sup>C]raclopride in the putamen of patients with MDD and psychomotor retardation, reflecting decreased dopamine levels in the synapse ([Meyer et al. 2006](#)).

The typical antipsychotics are generally defined by their high-affinity antagonism or blockade of the D<sub>2</sub> receptor, which substantially prevents synaptic dopamine from activating the postsynaptic receptor but also has a significant risk for extrapyramidal side effects (EPS) such as dystonia and akathisia in the short term and parkinsonism and tardive dyskinesia in the longer term (see [Figure 2-4B](#)). Medications with high anticholinergic properties, such as diphenhydramine and benztropine, are frequently used to avoid development of EPS, but tardive dyskinesia can develop nevertheless after many years of antipsychotic exposure. Cocaine and methylphenidate stimulation of D<sub>2</sub> receptors in the indirect, inhibitory striatal pathway, which mediates punishment, leads to sustained motivation to procure these drugs in the future ([Volkow and Morales 2015](#)).

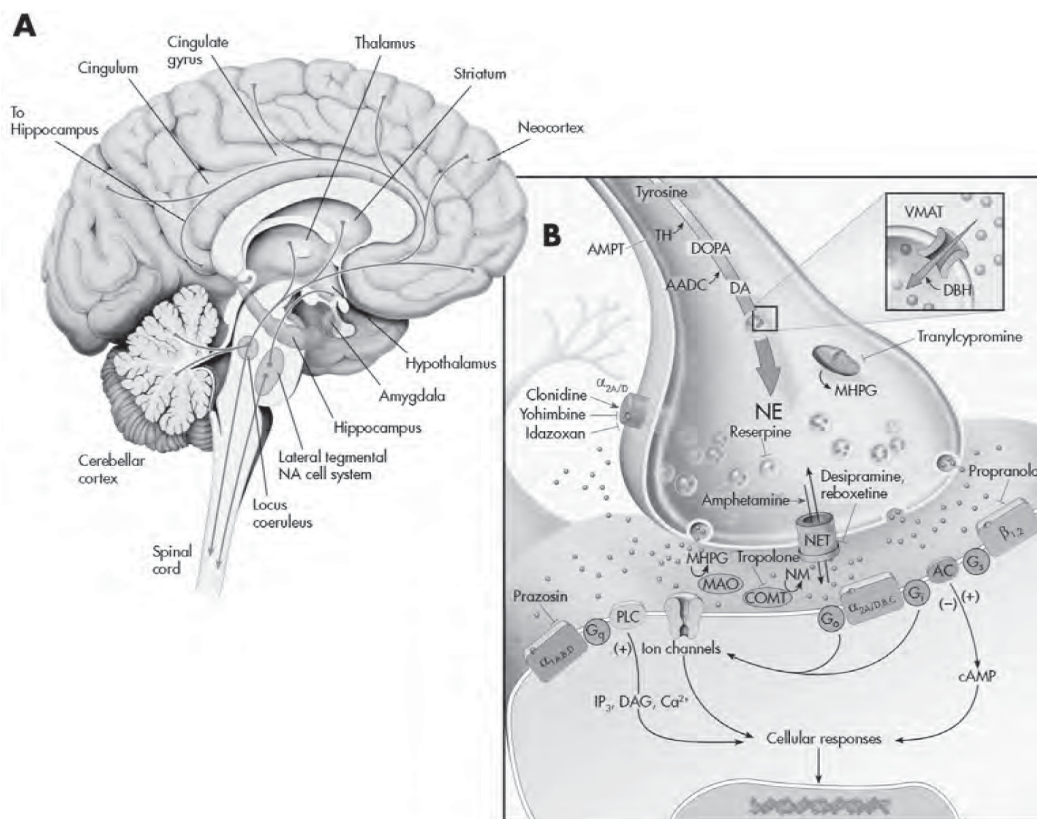
**D<sub>3</sub> receptors.** D<sub>3</sub> receptors possess a different anatomical distribution than D<sub>2</sub> receptors and, because of their preferential limbic expression, have been postulated to represent an important target for antipsychotic drugs. Numerous studies have investigated the position association of a polymorphism in the coding sequence of the D<sub>3</sub> receptor with schizophrenia, with equivocal results. It

has been suggested that brain-derived neurotrophic factor (BDNF) may regulate behavioral sensitization via its effects on D<sub>3</sub> receptor expression ([Guillin et al. 2001](#)). Cariprazine, an antipsychotic with possible efficacy in treating acute mania, has antagonist/partial agonist binding to D<sub>2</sub> and D<sub>3</sub> receptors, with a much higher affinity for D<sub>3</sub> receptors compared with other antipsychotics, but it still has significant D<sub>2</sub>-related EPS ([Altinbaş et al. 2013](#)). Bupropion, a 5-HT<sub>1a</sub> receptor partial agonist, also has D<sub>3</sub>/D<sub>4</sub> receptor antagonist activity, so it is being considered for treating methamphetamine and cocaine dependence, given the observation of increased brain D<sub>3</sub> receptors by PET studies in addicted individuals and the attenuation of self-administration in animals given D<sub>3</sub> receptor antagonists ([Paterson et al. 2014](#)).

**D<sub>4</sub> receptors.** The D<sub>4</sub> receptor has received much interest in psychopharmacological research because of the fact that clozapine has a high affinity for this receptor. More selective D<sub>4</sub> antagonists are being explored as adjunctive agents in the treatment of schizophrenia. Furthermore, considerable attention has focused on the possibility that genetic D<sub>4</sub> variants may be associated with thrill-seeking behavior ([Zuckerman 1985](#)), ADHD ([Roman et al. 2001](#)), and responsiveness to clozapine ([Van Tol et al. 1992](#)). A potent, selective antagonist of the D<sub>4</sub> receptor called ML398 has been developed that is still being investigated ([Berry et al. 2014](#)).

## Noradrenergic System

Named *sympathine* because it was initially encountered as being released by sympathetic nerve terminals, the molecule was later given the name *norepinephrine* after meeting the criteria for a neurotransmitter in the CNS (Cooper et al. 2003). Norepinephrine is produced from the amino acid precursor L-tyrosine found in neurons in the brain, chromaffin cells, sympathetic nerves, and ganglia. The enzyme dopamine  $\beta$ -hydroxylase converts dopamine to norepinephrine, and as is the case for dopamine synthesis, tyrosine hydroxylase is the rate-limiting enzyme for norepinephrine synthesis (Figure 2-5B). The dietary depletion of tyrosine and  $\alpha$ -methyl-*p*-tyrosine (a tyrosine hydroxylase inhibitor) has played an important part in efforts aimed at delineating the role of catecholamines in the pathophysiology and treatment of mood and anxiety disorders (Coupland et al. 2001; McCann et al. 1995).



---

## FIGURE 2-5. The noradrenergic system.

*See Plate 8 to view this figure in color.*

This figure depicts the noradrenergic projections throughout the brain **(A)** and the various regulatory processes involved in norepinephrine (NE) neurotransmission **(B)**. NE neurons innervate nearly all parts of the neuroaxis, with neurons in the locus coeruleus being responsible for most of the NE in the brain (90% of NE in the forebrain and 70% of total NE in the brain). The amino acid L-tyrosine is actively transported into presynaptic NE nerve terminals, where it is ultimately converted into NE. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase (TH).  $\alpha$ -Methyl-*p*-tyrosine (AMPT) is a competitive inhibitor of tyrosine hydroxylase and has been used to assess the impact of reduced catecholaminergic function in clinical studies. Aromatic amino acid decarboxylase (AADC) converts L-dopa to dopamine (DA). L-dopa then becomes decarboxylated by decarboxylase to form DA. DA is then taken up from the cytoplasm into vesicles, by vesicular monoamine transporters (VMATs), and hydroxylated by dopamine  $\beta$ -hydroxylase (DBH) in the presence of O<sub>2</sub> and ascorbate to form NE. Normetanephrine (NM), which is formed by the action of catechol-*O*-methyltransferase (COMT) on NE, can be further metabolized by monoamine oxidase (MAO) and aldehyde reductase to 3-methoxy-4-hydroxyphenylglycol (MHPG). Reserpine causes a depletion of NE in vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported with this hypertension). Once released from the presynaptic terminal, NE can interact with a variety of presynaptic and postsynaptic receptors. Presynaptic regulation of NE neuron firing activity and release occurs through somatodendritic (not shown) and nerve-terminal  $\alpha_2$  adrenoreceptors, respectively. Yohimbine potentiates NE neuronal firing and NE release by blocking these  $\alpha_2$  adrenoreceptors,



thereby disinhibiting these neurons from a negative feedback influence. Conversely, clonidine attenuates NE neuron firing and release by activating these receptors. Idazoxan is a relatively selective  $\alpha_2$  adrenoreceptor antagonist primarily used for pharmacological purposes. The binding of NE to G protein receptors ( $G_o$ ,  $G_i$ , etc.) that are coupled to adenylyl cyclase (AC) and phospholipase C- $\beta$  (PLC- $\beta$ ) produces a cascade of second-messenger and cellular effects (see diagram and later sections of the text). NE has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron via NE transporters (NETs). Once inside the neuron, it can either be repackaged into vesicles for reuse or undergo enzymatic degradation. The selective NE reuptake inhibitor and antidepressant reboxetine and older-generation tricyclic antidepressant desipramine are able to interfere/block the reuptake of NE. On the other hand, amphetamine is able to facilitate NE release by altering NET function. Green spheres represent DA neurotransmitters; blue spheres represent NE neurotransmitters. cAMP=cyclic adenosine monophosphate; DAG=diacylglycerol; DOPA=dihydroxyphenylalanine;  $IP_3$ =inositol-1,4,5-triphosphate; NA=nucleus accumbens.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Modified from Nestler et al. 2001.

The mammalian CNS has seven norepinephrine cell groups, designated A1 through A7. In the brain stem, these are the lateral tegmental neurons (A5 and A7) and the locus coeruleus neurons (A6) ([Dahlström 1971](#)) (see [Figure 2-5B](#)). In general, the projections from A5 and A7 are more



restricted to brain stem areas and do not interact with those of A6. The term *locus coeruleus* (LC) was derived from the Greek because of its saddle shape and its “blueish color” (*caeruleum*). The LC is the most widely projecting CNS nucleus known (Foote et al. 1983), responsible for approximately 90% of the norepinephrine innervation of the forebrain and 70% of the total norepinephrine in the brain (Figure 2-5A). Indeed, the LC norepinephrine neurons, although small in number, constitute a diffuse system of projections to widespread brain areas via highly branched axons. The extensive efferent innervation suggests that the LC plays a modulatory and integrative role rather than a role in specific sensory or motor processing (Foote et al. 1983).

Several physiological roles have been ascribed to the LC, notably in the control of vigilance and the initiation of adaptive behavioral responses (Foote et al. 1983). Considerable data support the hypothesis that norepinephrine neurons in the LC constitute a CNS response or defense system, because the neurons are activated by “challenges” in both the behavioral/environmental and the physiological domains (Jacobs et al. 1991). Thus, various sensory stimuli are capable of increasing LC activity, but noxious or stressful stimuli are particularly potent in this regard. Moreover, considerable evidence also supports a role for LC norepinephrine neurons in the learning of aversively motivated tasks and in the conditioned response to stressful stimuli (Rasmussen and Jacobs 1986; Rasmussen et al. 1986), with obvious implications for a variety of psychiatric conditions (Gould et al. 2002; Szabo and Blier 2001). Indeed, tonic activation of the LC occurs preferentially in the response to stressful stimuli, in contrast to stimuli

limited to simply evoking activation or arousal ([Rasmussen and Jacobs 1986](#); [Rasmussen et al. 1986](#)). Preclinical studies have found increased sensitivity of the LC norepinephrine system in females compared with males, which may help explain the increased incidence of posttraumatic stress disorder (PTSD) and depression in human females ([Bangasser et al. 2016](#)). Of note, the LC also releases neuropeptides such as galanin, NPY, cocaine- and amphetamine-related transcript, and BDNF; galanin specifically co-localizes with norepinephrine in LC neurons as they project to the PFC, hippocampus, and VTA and mediate stress responses and addictive behaviors ([Weinshenker and Holmes 2016](#)). Increased norepinephrine and activation of the LC may be involved in both fear and anger responses, and excessive anger may be a “vent” for fear of the unexpected, as suggested in one review ([Gu et al. 2016](#)).

## **Norepinephrine Transporter**

NET, the first of the monoamine transporters to be cloned in humans, transports norepinephrine from the synaptic cleft back into the neuron ([Pacholczyk et al. 1991](#)). Like other monoamine transporters, the NET comprises 12 putative transmembrane domains, and autoradiography with various norepinephrine reuptake inhibitors has been used to determine the brain distribution of NET. A high level of NET is found in the LC, with moderate to high levels found in the dentate gyrus, raphe nuclei, and hippocampus ([Tejani-Butt and Ordway 1992](#); [Tejani-Butt et al. 1990](#)). This pattern of expression is consistent with the norepinephrine innervation to these structures. The NET is expressed mainly on norepinephrine terminals, as shown by a drastic reduction in labeling following norepinephrine destruction

with the neurotoxin 6-hydroxydopamine or *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4) (Tejani-Butt and Ordway 1992; Tejani-Butt et al. 1990).

The NET is dependent on extracellular Na<sup>+</sup> to mediate norepinephrine reuptake and the effectiveness of norepinephrine reuptake inhibitors in inhibiting norepinephrine reuptake (Brüss et al. 1997, 1999; Harder and Bönisch 1985). The uptake of norepinephrine is chloride dependent, meaning that the electrogenic process of norepinephrine transport is Na<sup>+</sup> and Cl<sup>-</sup> driven (Harder and Bönisch 1985). In addition to the electrogenic process, the NET has properties of a channel-like pore, in that it can transport norepinephrine showing an infinite stoichiometry that can be blocked by cocaine and desipramine (Galli et al. 1995, 1996). Several studies suggest that the NET can be regulated by diverse stimuli, neuronal activity, and peptide hormones, as well as protein kinases. Indeed, studies have shown that all monoaminergic transporters (5-HTT, DAT, and NET) are rapidly regulated by direct or receptor-mediated activation of cellular kinases, particularly PKC (Bauman et al. 2000). PKC activation results in an activity-dependent transporter phosphorylation and sequestration. Protein phosphatase-1/2A (PP-1/PP-2A) inhibitors, such as okadaic acid and calyculin A, also promote monoaminergic transporter phosphorylation and functional downregulation (Bauman et al. 2000). These phenomena that occur beyond the receptor level may well be important in the long-term actions of psychotropic drugs known to regulate protein kinases (Chen et al. 1999; Manji and Lenox 1999). Given that norepinephrine neurons co-localize and release orexins, it is of interest that these neuropeptides have been implicated in sleep disorders and hypoglycemia through the glucose-sensing tandem membrane receptor K<sup>+</sup> channels

(K<sub>2P</sub> type) affecting coordinated arousal ([Scott et al. 2006](#)). It is also interesting that enkephalin, an endogenous opioid peptide, co-localizes with NET on the axon terminals of the basolateral amygdala, as indicated by transmission electron microscopy and immunohistochemistry ([Zhang and McDonald 2016](#)). The latest PET radiotracer developed for human brain NET showed high uptake in the LC as well as the raphe nucleus, red nucleus, and thalamus, which could aid in monitoring disease progression of various conditions with NET dysregulation, including Parkinson's disease, Alzheimer's disease, epilepsy, ADHD, depression, and anxiety ([Adhikarla et al. 2016](#)). Atomoxetine, a selective NET inhibitor and the first nonstimulant medication approved for the treatment of ADHD in humans, was found to occupy both the NET and the SERT at clinically relevant doses when tested in rhesus monkeys ([Ding et al. 2014](#)).

## Adrenergic Receptors

The  $\alpha$  and  $\beta$  catecholamine receptors were first discovered more than 50 years ago ([Ahlquist 1948](#)) and were later subdivided further into  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$  adrenoreceptors—all of which are GPCRs—on the basis of molecular cloning and pharmacological and biochemical studies (see [Figure 2-5B](#)). The crystal structures of these receptors were subsequently solved, along with those of other GPCRs, as reviewed elsewhere ([Millar and Newton 2010](#)).

**$\alpha$  Receptors.** The three subtypes of  $\alpha_1$  receptors are denoted 1A, 1B, and 1D; they are all positively coupled to PLC and possibly phospholipase A<sub>2</sub> (see [Figure 2-5B](#)). The  $\alpha_2$  family comprises the 2A/D, 2B, and 2C subtypes, which

couple negatively to adenylyl cyclase and regulate  $K^+$  and  $Ca^{2+}$  channels (see [Figure 2-5B](#)). The 2A, 2B, and 2C adrenoceptors correspond to the human genes *ADRA2A*, *ADRA2B*, and *ADRA2C*, respectively. The bovine, guinea pig, rat, and mouse  $\alpha_{2D}$  adrenoceptor is thought to be a species homologue or variant of the human  $\alpha_{2A}$  adrenoceptor ([Bylund et al. 1994](#)) and is often referred to as  $\alpha_{2A/D}$ . The  $\alpha_2$  receptors represent autoreceptors for norepinephrine neurons, and blockade of these autoreceptors results in increased norepinephrine release—a biochemical effect that has been postulated to play a role in the mechanisms of action of selected antidepressants (e.g., mianserin, mirtazapine) and antipsychotics (e.g., clozapine). In the LC,  $\alpha_2$ -adrenergic receptors converge onto similar  $K^+$  channels as  $\mu$  opioid receptors, and this convergence has been postulated to represent a mechanism for the efficacy of clonidine (an  $\alpha_2$  agonist) in attenuating some of the physical symptoms of opioid withdrawal. In addition, clonidine and another  $\alpha_2$  receptor agonist, guanfacine, have both been approved as nonstimulant medications to treat ADHD ([Chan et al. 2016](#)). The  $\alpha_2$  receptor antagonist yohimbine, which robustly increases norepinephrine neuron firing and norepinephrine release, has been used as a provocative challenge in clinical studies of anxiety disorders and as an antidepressant-potentiating agent. Yohimbine also has been used to explore the role of  $\alpha_2$  adrenoceptors in modulating different types of pain in healthy humans given high-frequency electrical stimulation ([Vo and Drummond 2016](#)).

**$\beta$  Receptors.** The  $\beta$  receptor family comprises  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$  adrenoceptors, which are all positively coupled to

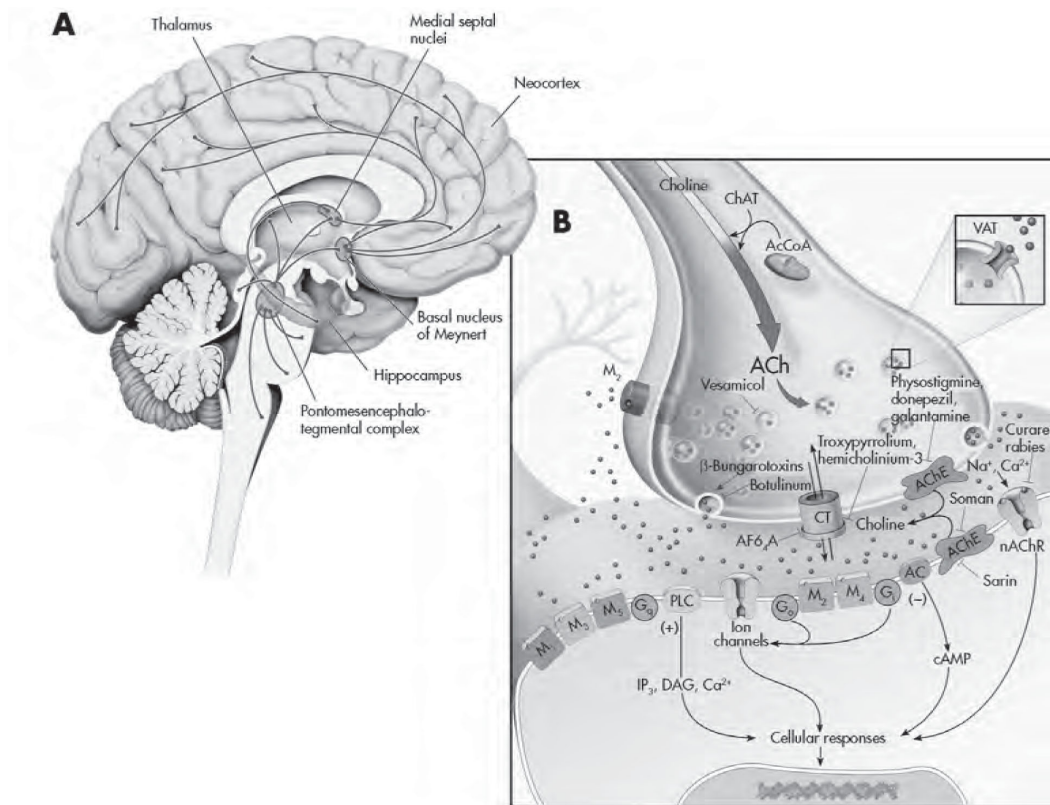
adenylyl cyclase ([Bylund et al. 1994](#)) (see [Figure 2-5B](#)). As is discussed in greater detail in the chapters on antidepressants (see [Chapters 8-23](#)), most effective antidepressants produce a downregulation/desensitization of  $\beta_1$  receptors in rat forebrain, leading to the suggestion that these effects may play a role in their therapeutic efficacy. Interestingly,  $\beta$  receptors also have been shown to play a role in regulating emotional memories, leading to the proposal that  $\beta$  antagonists may have utility in the treatment of PTSD ([Cahill et al. 1994](#); [Przybylski et al. 1999](#)). Propranolol, a combined  $\beta_1$ - $\beta_2$  receptor antagonist, has been used to try to prevent consolidation of traumatic memories in people who had just experienced trauma, such as rape victims or soldiers, but a meta-analysis suggested that it was not effective ([Argolo et al. 2015](#)). More recently, propranolol is being proposed to mitigate the development of intensive care unit-induced PTSD, which commonly stems from the trauma of hospitalization in an intensive care unit ([Gardner and Griffiths 2014](#)).  $\beta_3$  receptors are not believed to be present in the CNS but are abundantly expressed on brown adipose tissue (BAT), where they exert lipolytic and thermogenic effects. Not surprisingly, active researchers are attempting to develop selective  $\beta_3$  agonists for the treatment of obesity, and they are now called Class I BAT activators ([Mukherjee et al. 2016](#)).

## Cholinergic System

Acetylcholine (ACh) is the only major low-molecular-weight neurotransmitter substance that is not derived from an amino acid ([Kandel 2013](#)). ACh is synthesized from acetyl coenzyme A and choline in nerve terminals via the enzyme

choline acetyltransferase (ChAT). Choline is transported into the brain by uptake from the bloodstream and enters the neuron via both high-affinity and low-affinity transport processes ([Cooper et al. 2003](#)). In addition to the “standard” ChAT pathway, ACh can be synthesized by several possible mechanisms; the precise roles of these additional pathways and their physiological relevance in the CNS remain to be fully elucidated ([Cooper et al. 2003](#)). The highest activity of ChAT is observed in the interpeduncular nucleus, caudate nucleus, corneal epithelium, retina, and central spinal roots. In contrast to the other transmitters discussed thus far (which are most dependent on reuptake mechanisms), ACh has its signal terminated primarily by the enzyme ACh esterase, which degrades ACh ([Figure 2-6B](#)). Not surprisingly, therapeutic strategies to increase synaptic ACh levels (e.g., for the treatment of Alzheimer’s disease) have focused on inhibiting the activity of cholinesterases ([Nestler et al. 2015](#)).





**FIGURE 2-6.** The cholinergic system.

*See [Plate 9](#) to view this figure in color.*

This figure depicts the cholinergic pathways in the brain **(A)** and various regulatory processes involved in cholinergic neurotransmission **(B)**. Choline crosses the blood-brain barrier to enter the brain and is actively transported into cholinergic presynaptic terminals by an active uptake mechanism (requiring adenosine triphosphate [ATP]). This neurotransmitter is produced by a single enzymatic reaction in which acetyl coenzyme A (AcCoA) donates its acetyl group to choline by means of the enzyme choline acetyltransferase (ChAT). AcCoA is primarily synthesized in the mitochondria of neurons. Upon its formation, acetylcholine (ACh) is sequestered into secretory vesicles by vesicle ACh transporters (VATs), where it is stored. Vesamicol effectively blocks the transport of ACh into vesicles. An agent such as  $\beta$ -bungarotoxin or AF6<sub>4</sub>A is capable of increasing synaptic concentration of ACh by acting as a



releaser or a noncompetitive reuptake inhibitor, respectively. In turn, agents such as botulinum toxin are able to attenuate ACh release from nerve terminals. Once released from the presynaptic terminals, ACh can interact with a variety of presynaptic and postsynaptic receptors. In contrast to many other monoaminergic neurotransmitters, the ACh signal is terminated primarily by degradation by the enzyme acetylcholinesterase (AChE) rather than by reuptake. Interestingly, AChE is present on both presynaptic and postsynaptic membranes and can be inhibited by physostigmine (reversible) and soman (irreversible). Currently, AChE inhibitors such as donepezil and galantamine are the only classes of agents that are FDA approved for the treatment of Alzheimer's disease. ACh receptors are of two types: muscarinic (G protein-coupled) and nicotinic (ionotropic). Presynaptic regulation of ACh neuron firing activity and release occurs through somatodendritic (not shown) and nerve terminal M2 autoreceptors, respectively. The binding of ACh to G protein-coupled muscarinic receptors that are negatively coupled to adenylyl cyclase (AC) or coupled to phosphoinositol hydrolysis produces a cascade of second-messenger and cellular effects (see diagram). ACh also activates ionotropic nicotinic acetylcholine (nACh) receptors. ACh has its action terminated in the synapse through rapid degradation by AChE, which liberates free choline to be taken back into the presynaptic neuron through choline transporters (CTs). Once inside the neuron, it can be reused for the synthesis of ACh, can be repackaged into vesicles for reuse, or undergoes enzymatic degradation. There are some relatively new agents that selectively antagonize the muscarinic receptors, such as CI-1017 for M<sub>1</sub>, methoctramine for M<sub>2</sub>, 4-DAMP for M<sub>3</sub>, PD-102807 for M<sub>4</sub>, and scopolamine (hardly a new agent) for M<sub>5</sub> (although it also has affinity for the M<sub>3</sub> receptor). Nicotine receptors (or nACh receptors) are activated by nicotine and the specific alpha(4)beta(2\*) agonist metanicotine. Mecamylamine is an ACh receptor antagonist. cAMP=cyclic adenosine monophosphate;

DAG=diacylglycerol;

IP<sub>3</sub>=inositol-1,4,5-triphosphate;

PLC=phospholipase C.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Modified from Nestler et al. 2001.

In brief, cholinergic neurons can act as local circuit neurons (interneurons) and are found in the caudate, putamen, nucleus accumbens, olfactory tubercle, and islands of Calleja complex (Cooper et al. 2003). They also function as projection neurons that connect different brain regions; one fairly well-characterized pathway runs from the septum to the hippocampus (Figure 2-6A). The cholinergic complex is composed of eight cholinergic nuclei from which cholinergic neurons originate, designated Ch1 to Ch8. The basal forebrain cholinergic nuclei include the medial septal nucleus (Ch1), the vertical nucleus of the diagonal band (Ch2), the horizontal limb of the diagonal band (Ch3), and the nucleus basalis of Meynert (Ch4); brain stem cholinergic nuclei include the pedunculopontine nucleus (Ch5), the laterodorsal tegmental nucleus (Ch6), the medial habenula (Ch7), and the parabigeminal nucleus (Ch8) (Nestler et al. 2015). These nuclei project cholinergic neurons to the entire nonstriatal telencephalon, pontomesencephalotegmental cholinergic complex, thalamus, and other diencephalic loci (see Figure 2-6A). Descending cholinergic projections from these nuclei also innervate pontine and medullary reticular formations, deep cerebellar and vestibular nuclei, and cranial nerve nuclei (Cooper et al. 2003; Nestler et al. 2015). Basal forebrain

cholinergic nuclei significantly degenerate in Alzheimer's disease, which can be mitigated to some extent with cholinergic agents that increase synaptic ACh, such as donepezil; conversely, anticholinergic agents such as benztropine and trihexyphenidyl, through brain stem cholinergic interneurons, modulate striatal dopaminergic neurons and partially counteract motor symptoms of Parkinson's disease ([Nestler et al. 2015](#)).

## Cholinergic Receptors

The two major distinct classes of cholinergic receptors are the *muscarinic* and *nicotinic* receptors. Five muscarinic receptors ( $M_1$  through  $M_5$ ) have been cloned ([Kandel 2013](#)). These receptors are G protein-coupled and act either by regulating ion channels (in particular,  $K^+$  or  $Ca^{2+}$ ) or through being linked to second-messenger systems. Generally speaking,  $M_1$ ,  $M_3$ , and  $M_5$  are coupled to phosphoinositol hydrolysis, whereas  $M_2$  and  $M_4$  are coupled to inhibition of adenylyl cyclase and regulation of  $K^+$  and  $Ca^{2+}$  channels ([Cooper et al. 2003](#)) (see [Figure 2-6B](#)).  $M_1$ ,  $M_3$ , and  $M_4$  receptors are located in the cerebral cortex and hippocampus, with the  $M_1$  and  $M_4$  receptors concentrated in the striatal motor and reward circuits; the  $M_5$  receptors are expressed widely at low levels; and the  $M_2$  presynaptic autoreceptors (which decrease ACh release into the synapse) are located in the basal forebrain ([Cannon et al. 2011](#); [Nestler et al. 2015](#)). Many older medications such as chlorpromazine (antipsychotic), benztropine (used for EPS), tricyclic antidepressants, and antihistamines also are antagonists of muscarinic receptors, and they cause common side effects such as dry mouth and constipation. One older muscarinic antagonist, scopolamine, commonly

known to help with seasickness, more recently was found in humans to have rapid antidepressant properties, and in rats, a single dose reversed chronic unpredictable stress anhedonia, potentially through a burst increase in glutamate, mTORC1 (mechanistic target of rapamycin complex 1), and synaptic spines in the medial PFC (Drevets et al. 2013; Navarria et al. 2015). Furthermore, one study showed that a TT homozygous polymorphism rs324650 in the fifth intron of the presynaptic M<sub>2</sub> autoreceptor gene (*CHRM2*) resulted in more severe illness, including increased risk for suicide, that was potentially related to the observed reduced total volume of distribution (V<sub>T</sub>) of M<sub>2</sub> receptors in the cingulate cortex of depressed bipolar patients, as measured by the high-affinity PET ligand M<sub>2</sub> receptor agonist [<sup>18</sup>F]FP-TZTP (Cannon et al. 2011). A conflicting postmortem observation detected no difference between bipolar patients and control subjects with the M<sub>2</sub>/M<sub>4</sub> receptor antagonist [<sup>3</sup>H]AFDX (Smith and Jakobsen 2009). This negative result with [<sup>3</sup>H]AFDX, as compared with the positive result with [<sup>18</sup>F]FP-TZTP, was potentially explained by a difference in the binding properties of the two radioligands (Cannon et al. 2011).

By contrast, the nicotinic receptors are ionotropic receptors, and at least 12 different functional receptors (based on different subunit composition) have been identified (Nestler et al. 2015). Biochemical and biophysical data indicate that the nicotinic receptors in the muscle are formed from five protein subunits around a central pore, with the stoichiometry of  $\alpha_2\beta\gamma\delta$  (Kandel 2013). The binding of ACh molecules on the  $\alpha$  subunit is necessary for channel activation. By contrast, neuronal nicotinic receptors contain only two types of subunits ( $\alpha$  and  $\beta$ ), with the  $\alpha$  occurring in

at least eight different forms and the  $\beta$  in three ([Cooper et al. 2003](#); [Nestler et al. 2015](#)). The most common nicotinic receptor subtypes are  $\alpha 4\beta 2$ -nACh and  $\alpha 7$ -nACh ([Horti et al. 2013](#)). Nicotinic receptors are the targets of considerable cross-talk, as a variety of kinases (including PKA, PKC, and tyrosine kinases) are able to regulate the sensitivity of this receptor. Several regulatory mechanisms exist. For example, the mammalian prototoxin lynx1 acts as an allosteric modulator of the nicotinic receptor ([Miwa et al. 2006](#)). Curare (a poisonous full nicotinic receptor antagonist used in poison-tipped arrows and so forth) and succinylcholine (a weak partial nicotinic receptor agonist and routine surgical muscle relaxant) are two examples of compounds affecting nicotinic receptors ([Nestler et al. 2015](#)).

From a clinical standpoint, a long-standing observation is that patients with schizophrenia have a rate of nicotine use disorder that is substantially higher than that in the general population, in both the prevalence (~90%) and the quantity of cigarettes smoked (chain smoking). This observation has led to numerous studies of medication targeting nicotinic receptors to try to alleviate symptoms of psychosis, including the use of nicotine replacement, but the results have been disappointing in terms of treating psychosis even though the nicotine replacement maintains cognitive functioning ([AhnAllen et al. 2015](#)). One report ([Freedman et al. 1997](#)) determined that in a cohort of patients with schizophrenia, abnormal P50 auditory evoked potentials were linked to a susceptibility locus for this disease on chromosome 15. Notably, this is where a nicotinic receptor subunit is found, providing indirect genetic and phenotypic support for the long-standing contention that the high rates of cigarette smoking in patients with schizophrenia may

represent some attempt by patients to self-medicate for their underlying nicotinic receptor defect. Varenicline, a partial agonist at the  $\alpha 4\beta 2$ -nACh receptor subtype developed for smoking cessation, helped patients with schizophrenia quit smoking but did not help them with their psychotic symptoms or cognitive deficits ([Smith et al. 2016](#)).

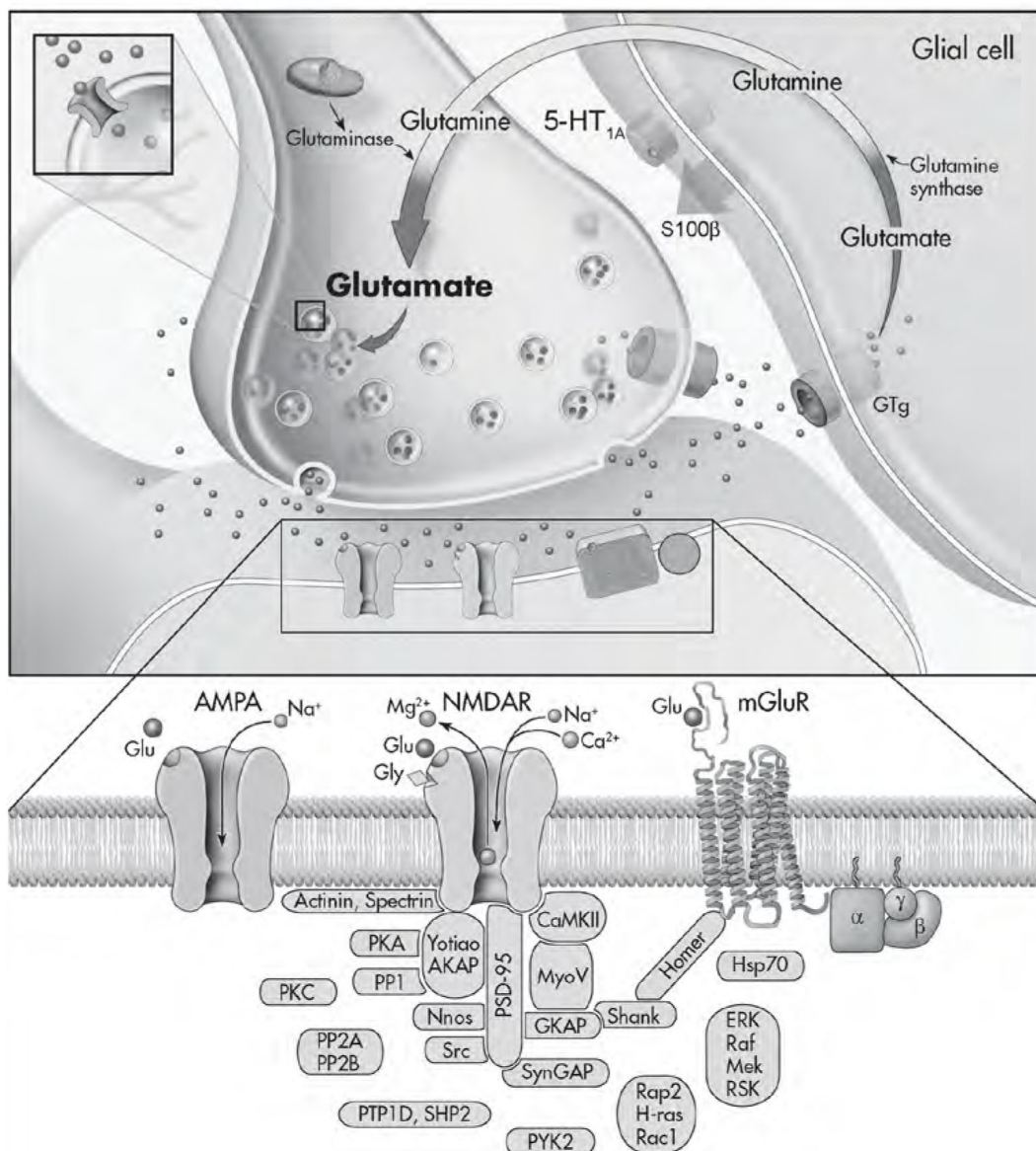
Although the PET radioactive ligand [ $^{11}\text{C}$ ]nicotine was one of the earliest human radioligands developed, it had problematic qualities as a PET ligand because of poor specificity and fast metabolism; the latest generation nicotinic ligand [ $^{18}\text{F}$ ]AZAN has some of the highest specific activity observed for the  $\alpha 4\beta 2$ -nACh receptor, and it was shown to be only partially blocked in the human brain by nicotine gum or secondhand smoke but completely blocked by the specific agonist varenicline ([Horti et al. 2013](#)). Despite the well-publicized long-term negative health consequences of smoking, tobacco products that contain nicotine remain one of the most widely used addictive legal substances in the world.

## Glutamatergic System

Glutamate and aspartate are the two major excitatory amino acids in the CNS and are present in high concentrations ([Nestler et al. 2015](#); [Squire 2013](#)). As the principal mediators of excitatory synaptic transmission in the mammalian brain, they participate in wide-ranging aspects of both normal and abnormal CNS function. Physiologically, glutamate appears to play a prominent role in synaptic plasticity, learning, and memory. However, glutamate can also be a neuronal excitotoxin under a variety of experimental conditions, triggering either rapid

or delayed neuronal death. Unlike the monoamines, which require transport of amino acids through the blood-brain barrier, glutamate and aspartate cannot adequately penetrate into the brain from the periphery and are produced locally by specialized brain machinery. The metabolic and synthetic enzymes responsible for the formation of these nonessential amino acids are located in glial cells and neurons ([Squire 2013](#)).

The major metabolic pathway in the production of glutamate is derived from glucose and the transamination of  $\alpha$ -ketoglutarate; however, a small proportion of glutamate is formed directly from glutamine. The latter is actually synthesized in glia, via an active process (requiring adenosine triphosphate [ATP]), and is then transported to neurons, where glutaminase is able to convert this precursor to glutamate ([Figure 2-7](#)). Following release, the concentration of glutamate in the extracellular space is highly regulated and controlled, primarily by a  $\text{Na}^+$ -dependent reuptake mechanism involving several transporter proteins.



### Glutamate receptor subtypes: new classification

Ionotropic			Metabotropic		
NMDA	AMPA	Kainate	Group I	Group II	Group III
GluN1	GluA1	GluK1	mGlu1 a-b-c-d	mGlu2	mGlu4 a-b
GluN2A-B-C-D	GluA2	GluK2	mGlu5 a-b	mGlu3	mGlu6
GluN3A-B	GluA3	GluK3			mGlu7 a-b
	GluA4	GluK4			mGlu8 a-b
		GluK5			



---

**FIGURE 2-7.** The glutamatergic system.

*See **Plate 10** to view this figure in color.*

This figure depicts the various regulatory processes involved in glutamatergic neurotransmission. The biosynthetic pathway for glutamate involves synthesis from glucose and the transamination of  $\alpha$ -ketoglutarate; however, a small proportion of glutamate is formed more directly from glutamine by glutamine synthetase. The latter is actually synthesized in glia and, via an active process (requiring adenosine triphosphate [ATP]), is transported to neurons, where in the mitochondria glutaminase is able to convert this precursor to glutamate. Furthermore, in astrocytes glutamine can undergo oxidation to yield  $\alpha$ -ketoglutarate, which can also be transported to neurons and participate in glutamate synthesis. Glutamate is either metabolized or sequestered and stored in secretory vesicles by vesicle glutamate transporters (VGluTs). Glutamate can then be released by a calcium-dependent excitotoxic process. Once released from the presynaptic terminal, glutamate is able to bind to numerous excitatory amino acid (EAA) receptors, including both ionotropic (e.g., NMDA [*N*-methyl-D-aspartate]) and metabotropic (mGlu) receptors. Presynaptic regulation of glutamate release occurs through metabotropic glutamate receptors (mGlu2 and mGlu3), which subserve the function of autoreceptors; however, these receptors are also located on the postsynaptic element. Glutamate has its action terminated in the synapse by reuptake mechanisms utilizing distinct glutamate transporters that exist on not only presynaptic nerve terminals but also astrocytes; indeed, current data suggest that astrocytic glutamate uptake may be more important for clearing excess glutamate, raising the possibility that astrocytic loss (as has been documented in mood disorders) may contribute to deleterious glutamate signaling, but more so by astrocytes. It is now known that a number of important intracellular proteins are able to alter the function of glutamate receptors (see

diagram). Also, growth factors such as glial-derived neurotrophic factor (GDNF) and S100 $\beta$  secreted from glia have been demonstrated to exert a tremendous influence on glutamatergic neurons and synapse formation. Of note, serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) receptors have been documented to be regulated by antidepressant agents; this receptor is also able to modulate the release of S100 $\beta$ . AKAP=A kinase anchoring protein; AMPA= $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CaMKII=Ca<sup>2+</sup>/calmodulin-dependent protein kinase II; ERK=extracellular response kinase; H-ras=Harvey rat sarcoma proto-oncogene; GKAP=guanylate kinase-associated protein; Glu=glutamate; Gly=glycine; GTg=glutamate transporter glial; GTn=glutamate transporter neuronal; Hsp70=heat shock protein 70; MEK=mitogen-activated protein kinase/ERK; mGluR=metabotropic glutamate receptor; MyoV=myosin V; NMDAR=NMDA receptor; nNOS=neuronal nitric oxide synthase; PKA=phosphokinase A; PKC=phosphokinase C; PP1, PP2A, PP2B=protein phosphatases; PSD-95=an abundant postsynaptic density (PSD) protein that forms a two-dimensional lattice immediately under the postsynaptic membrane; PTP1D=a protein tyrosine phosphatase; PYK2=protein tyrosine kinase 2; Rac1=Ras-related C3 botulinum toxin substrate 1; Raf=Raf-1 proto-oncogene, serine/threonine kinase; Rap2=related to AP2 domain protein; RSK=ribosomal S6 kinase; SHP2=src homology 2 (SH2) domain-containing tyrosine phosphatase; Src=SRC proto-oncogene, non-receptor tyrosine kinase; SynGAP=synaptic Ras-GTPase activating protein.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Table modified from [Nestler et al. 2015](#).

The major glutamate transporter proteins found in the CNS, all of which clear the released glutamate from synapses, include the Na<sup>+</sup>-dependent excitatory amino acid transporters (EAATs): the “faster turnover” EAATs—EAAT1 (or GLAST), EAAT2 (or GLT-1), and EAAT3 (or EAAC1); and the “slower turnover” EAATs—EAAT4 and EAAT5 ([Robinson and Jackson 2016](#)). The corresponding human gene names are *SLC1A3*, *2*, *1*, *6*, and *7*, respectively ([Robinson and Jackson 2016](#)). Additionally, these transporters are differentially expressed in specific cell types, with EAAT1 and EAAT2 being found primarily in glial cells, responsible for most of the glutamate reuptake, and EAAT3 being localized on both excitatory and inhibitory neurons and oligodendrocytes ([Robinson and Jackson 2016](#)). EAAT2 is the most predominantly expressed form in the forebrain; EAAT4 is mainly localized in Purkinje cells of the cerebellum but also found elsewhere; EAAT5 is on the presynaptic termini of bipolar neuronal cells of the retina ([Robinson and Jackson 2016](#); [Squire 2013](#)). Evidence indicates that phosphorylation of the transporters by protein kinases differentially regulates glutamate transporters and therefore glutamate reuptake ([Casado et al. 1993](#); [Conradt and Stoffel 1997](#); [Pisano et al. 1996](#)). Glutamate concentrations have been shown to rise to excitotoxic levels within minutes following traumatic or ischemic injury, and evidence indicates that the function of the glutamate transporters becomes impaired under these excitotoxic conditions ([Faden et al. 1989](#)). It is surprising that the glutamatergic system has only recently undergone extensive investigation with regard to its possible involvement in the pathophysiology of major mental illnesses, because it is the major excitatory neurotransmitter in the CNS and is known to play a role in

regulating the threshold for excitation of most other neurotransmitter systems. After decades of research exploring the classic dopamine dysfunction hypothesis as the pathophysiological basis for schizophrenia, the glutamate dysfunction hypothesis became an equally vigorous research effort on the basis of initial observations of the psychotogenic properties of phencyclidine (PCP) and ketamine. Both are NMDA receptor antagonists that acutely increase glutamate levels in the synapses, causing many of the core features of schizophrenia (psychosis, thought disorder, negative symptoms, and executive cognitive deficits) to emerge from otherwise healthy human subjects ([Moghaddam and Krystal 2012](#)). However, the enthusiasm for the use of ketamine-induced psychosis as a model for schizophrenia has dampened because of the lack of efficacy of haloperidol (a D<sub>2</sub> receptor antagonist) and group II metabotropic glutamate receptor (mGlu2/3) agonists in ameliorating ketamine-induced psychosis and the lack of genetic and postmortem data to support NMDA receptor dysfunction in schizophrenia ([Moghaddam and Krystal 2012](#)).

It is now clear that modification of the levels of synaptic AMPA-type glutamate receptors—in particular, by receptor subunit trafficking, insertion, and internalization—is a critically important mechanism for regulating various forms of synaptic plasticity and behavior. Studies have identified region-specific alterations in expression levels of AMPA and NMDA glutamate receptor subunits in patients with mood disorders ([Beneyto et al. 2007](#)). Supporting the suggestion that abnormalities in glutamate signaling may be involved in mood pathophysiology, AMPA receptors have been shown to regulate affectivelike behaviors in rodents. AMPA receptor antagonists have been found to attenuate

amphetamine- and cocaine-induced hyperactivity and psychostimulant-induced sensitization and hedonic behavior ([Goodwin et al. 2007](#)). Patients with treatment-resistant unipolar and bipolar depression given one intravenous dose of ketamine had strong relief of their depressive symptoms ([Berman et al. 2000](#); [Diazgranados et al. 2010](#); [Zarate et al. 2006a](#)). Ketamine antidepressant efficacy typically has been assumed to depend on direct glutamate NMDA receptor inhibition, which is how it works as an anesthetic ([Leung and Baillie 1986](#)). However, the results of human treatment trials indicate that alternative NMDA receptor antagonists lack the strong, rapid, or sustained antidepressant properties of ketamine ([Newport et al. 2015](#)). It has recently been shown that the metabolism of ketamine to one of its major metabolites, (2S,6S;2R,6R)-hydroxynorketamine, is essential for its antidepressant effects in mice ([Zanos et al. 2016](#)). These antidepressant actions are NMDA receptor inhibition independent, which requires activation of a different subtype of glutamate receptors, the AMPA receptors ([Zanos et al. 2016](#)).

## Glutamatergic Receptors

The many subtypes of glutamatergic receptors in the CNS can be classified into two major subtypes: ionotropic and metabotropic receptors (see [Figure 2-7](#)).

**Ionotropic glutamate receptors.** The ionotropic glutamate receptor ion channels are assemblies of homo- or hetero-oligomeric subunits integrated into the neuron's membrane. Every channel is assembled of (most likely) four subunits associated into a dimer of dimers, as has been observed in crystallographic studies ([Ayalon and Stern-Bach 2001](#); [Madden 2002](#); [Nestler et al. 2015](#)). Every

subunit consists of an extracellular amino-terminal and ligand binding domain, three transmembrane domains, a reentrant pore loop (located between the first and the second transmembrane domains), and an intracellular carboxyl-terminal domain ([Hollmann et al. 1994](#)). The subunits associate through interactions between their amino-terminal domains, forming a dimer that undergoes a second dimerization mediated by interactions between the ligand binding domains and/or between the transmembrane domains ([Ayalon and Stern-Bach 2001](#); [Madden 2002](#)). Three different subgroups of glutamatergic ion channels have been identified on the basis of their pharmacological ability to bind different synthetic ligands, each of which is composed of a different set of subunits. The three subgroups are the NMDA receptors, the AMPA receptors, and the kainate (KA) receptor. In the adult mammalian brain, NMDA and AMPA glutamatergic receptors are collocated in approximately 70% of the synapses ([Bekkers and Stevens 1989](#)). By contrast, at early stages of development, synapses are more likely to contain only NMDA receptors. Radioligand binding studies have shown that NMDA receptors and AMPA receptors are found at high densities in the cerebral cortex, hippocampus, striatum, septum, and amygdala.

*NMDA receptors.* The NMDA receptor is activated by glutamate and requires the presence of a co-agonist—namely, glycine or D-serine—to be activated, a process that likely varies in importance according to brain region ([Panatier et al. 2006](#)). However, the binding of both glutamate and glycine is still not sufficient for the NMDA receptor channel to open, because at resting membrane potential, the NMDA ion channel is blocked by  $Mg^{2+}$  ions.

Only when the membrane is depolarized (e.g., by the activation of AMPA or KA receptors on the same postsynaptic neuron) is the  $Mg^{2+}$  blockade relieved. Under these conditions, the NMDA receptor channel will open and permit the entry of both  $Na^+$  and  $Ca^{2+}$  (see [Figure 2-7](#)).

The NMDA receptor channel is composed of a combination of GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, and GluN3B subunits (see [Figure 2-7](#)). The binding site for glutamate has been localized to the GluN2 subunit, and the site for the co-agonist glycine has been localized to the GluN1 subunit, which is required for receptor function. Two molecules of glutamate and two of glycine are thought to be necessary to activate the ion channel. Within the ion channel, two other sites have been identified—the sigma ( $\sigma$ ) site and the PCP site. The hallucinogenic drugs PCP, ketamine, and the experimental drug dizocilpine (MK-801) all bind at the latter site and are considered noncompetitive receptor antagonists that inhibit NMDA receptor channel function.

In clinical psychiatric studies, ketamine has been shown to transiently induce psychotic symptoms in schizophrenic patients and to produce antidepressant effects in some depressed patients ([Krystal et al. 2002](#)). Building on these preclinical and preliminary clinical data, clinical trials have investigated the clinical effects of glutamatergic agents in patients with mood disorders. These and other data have led to the hypothesis that alterations in neural plasticity in critical limbic and reward circuits, mediated by AMPA and NMDA receptors, may represent a convergent mechanism for antidepressant action ([Zarate et al. 2006b](#)). Suicidal ideation also was rapidly improved with ketamine infusion ([Ballard et al. 2015](#)). This line of research holds considerable promise for developing new rapid-acting



treatments for refractory MDD and refractory bipolar depression. NMDA receptors in the amygdala also may be of critical importance in the process of transforming a fixed and consolidated fear memory to labile states ([Ben Mamou et al. 2006](#)). The hope of cognitive improvements through NMDA modulation was dashed by a meta-analysis of 17 studies of NMDA receptor agonists glycine, D-serine, and D-cycloserine and other glutamate-enhancing agents that did not show improvement in cognition in patients with schizophrenia ([Coyle et al. 2002](#); [Iwata et al. 2015](#)).

NMDA receptors play a critical role in regulating synaptic plasticity ([Malenka and Nicoll 1999](#); [Nestler et al. 2015](#)). The best-studied forms of synaptic plasticity in the CNS are *long-term potentiation* (LTP) and *long-term depression* (LTD) of excitatory synaptic transmission. The molecular mechanisms of LTP and LTD have been extensively characterized and have been proposed to represent cellular models of learning and memory ([Malenka and Nicoll 1999](#)). Induction of LTP and LTD in the CA1 region of the hippocampus and in many regions of the brain has now clearly been shown to be dependent on NMDA receptor activation. During NMDA receptor-dependent synaptic plasticity,  $\text{Ca}^{2+}$  influx through NMDA receptors can activate a wide variety of kinases and/or phosphatases that modulate synaptic strength. An important development was the finding that two of the primary molecules involved—CaMKII and the NMDA subtype of glutamate receptor—form a tight complex with each other at the synapse ([Lisman and McIntyre 2001](#)). Interestingly, this binding appears to enhance both the autophosphorylation of the kinase and the ability of the entire holoenzyme, which has 12 subunits, to become hyperphosphorylated ([Lisman and McIntyre 2001](#)). This hyperphosphorylated state has been



postulated to represent a “memory switch” that can lead to long-term strengthening of the synapse by multiple mechanisms. One important mechanism involves direct phosphorylation of the glutamate-activated AMPA receptors, which increases their conductance. Furthermore, CaMKII, once bound to the NMDA receptor, may organize additional anchoring sites for AMPA receptors at the synapse. Switching of synaptic NMDA receptor subunits, which bind CaMKII, for other NMDA receptor subunits having no affinity for this enzyme dramatically reduces LTP, highlighting glutamate and calcium signaling interactions critical for learning and memory ([Barria and Malinow 2005](#)).

Although the NMDA receptor clearly plays important roles in plasticity, abundant evidence has shown that excessive glutamatergic signaling is also involved in neuronal toxicity. With anoxia or hypoglycemia, the highly energy-dependent uptake mechanisms that keep glutamate compartmentalized in presynaptic terminals fail. Within minutes, glutamate is massively released into the synaptic space, resulting in activation of excitatory amino acid receptors. This leads to depolarization of target neurons via AMPA receptors and KA receptors and then to inappropriate and excessive activation of NMDA receptors ([Farber et al. 2002](#)). Considerable data suggest that the large excess of  $\text{Ca}^{2+}$  entering cells via the NMDA receptor channel may represent an important step in the rapid cell death that occurs via excitotoxicity ([Nestler et al. 2015](#)).

The hypothesis from the 1990s that NMDA receptor hypofunction is related to psychosis is supported by the observation of patients with autoimmune antibodies to the NMDA receptor (GluN1 subunit) who developed psychosis that reversed when the autoantibodies were removed by

plasmapheresis and immunosuppression ([Masdeu et al. 2016](#)). Anti-NMDA receptor encephalitis was first described in young women who had psychosis and ovarian teratomas in 2005, but it has since been found in both men and women who have no known malignancy, and even with treatment, patients have a high recurrence rate of 12% 2 years after treatment ([Pollak et al. 2014](#)). In one review of the literature, 1.46% of 1,441 psychotic patients who were tested had the immunoglobulin G antibodies, and an increase in extracellular glutamate was reported in rats injected with CSF from affected patients ([Manto et al. 2010](#); [Pollak et al. 2014](#)). Memantine, a noncompetitive NMDA receptor antagonist approved for the treatment of dementia, could be used as a possible treatment, especially in patients who proceed to develop catatonia or treatment-resistant schizophrenia ([Pollak et al. 2014](#)). Of note, patients with systemic lupus erythematosus also may develop antibodies to GluN2A and GluN2B subunits of the NMDA receptor treatment and have associated psychosis ([Pollak et al. 2014](#)). Encephalopathies have been found to be caused by an expanding list of autoimmune markers, including AMPA receptors, glycine receptors, and GABA<sub>A</sub> and GABA<sub>B</sub> receptors, all to be discussed later in this chapter ([McKeon 2016](#)).

In postmortem studies of patients with MDD who committed suicide, the PFC region had decreased levels of GluN2A and GluN2B subunits and the postsynaptic density protein-95 but no change in the level of the mandatory GluN1 subunits as compared with control subjects ([Feyissa et al. 2009](#)). Acamprosate (*N*-acetylhomotaurine) is an NMDA receptor antagonist approved for the treatment of alcohol use disorder, based on its success in decreasing cravings in clinical trials, but because it is short acting,

patients must take this medication three times a day ([Haass-Koffler et al. 2014](#)).

*AMPA receptors.* The AMPA receptor is stimulated by the presence of glutamate and characteristically produces a fast excitatory synaptic signal that is responsible for the initial reaction to glutamate in the synapse. In fact, as discussed earlier, researchers generally believe that the activation of the AMPA receptor results in neuronal depolarization sufficient to liberate the  $Mg^{2+}$  cation from the NMDA receptor, thereby permitting its activation. The AMPA receptor channel is composed of the combination of the GluA1, GluA2, GluA3, and GluA4 subunits and requires two molecules of glutamate to be activated (see [Figure 2-7](#)). AMPA receptors have a lower affinity for glutamate than does the NMDA receptor, thereby allowing for more rapid dissociation of glutamate and, therefore, a rapid deactivation of the AMPA receptor ([Henley and Wilkinson 2016](#)).

Studies have indicated that AMPA receptor subunits are direct substrates of protein kinases and phosphatases. Phosphorylation of the receptor subunits regulates not only the intrinsic channel properties of the receptor but also the interaction of the receptor with associated proteins that modulate the membrane trafficking and synaptic targeting of the receptors ([Malinow and Malenka 2002](#)). Additionally, protein phosphorylation of other synaptic proteins has been proposed to indirectly modulate AMPA receptor function by affecting the macromolecular complexes that are important for the presence of AMPA receptors at the synaptic plasma membrane ([Malinow and Malenka 2002](#); [Nestler et al. 2015](#)). Studies have been elucidating the cellular mechanisms by which AMPA receptor subunit insertion and

trafficking occur and have identified two major mechanisms ([Malinow and Malenka 2002](#); [Nestler et al. 2015](#)). The first mechanism is used for GluA1-containing AMPA receptor insertion and is regulated by activity. The second mechanism is governed by constitutive receptor recycling, mainly through GluA2/3 heteromers in response to activity-dependent signals. Data suggest that AMPA receptor subunit trafficking may play an important role in neuropsychiatric disorders and addictions. Thus, Nestler and associates have shown that the ability of drugs of abuse to elevate levels of the GluA1 subunit of AMPA glutamate receptors in the VTA of the midbrain is crucial for the development of sensitization ([Carlezon and Nestler 2002](#)). They have found that even transient increases in GluA1 levels within VTA neurons can trigger complex cascades of other molecular adaptations in these neurons and, within larger neural circuits, can cause enduring changes in the responses of the brain to drugs of abuse. Chronic lithium and valproate have been shown to reduce GluA1 expression in hippocampal synaptosomes, which may play a role in the delayed therapeutic effects of these agents ([Du et al. 2003](#); [Szabo et al. 2009](#)).

Differential trafficking of AMPA receptor subunits as the sole, classic mechanism for regulation and induction of LTP was recently challenged when knockout mouse models demonstrated that LTP occurred even with no AMPA receptors but only KA receptors ([Henley and Wilkinson 2016](#)). One possible hypothesis that results from this observation would be that the subunits of the AMPA receptors do not dictate plasticity, but perhaps the numbers of “slot proteins” or “placeholder proteins” influence the development of LTP, and LTP is AMPA receptor subunit independent ([Henley and Wilkinson 2016](#)).

Investigators have sought to test the hypothesis that these “antidepressant anticonvulsants,” like traditional antidepressants, would enhance surface AMPA receptors ([Du et al. 2007](#)). It was found that lamotrigine and riluzole significantly enhanced the surface expression of GluA1 and GluA2 in a time- and dose-dependent manner in cultured hippocampal neurons. By contrast, the antimanic anticonvulsant valproate significantly reduced surface expression of GluA1 and GluA2. Concomitant with the GluA1 and GluA2 changes, the peak value of depolarized membrane potential evoked by AMPA was significantly higher in lamotrigine- and riluzole-treated neurons, supporting the surface receptor changes. In addition, lamotrigine and riluzole, as well as the traditional antidepressant imipramine, increased GluA1 phosphorylation at GluA1 (S845) in the hippocampus after chronic in vivo treatment.

Clinical studies have reported a consistent and rapid antidepressant effect of ketamine. Studies were therefore undertaken to test the hypothesis that ketamine brings about its rapid antidepressant effect via an AMPA receptor-dependent mechanism ([Maeng et al. 2008](#)). The AMPA receptor antagonist NBQX was without behavioral effects alone but blocked the antidepressant-like effects of ketamine. AMPA receptor antagonists also blocked the ketamine-induced changes in hippocampal GluA1 AMPA receptor phosphorylation ([Maeng et al. 2008](#)). It was also recently observed that these actions are observed with a metabolite of ketamine, (2R,6R)-hydroxynorketamine, which also causes strong and rapid potentiation of AMPA receptors ([Zanos et al. 2016](#)). Together, these results suggest that increased AMPA receptor activity in critical

mood-relevant circuits may play an important role in antidepressant action.

*Kainate receptors.* The KA receptor has pre- and postsynaptic roles, sharing some properties with AMPA receptors. It is composed of the combination of the GluK1, GluK2, and GluK3 low-affinity subunits co-assembling with the GluK4 or GluK5 high-affinity subunits (formerly called the GluR5, GluR6, GluR7, KA1, and KA2 subunits, respectively) to form a dimer of dimers (tetrameric complex) (see [Figure 2-7](#)) ([Møllerud et al. 2017](#)). The crystal structures suggest that the pore remains closed even with glutamate bound to it, indicating that an additional mechanism is required to induce conformational change to open the pore ([Møllerud et al. 2017](#)). The precise role of KA receptors in the mature CNS is unknown, although the activity of the receptors clearly plays a role in synaptic function in many brain areas. Increasing data suggest the involvement of aberrant synaptic plasticity in the pathophysiology of bipolar disorder. KA receptors contribute to synaptic plasticity in different brain regions involved in mood regulation, including PFC, hippocampus, and amygdala. GluK2 (formerly called GluR6; the gene name continues to be *GRIK2*) is a subtype of KA receptor whose chromosomal loci of 6q16.3-q21 was identified as potentially harboring genetic polymorphism(s) contributing to the increased risk of mood disorders. The role of GluK2 in modulation of animal behaviors correlated with mood symptoms was investigated with GluK2 knockout mice and wild-type mice ([Shaltiel et al. 2007](#)). GluK2 knockout mice appeared to attain normal growth and lacked neurological abnormalities. The GluK2 knockout mice showed increased basal- or amphetamine-induced activity, were extremely

aggressive, took more risks, and consumed more saccharin (a measure of hedonic drive). Notably, most of these aberrant behaviors responded to chronic lithium administration. These results suggest that abnormalities in KA receptor throughput generated by GluK2 gene disruption may lead to the concurrent appearance of a constellation of behaviors related to manic symptoms, including persistent hyperactivity, escalated irritability and aggression, risk taking, and hyperhedonia.

KA receptors play an important role in the hippocampus with place cell activity patterns and working memory ([Sihra and Rodríguez-Moreno 2013](#)). KA receptors modulate glutamate release between the mossy fibers of the granular cells of the dentate gyrus and the principal cells of the CA3 region, and there is high expression of KA receptors at those mossy fiber-CA3 synapses ([Sihra and Rodríguez-Moreno 2013](#)). KA receptors both prevent excessive glutamate release and facilitate increased glutamate release when the levels of glutamate are low in those same synapses ([Sihra and Rodríguez-Moreno 2013](#)). Recovery of the synapses with KA receptors is long and slow compared with the fast NMDA receptors, which may assist with memory formation ([Sihra and Rodríguez-Moreno 2013](#)). The CA3 may be more prone to develop seizures as a result of the KA receptors facilitating glutamate release ([Sihra and Rodríguez-Moreno 2013](#)).

**Metabotropic glutamate receptors.** The metabotropic glutamate (mGlu) receptors are GPCRs. The eight types of receptors that have been cloned can be organized into three different subgroups (groups I, II, and III) based largely on the signaling transduction pathways that they activate (see [Figure 2-7](#)). These receptors have a



large extracellular N-terminal consisting of two lobes forming a “venus flytrap” binding pocket involved in glutamate recognition and a cysteine-rich extracellular domain that connects with seven transmembrane domains separated by short intra- and extracellular loops (see [Figure 2-7](#)). The intracellular loop plays an important role in the coupling with and selectivity of the G protein. The cytoplasmic carboxyl-terminal domain is variable in length and is involved with G protein activation and coupling efficacy ([Bruno et al. 2001](#); [Conn and Pin 1997](#); [Nestler et al. 2015](#)).

The mGlu receptor group I includes the mGlu1 (a, b, c, d) and mGlu5 (a, b) receptors (see [Figure 2-7](#)). They preferentially interact with the  $G_{\alpha q/11}$  subunit of G proteins, leading to activation of the  $IP_3$ /calcium and DAG/PKC cascades. The receptors are located on both pre- and postsynaptic neurons. Group II metabotropic receptors include mGlu2 and mGlu3, which have been best characterized as inhibiting adenylyl cyclase, but, like many receptors coupled to  $G_i/G_o$ , may also regulate ion channels. Group III receptors, which include mGlu4 (a, b), mGlu6, mGlu7 (a, b), and mGlu8 (a, b), are reported to produce inhibition of adenylyl cyclase as well but also to interact with the phosphodiesterase enzyme regulating guanosine monophosphate levels ([Cooper et al. 2003](#); [Squire 2013](#)). The group II and III receptors are located in the presynaptic membrane and, because of their coupling with  $G_i/G_o$  proteins, appear to negatively modulate glutamate and GABA neurotransmission output when activated (i.e., they serve as inhibitory auto- and heteroreceptors). Preclinical studies suggest that mGlu group II and III receptors are “extrasynaptic” in their localization; that is,



they are located some distance from the synaptic cleft and are thus activated only under conditions of excessive (pathological?) glutamate release, when glutamate is sufficient to diffuse out of the synapse to these receptors ([Schoepp 2001](#)). In preclinical studies, mGlu2/3 receptor agonists have been found to exert anxiolytic, antipsychotic, and neuroprotective properties ([Schoepp 2001](#)). However, subsequent clinical trials in humans have not sustained the promise of the preclinical studies ([Moghaddam and Krystal 2012](#)). mGlu receptors of all three groups appear to work as inhibitory autoreceptors, decreasing release of glutamate from the synapse, modulating glutamate release ([Nestler et al. 2015](#)).

Postmortem studies of the brains of patients with MDD who committed suicide reported several changes in expression of mGlu receptors. Patients with MDD have higher levels of RNA gene expression as measured by quantitative polymerase chain reaction for NMDA receptor subunits GluN2B and GluN2C, as well as for metabotropic receptors mGlu4 and mGlu5 in the neurons of the locus coeruleus, which together serve to stimulate noradrenergic neurons located there ([Chandley et al. 2014](#)). According to one study, Brodmann area 10 of the PFC of depressed and/or suicidal individuals had a 67% increase in (mostly presynaptic) mGlu2 and mGlu3 protein levels compared with healthy control subjects ([Feyissa et al. 2010](#)). Another study showed decreased mGlu5 protein expression in postmortem brain samples corresponding to decreased regional binding of a PET ligand to mGlu5 receptors in living depressed patients ([Deschwanden et al. 2011](#)). These observations suggest that there may be a relative glutamate “deficiency” in the synapse, leading to increased expression of glutamate receptors in depressed patients.

---

# Glycine

---

Glycine is a nonessential amino acid that also functions as a neurotransmitter in the CNS, serving as a co-agonist for NMDA receptor activation. Glycine may be produced in the CNS by two distinct pathways. First, glycine is produced from serine by the enzyme serine-*trans*-hydroxymethylase in a reversible, folate-dependent reaction ([Cooper et al. 2003](#); [Nestler et al. 2015](#); [Squire 2013](#)). Second, a smaller proportion of glycine also may be produced from glyoxylate by the enzyme D-glycerate dehydrogenase. Glycine is found in higher concentrations in the spinal cord than in the rest of the CNS, and it acts as an inhibitory neurotransmitter predominantly in the brain stem and spinal cord ([Nestler et al. 2015](#)). As discussed earlier, a very important role that glycine also plays is to augment the NMDA-mediated frequency of NMDA receptor channel opening. This effect is strychnine-insensitive and pharmacologically suggests that the actions of glycine on NMDA receptor function are different from its effect on the spinal cord, where glycine's inhibitory effect is blocked by strychnine ([Cooper et al. 2003](#)). The allosteric modulation of NMDA receptors via a glycine site is further underscored by receptor binding experiments yielding an anatomical distribution similar to that of NMDA receptors. Functionally, it has been postulated that glycine is able to augment the NMDA-mediated responses by speeding up the recovery process of the NMDA receptor ([Cooper et al. 2003](#)).

Glycine receptors, similar to GABA<sub>A</sub> receptors, contain a chloride channel, and are composed of a combination of three  $\alpha$  subunits containing the glycine binding site and two  $\beta$  subunits, which associate with gephyrin, a cytoplasmic

protein ([Nestler et al. 2015](#)). Glycine receptors are bound by the compounds strychnine, a selective glycine receptor antagonist, and picrotoxin, a noncompetitive inhibitor, which block the chloride channel pore and cause seizures ([Nestler et al. 2015](#)). Synaptic glycine is removed mostly through the glycine transporter GlyT1. Ligands to GlyT1 are being explored as potential candidates for the treatment of schizophrenia, and a specific PET ligand, [ $^{18}\text{F}$ ]MK6577, recently has been developed ([Xia et al. 2015](#)). The endogenous ligands for the glycine receptor are actually D-serine and D-cycloserine ([Labrie and Roder 2010](#)). Glycine receptor agonism (D-serine) or GlyT antagonism (sarcosine) effectively increases glycine in the synapse, causing an increase in NMDA GluN1 receptor activation, which may ameliorate symptoms of schizophrenia, and clinical trials have suggested that these compounds may be helpful as augmentation agents together with other antipsychotics ([Labrie and Roder 2010](#)).

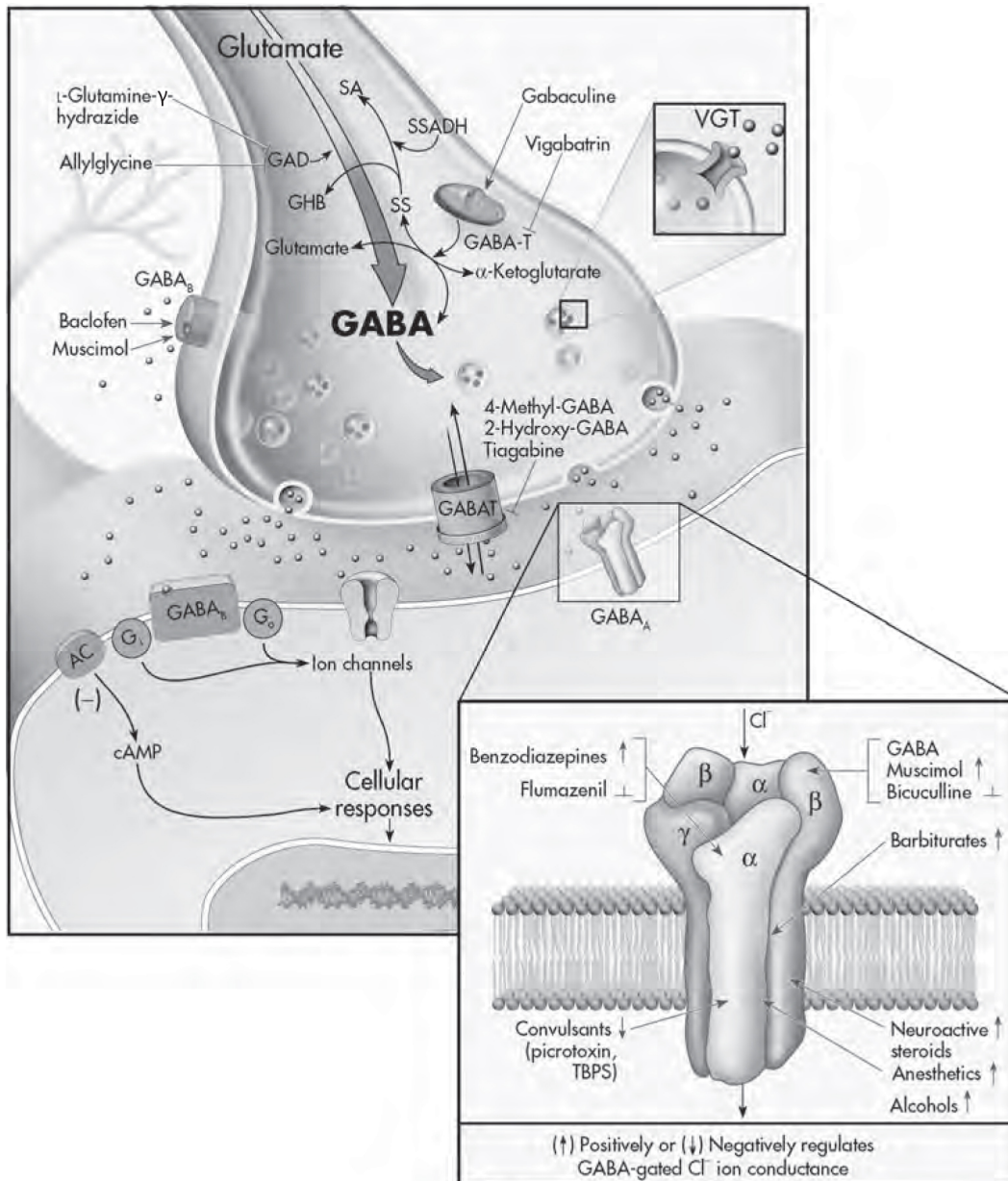
---

## GABAergic System

---

GABA—the major inhibitory neurotransmitter system in the CNS—is one of the most abundant neurotransmitters, and GABA-containing neurons are located in virtually every area of the brain. Unlike the monoamines, GABA occurs in the brain in high concentrations on the order of micromoles per milligrams (about 1,000-fold higher than concentrations of monoamines) ([Cooper et al. 2003](#); [Nestler et al. 2015](#); [Squire 2013](#)). GABA is produced when glucose is converted to  $\alpha$ -ketoglutarate, which is then transaminated to

glutamate by GABA  $\alpha$ -oxoglutarate transaminase (GABA-T). Glutamic acid is decarboxylated by glutamic acid decarboxylase, which leads to the formation of GABA (Figure 2-8). Indeed, the neurotransmitter and the rate-limiting enzyme are localized together in the brain and at approximately the same concentration. Catabolism of GABA occurs via GABA-T, which is also important in the synthesis of this transmitter.



---

## **FIGURE 2-8.** The GABAergic system.

*See [Plate 11](#) to view this figure in color.*

This figure depicts the various regulatory processes involved in GABAergic neurotransmission. The amino acid (and neurotransmitter) glutamate serves as the precursor for the biosynthesis of  $\gamma$ -aminobutyric acid (GABA). The rate-limiting enzyme for the process is glutamic acid decarboxylase (GAD), which utilizes pyridoxal phosphate as an important cofactor. Furthermore, agents such as L-glutamine- $\gamma$ -hydrazide and allylglycine inhibit this enzyme and, thus, the production of GABA. Once released from the presynaptic terminal, GABA can interact with a variety of presynaptic and postsynaptic receptors. Presynaptic regulation of GABA neuron firing activity and release occurs through somatodendritic (not shown) and nerve-terminal GABA<sub>B</sub> receptors, respectively. Baclofen is a GABA<sub>B</sub> receptor agonist. The binding of GABA to ionotropic GABA<sub>A</sub> receptors and metabotropic GABA<sub>B</sub> receptors mediates the effects of this receptor. The GABA<sub>B</sub> receptors are thought to mediate their actions by being coupled to  $\text{Ca}^{2+}$  or  $\text{K}^{+}$  channels via second-messenger systems. Many agents are able to modulate GABA<sub>A</sub> receptor function. Benzodiazepines, such as diazepam, increase  $\text{Cl}^{-}$  permeability, and there are numerous available antagonists directed against this site. There is also a distinctive barbiturate binding site on GABA<sub>A</sub> receptors, and many psychotropic agents are capable of influencing the function of this receptor (see blown-up diagram). GABA is taken back into presynaptic nerve endings by a high-affinity GABA uptake transporter (GABAT) similar to that of the monoamines. Once inside the neuron, GABA can be broken down by GABA transaminase (GABA-T), which is localized in the mitochondria; GABA that is not degraded is sequestered and stored in secretory vesicles by vesicular GABA transporters (VGATs), which differ from vesicular monoamine transporters (VMATs) in their bioenergetic dependence.

The metabolic pathway that produces GABA, mostly from glucose, is referred to as the *GABA shunt*. The conversion of  $\alpha$ -ketoglutarate into glutamate by the action of GABA-T and GAD catalyzes the decarboxylation of glutamic acid to produce GABA. GABA can undergo numerous transformations, of which the simplest is the reduction of succinic semialdehyde (SS) to  $\gamma$ -hydroxybutyrate (GHB). On the other hand, when SS is oxidized by succinic semialdehyde dehydrogenase (SSADH), the production of succinic acid (SA) occurs. GHB has received attention because it regulates narcoleptic episodes and may produce amnestic effects. The mood stabilizer and antiepileptic drug valproic acid is reported to inhibit SSADH and GABA-T. AC=adenylyl cyclase; TBPS=*t*-butylbicyclophosphorothionate.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

The contrasting functions of GABA-T, an enzyme able to synthesize both glutamate and the opposing GABA neurotransmitters as well as to catabolize GABA, become apparent when GABA-T is placed in the context of its role in the metabolic process. GABA-T converts GABA to succinic acid, and subsequent removal of the amino group yields  $\alpha$ -ketoglutarate. Thus,  $\alpha$ -ketoglutarate is able to be used by GABA-T in GABA biosynthesis as mentioned earlier ([Cooper et al. 2003](#)). This process, called the *GABA shunt*, maintains a steady GABA supply in the brain. As with the monoamines, the major mechanism by which the effects of GABA are terminated in the synaptic cleft is by reuptake through GABA transporters. The GABA transporters have a high



affinity for GABA and mediate their reuptake via a  $\text{Na}^+$  and  $\text{Cl}^-$  gradient ([Squire 2013](#)).

Studies have measured the density and size of calbindin-immunoreactive neurons (presumed to be GABAergic) in layers II and III of the dorsolateral PFC, reporting a 43% reduction in the density of these neurons in patients with MDD compared with control subjects ([Rajkowska 2002](#)). Of particular note, in the rostral orbitofrontal cortex, there was a trend toward a negative correlation between the duration of depression and the size of neuronal cell bodies, suggesting changes associated with disease progression. Valproate also has been shown to have neurogenic effects in at least one study. In cultured embryonic rat cortical cells and striatal primordial stem cells, valproate markedly increased the number and percentage of primarily GABAergic neurons and increased neurite outgrowth ([Laeng et al. 2004](#)).

Low levels of GABA were observed in patients with MDD, particularly in the occipital and prefrontal cortex of living patients as well as in postmortem brain samples of people with MDD, some of whom committed suicide ([Maciag et al. 2010](#)). Specifically, the calbindin immunoreactive GABAergic neurons of the occipital lobe were decreased by 28% in depressed individuals as compared with control subjects, consistent with previous observations of differences in visual evoked potentials between depressed and healthy populations ([Maciag et al. 2010](#)). In addition, a PET study that used [ $^{11}\text{C}$ ]flumazenil, a ligand for the benzodiazepine site of the  $\text{GABA}_A$  receptor, reported decreased GABA transmission in the medial temporal lobe of living antipsychotic-naïve patients with schizophrenia, consistent with postmortem studies showing lower GABA in the cortex ([Frankle et al. 2015](#); [Lewis et al. 2005](#)).

# GABA Receptors

The two major types of well-characterized GABA receptors are GABA<sub>A</sub> and GABA<sub>B</sub>, and most neurons in the CNS possess at least one of these types. The GABA<sub>A</sub> receptor is the more prevalent of the two in the mammalian CNS, and as a result has been extensively studied and characterized. GABA<sub>A</sub> contains an integral transmembrane chloride channel, which is opened on receptor activation, generally resulting in hyperpolarization of the neuron (i.e., suppressing excitability) ([Nestler et al. 2015](#)). The GABA receptor is a heteropentameric glycoprotein of approximately 275 kDa composed of a combination of multiple polypeptide subunits. GABA<sub>A</sub> shows enormous heterogeneity, being composed of a combination of five classes of polypeptide subunits ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ), of which there are at least 18 total subtypes ([Nestler et al. 2015](#)). The various receptors have variation in functional pharmacology, hinting at the multiple finely tuned roles that inhibitory neurotransmission plays in brain function.

It is now well established that benzodiazepines function by binding to a potentiator site on the GABA<sub>A</sub> receptor, increasing the amplitude and duration of inhibitory postsynaptic currents in response to GABA binding. Coexpression of additional  $\gamma$  subunits is believed to be necessary for the potentiation of GABA-mediated responses by benzodiazepines. In addition to benzodiazepines, barbiturates and ethanol are believed to exert many of their effects by potentiating the opening of the GABA<sub>A</sub> receptor chloride channel (see [Figure 2-8](#)) ([Nestler et al. 2015](#)). As noted earlier, GABA<sub>A</sub> receptors have a widespread distribution in the brain, and most of these receptors in the



brain are targets of the currently available benzodiazepines. For this reason, there has been considerable interest in determining whether the desirable and undesirable effects of benzodiazepines can be differentiated on the basis of the presence of a different subunit composition. Much of the work has used gene knockout technology; thus, mutation of the benzodiazepine binding site of the  $\alpha_1$  subunit in mice blocks the sedative, anticonvulsive, and amnesic, but not the anxiolytic, effects of diazepam ([Gould et al. 2003](#); [Möhler et al. 2002](#)). In contrast, the  $\alpha_2$  subunit (expressed highly in the cortex and hippocampus) is necessary for diazepam anxiolysis and myorelaxation. Thus, an  $\alpha_2$ -selective ligand would provide effective acute treatment of anxiety disorders without the unfavorable side-effect profile of benzodiazepines. A compound with this preferential affinity for  $\alpha_2$  has been reported to exert fewer sedative and depressant effects than diazepam in rat behavioral studies ([Gould et al. 2003](#); [Möhler et al. 2002](#)).

The phosphorylation of GABA<sub>A</sub> receptors is another mechanism by which this receptor complex can be regulated in function and expression. In this context, it is noteworthy that studies have shown that knockout mice deficient in PKC  $\epsilon$  isoforms show reduced anxiety and alcohol consumption and an enhanced response to effects of benzodiazepines (discussed in [Gould et al. 2003](#)). Furthermore,  $\alpha/\delta$  subunit assemblies are a novel neuronal GABA<sub>A</sub> receptor subunit partnership present in hippocampal interneurons, which functions to mediate tonic inhibitory currents. Notably, this assembly results in a complex that is highly sensitive to low concentrations of ethanol ([Glykys et al. 2007](#)).

The GABA<sub>B</sub> receptors are coupled to G<sub>i</sub> and G<sub>o</sub> and thereby regulate adenylyl cyclase activity (generally inhibit), K<sup>+</sup> channels (open), and Ca<sup>2+</sup> channels (close). GABA<sub>B</sub> receptors can function as an autoreceptor but are also found abundantly postsynaptically on non-GABAergic neurons. Of interest, mounting evidence indicates that receptor dimerization may be required for the activation of GABA<sub>B</sub> and possibly other GPCRs; although receptor dimerization has long been known to occur for growth factor and JAK (Janus tyrosine kinase)/STAT (signal transducers and activators of transcription) receptors, this was not expected for GPCRs. However, studies have reported that coexpression of two GABA<sub>B</sub> receptor subunits—subunit 1 (GABA<sub>B1</sub>) and subunit 2 (GABA<sub>B2</sub>)—is necessary for the formation of a functional GABA<sub>B</sub> receptor ([Bouvier 2001](#)). Data suggest that GABA<sub>B2</sub> receptor subunits may be necessary for proper protein folding of GABA<sub>B1</sub> receptor subunits (acting as a molecular chaperone) in the endoplasmic reticulum, but this remains to be definitively established. Support for the physiological relevance of this dimerization comes from studies showing that the GABA<sub>B1</sub> and GABA<sub>B2</sub> receptor subunits can be co-immunoprecipitated in rat cortical membrane preparations ([Kaupmann et al. 1997](#)); thus, the dimerization is not simply an in vitro phenomenon.

Relatively new GABAergic agents include zolpidem, a short-acting, positive allosteric modulator of the benzodiazepine site of the GABA<sub>A</sub> receptor that is used for initial insomnia; gaboxadol, a  $\delta$ -subunit-selective extrasynaptic GABA<sub>A</sub> receptor agonist; and tiagabine, a GABA reuptake inhibitor (blocks the GABA membrane

transporter GAT1) used as an anticonvulsant ([Nutt et al. 2015](#)). Alcohol and benzodiazepines both notably bind GABA<sub>A</sub> receptors and are cross-reactive with each other, to the point that benzodiazepines are used routinely to detoxify patients from alcohol intoxication while simultaneously avoiding precipitating seizures. Baclofen is a GABA<sub>B</sub> receptor agonist used to treat muscle spasms. Methaqualone, a sedative GABA<sub>A</sub> receptor agonist widely prescribed in the 1960s as a safe alternative to barbiturates, was taken off the market when it was found to be highly addictive and was abused in combination with alcohol ([Hammer et al. 2015](#)). Propofol, an anesthetic agent that has been in the news for abuse potential and accidental overdoses among famous celebrities, also binds the GABA<sub>A</sub> receptor in a manner similar to barbiturates and methaqualone, which all are highly addictive and keep the chloride channel open longer ([Hammer et al. 2015](#)).

---

## Purinergic Neurotransmission: Focus on Adenosine

---

It has been known for quite some time that ATP is capable of exerting profound effects on the nervous system ([Drury and Szent-Györgyi 1929](#)). However, adenosine and adenosine nucleotides have become more widely accepted as neuroactive substances in the CNS ([Cooper et al. 2003](#)). Adenosine is released from neurons and glia, but many of the neurotransmitter criteria outlined in the beginning of this chapter are not met. Nonetheless, adenosine is able to activate many cellular functions that can produce changes

in neuronal and behavioral states. For instance, adenosine stimulates cAMP in vitro in brain slices, and caffeine (which in addition to being a phosphodiesterase inhibitor is a well-known adenosine receptor antagonist) is able to block this response.

In the P1 (for purine) adenosine receptor class, four adenosine receptors have been cloned ( $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and  $A_3$ ), each of which has a unique tissue distribution, ligand binding affinity (nanomolar range), and signal transduction mechanisms ([Cooper et al. 2003](#)). Data suggest that the high-affinity adenosine receptors ( $A_1$  and  $A_{2A}$ ) may be activated under normal physiological conditions, whereas in pathological states such as hypoxia and inflammation (in which high adenosine concentrations [micromolar range] are present), low-affinity  $A_{2B}$  and  $A_3$  receptors are also activated.  $A_{2B}$  receptors are expressed in low levels in the brain but are ubiquitous in the rest of the body, whereas  $A_{2A}$  receptors are found in high concentrations in areas of the brain that receive dopaminergic projections (i.e., striatum, nucleus accumbens, and olfactory tubercle) ([Nestler et al. 2015](#)). Given this receptor's distribution, and the inverse relation between dopamine and adenosine, it has been postulated that  $A_{2A}$  antagonists may have some utility in the treatment of Parkinson's disease ([Nestler et al. 2015](#)). The mood stabilizer and antiepileptic drug carbamazepine, which primarily works through blocking voltage-gated sodium channels, also acts as an antagonist of the  $A_1$  subtype, which is epileptogenic in some vulnerable populations, such as children ([Booker et al. 2015](#); [Gould et al. 2002](#)).

Adenosine is also able to alter the function (both pre- and postsynaptically) of numerous neurotransmitters and their

receptors, including NMDA, mGlu receptors, ionotropic nicotinic receptors, norepinephrine, serotonin, dopamine, GABA, and various peptidergic receptors. Adenosine is widely regarded as a major component that regulates homeostasis of blood flow and metabolic demands in peripheral tissue physiology. Evidence suggests that adenosine is implicated as a fatigue factor to decrease cholinergic activity-arousal via presynaptic inhibition of glutamate release ([Brambilla et al. 2005](#)). In addition, the ionotropic ligand-gated P2X trimeric receptor class (containing seven subtypes: P2X<sub>1</sub> through P2X<sub>7</sub>) and the metabotropic GPCR P2Y receptor class (containing subtypes P2Y<sub>1</sub>, P2Y<sub>2</sub>, P2Y<sub>4</sub>, P2Y<sub>6</sub>, P2Y<sub>11</sub>, P2Y<sub>12</sub>, P2Y<sub>13</sub>, and P2Y<sub>14</sub>) are purine receptors that can be activated by ATP ([Nestler et al. 2015](#); [Ortiz et al. 2015](#)). It has been found that ATP is released from astrocytes (through an unknown mechanism) and that the release is accompanied by glutamate release (Ca<sup>2+</sup>-dependent) ([Innocenti et al. 2000](#)). However, more data suggest adenosine (which is derived from ATP) may serve as the true ligand for these purinergic receptors ([Fields and Stevens-Graham 2002](#)). The ATP/adenosine is then able to activate purine receptors (P2Y receptors) on neighboring astrocytes, and this stimulates Ca<sup>2+</sup> influx and subsequent release of glutamate and ATP to then affect other astrocytes and neurons. This may be a critical component in the communication process between glial cells, as well as representing a signaling molecule from glia to neurons ([Fields and Stevens-Graham 2002](#)).

Caffeine in coffee, theophylline in tea, and theobromine in cocoa are all methylxanthine compounds that at moderate doses cause increased alertness through antagonizing the

A<sub>1</sub>—and, to a lesser extent, the A<sub>2A</sub>—receptors, but in susceptible people at higher doses, they cause anxiety and even panic attacks ([Nestler et al. 2015](#)). Adenosine A<sub>1</sub> agonists may have neuroprotective effects in stroke both by inhibiting glutamate release (excitotoxicity) presynaptically and by inhibiting postsynaptic membrane depolarization and calcium influx (exacerbating excitotoxicity) ([Nestler et al. 2015](#)). Because the striatum has high levels of A<sub>2A</sub> receptors, A<sub>2A</sub> receptor antagonists are being explored for the treatment of Parkinson's disease-related L-dopa-induced hyperkinesia due to the inverse relation between adenosine and dopamine in the striatum. P2X<sub>3</sub> and P2X<sub>2/3</sub> receptors are being explored for pain modulation ([Nestler et al. 2015](#)). The literature is conflicted as to whether adenosine analogues cause depression or treat depression, but low brain purine levels have been reported in depressed female patients ([Krügel 2016](#)). Evidence has also increased in the literature that schizophrenia may be a hypoadenosinergic state, such as reduced A<sub>2A</sub> receptors in postmortem brain samples ([Krügel 2016](#)). Numerous adenosine PET ligands to adenosine receptors have been developed ([Mishina and Ishiwata 2014](#)).

---

## Peptidergic Neurotransmission

---

Neuropeptides have garnered increasing attention as critical modulators of CNS function. In general, peptide transmitters are released from neurons when they are stimulated at higher frequencies than those required to facilitate release of traditional neurotransmitters but can also be co-localized and co-released together with other

neurotransmitters ([Cooper et al. 2003](#); [Nestler et al. 2015](#)). Modulation of the firing rate pattern of neurons and subsequent release of neurotransmitters and peptides in a circumscribed fashion are likely important in the basal functioning of the brain, as well as response to specific stimuli. Interestingly, cannabinoids, an example of a neuropeptide neurotransmitter, do not alter firing rates of hippocampal neurons but change temporal coordination, an effect that correlates with memory deficits in individuals ([Soltesz and Staley 2006](#)). Localization of brain stem cannabinoid receptors (CB<sub>1</sub> and CB<sub>2</sub>) provided clues to how cannabinoids regulate brain function ([Van Sickle et al. 2005](#)). Virtually every known mammalian bioactive peptide is synthesized first as a precursor protein in which product peptides are flanked by cleavage sites. Neuropeptides are generally found in large dense-core vesicles, whereas other neurotransmitters, such as the monoamines, are packaged in small synaptic vesicles (approximately 50 nm) and are usually half the size of their peptidergic counterparts ([Kandel 2013](#); [Squire 2013](#)).

Space limitations preclude an extensive discussion of the diverse array of neuropeptides known to exist in the mammalian brain. [Table 2-2](#) highlights some of the major neuropeptides that may be of particular psychiatric relevance. In the remainder of this section, we highlight the basic aspects of peptidergic transmission vis-à-vis an overview of opiodergic neurotransmission. We briefly discuss selected neuropeptides here; a general review of neuropeptides as potential drug targets can be found elsewhere ([Hoyer and Bartfai 2012](#)).

## Corticotropin-Releasing Factor

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis may relate to the pathophysiology of mental illness. Corticotropin-releasing factor (CRF) is a key neuropeptide controlling the HPA axis with a 41-amino acid sequence that is identical in humans and in rats ([Montecucchi et al. 1980](#)). CRF is produced in the paraventricular nucleus (PVN) of the hypothalamus, and once secreted into pituitary portal blood, it binds to G<sub>s</sub>-coupled receptors on cells in the pituitary to increase adenylate cyclase, cAMP-dependent protein kinase, and cytosolic calcium concentrations ([Lovejoy et al. 2014](#)). CRF is also capable of activating G<sub>q</sub>-, G<sub>i</sub>-, G<sub>o</sub>-, and G<sub>z</sub>-coupled receptors ([Grammatopoulos et al. 2001](#)). CRF receptors are classified into CRF1 and CRF2 ([Chen et al. 1993](#); [Liaw et al. 1996](#); [Lovejoy et al. 2014](#)). The CRF1A receptor is the dominant subtype in the brain and peripheral tissue, whereas the CRF1D receptor is thought to play a competing role against CRF1A, with CRF1B and CRF1C also being identified ([Hillhouse and Grammatopoulos 2006](#)). Although CRF2 receptors and their spliced variants CRF2A, CRF2B, and CRF2C are localized in the brain, they exist to a greater degree in peripheral tissue ([Hillhouse and Grammatopoulos 2006](#)).

**TABLE 2-2.     Selected peptides and their presumed relevance to psychiatric disorders and treatment**

Group	Potential clinical relevance
<b>Opioid and related peptides</b>	
Endorphin	Analgesia for chronic pain
Enkephalin	Analgesia



<b>Group</b>	<b>Potential clinical relevance</b>
Dynorphin	Analgesia
Nociceptin	Binds ORL1 receptor; increased pain perception
<b>Gut-derived peptides</b>	
Vasoactive intestinal peptide	Sexual behavior
Cholecystokinin	Anxiety/panic
Secretin	Brief reports of help with autism and transient antipsychotic properties
Somatostatin	Mood disorders and treatment
<b>Tachykinin peptides</b>	
Substance P (substance K)	Receptor is NK <sub>1</sub> , no efficacy shown for depression; inflammation
Neurotensin/neuromedin N	Analgesia, hypothermia; regulated by lithium, involved in dopamine signaling
<b>Pituitary peptides</b>	
Oxytocin	Affiliative, prosocial, bonding behavior; decreases fear; may help increase sociability in autism

<b>Group</b>	<b>Potential clinical relevance</b>
Vasopressin	Also called antidiuretic hormone; receptors are $V_{1a}$ , $V_{1b}$ , $V_2$ ; antagonists have anxiolytic, anti-aggression, and anti-irritability properties
Adrenocorticotrophic hormone	Dysregulated in mood disorders
Melanocyte-stimulating hormone	Antidepressant and anti-anxiety properties
<b>Hypothalamic-releasing factors</b>	
Corticotropin-releasing factor	Anxiety and fear
Thyrotropin-releasing factor	Potential antidepressant effects
<b>Others</b>	
Calcitonin gene-related peptide	Regulated by ECT and lithium
Angiotensin	Mood disorders, bipolar disorder
Leptin	Satiety signal; inhibits feeding drive
Cocaine- and amphetamine-related transcript	Drug addiction, eating disorders

<b>Group</b>	<b>Potential clinical relevance</b>
Galanin	Potentially relevant for Alzheimer's diagnosis and other cognitive disorders
Neuropeptide Y	Potential endogenous anxiolytic; regulated by antidepressants/lithium; reduced by early maternal separation; antagonists may decrease appetite
Orexin/hypocretin	Narcolepsy and other sleep abnormalities; eating disorders

*Note.* This table summarizes selected peptides and their presumed relevance for psychiatric disorders and their treatment; it is not meant to be an exhaustive listing of findings. It should also be noted that in some cases—for example, CRF (mood/anxiety), NPY and neurotensin (regulation by medications), oxytocin (affiliative behavior), and orexin (narcolepsy)—the data are quite convincing. In many of the other examples noted, the evidence must be considered preliminary but is, in our opinion, quite noteworthy and warrants further investigation. A discussion of these peptides is beyond the scope of this introductory chapter; nevertheless, readers are encouraged to explore the latest research in this rapidly evolving and exciting literature. ECT=electroconvulsive therapy.

Stressful life events and chronic stress can induce brain circuit changes that are thought to relate to the pathophysiology of some anxiety disorders and PTSD. Increased CRF secretion from the hypothalamus and adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland are associated with aberrant cortisol responses to stress. Depressed patients and suicide victims have elevations of CRF concentrations in the CSF, increased cerebrocortical CRF immunoreactivity, and decreased CRF1 receptor binding; furthermore, decreased CRF1 mRNA expression has been reported in postmortem brain tissue of suicide victims ([Sanders and Nemeroff 2016](#)). Although probes of HPA function, such as the dexamethasone/CRF suppression tests, indicate hyperactivity of the axis in depressed patients, it is largely a nonspecific finding and can occur in other psychiatric illnesses.

## Oxytocin and Vasopressin

Other brain-related peptides of interest to psychiatric illnesses that can be co-secreted with CRF from the hypothalamus are oxytocin and vasopressin, but treatments in psychiatry directed at these receptors have not yet received clinical use. Oxytocin and vasopressin are both 9-amino acid peptide hormones. Oxytocin has a 6-amino acid ring and a 3-amino acid tail with the ability to exert disulfide bonds that may relate to its neurophysiological mode of action. PVN and supraoptic nuclei of the hypothalamus are known to contain high levels of oxytocin, whereas vasopressin is localized in other cells in the hypothalamus; however, both can extend cellular processes into the posterior pituitary. These neuropeptides do not

function as traditional neurotransmitters, but rather permeate through neural tissue by volume transmission (Neumann and Landgraf 2012). It is noteworthy that oxytocin may modulate the amygdala and brain stem neurons to facilitate fear avoidance, whereas vasopressin may exert a role in PTSD (Carter 1998; Wentworth et al. 2013). Furthermore, oxytocin and vasopressin bind to distinct brain receptors that can be modulated by epigenetics (Ebstein et al. 2012). The oxytocin receptor is a GPCR located on 3p24-26, whereas three receptor subtypes have been identified for vasopressin (V1a, V1b, V2), with V1a and V1b currently associated with modulation of behaviors (Gimpl and Fahrenholz 2001).

## Opiates

*Opioids* are a family of peptides that occur endogenously in the brain (endorphins), as botanicals, or as drugs. POMC is a precursor protein characterized in the 1980s that gives rise to ACTH and a class of endogenous opiates called endorphins. POMC, proenkephalin-derived peptides, and prodynorphin-derived peptides yield opioid peptides on cleavage. Three opioid peptide families exist: enkephalins, endorphins, and dynorphins. POMC gene expression occurs in various areas of the brain and in other tissues. POMC has tissue- and cell-specific regulatory factors at every step from gene transcription to its posttranslational processing. Opioid peptides are stored in large dense-core vesicles and are co-released from neurons that usually contain a classic neurotransmitter agent (e.g., glutamate and norepinephrine). Opiorphin, an endogenously derived enkephalin that inactivates zinc ectopeptidase, has been

described as equal to morphine in the perception of pain (Wisner et al. 2006). Although opiates are widely associated with and used therapeutically in pain modulation, evidence indicates that dynorphin can actually activate bradykinin receptors and contribute to neuropathic pain (Altier and Zamponi 2006).

Opioids activate a variety of signal transduction processes, and different mechanisms in their regulation are in place for different cell types. The opioid receptors are GPCRs and exert their cellular effects by inhibiting adenylyl cyclase and regulating  $K^+$  and  $Ca^{2+}$  channels, via activation of  $G_i/G_o$ . There are three types of opioid receptors— $\mu$ ,  $\delta$ , and  $\kappa$ , each of which is further subclassified—in addition to opioid receptor like-1 (ORL1) receptor. These receptors are 7-transmembrane-spanning proteins that couple to inhibitory G-proteins or form homo- and heterodimeric complexes. They also alter calcium signaling through dissociation of  $G_{\beta\gamma}$  subunits and by reducing sensitivity to L-type, N-type, and P/Q-type channels. Also, numerous mechanisms have been described that allow opiates and synthetic opiate agents (i.e., morphine, fentanyl) to regulate receptor signaling, which can occur from the receptor being phosphorylated, desensitized, and internalized. Once the receptor is phosphorylated, recruitment of arrestins to the receptor occurs and can prime for sequestration. Interestingly, arrestin-3-deficient mice have tolerance to morphine and other  $\mu$  opioid receptor agents, whereas polymorphisms in *OPRM1* have been associated with opioid dependency. Intracellular cascades associated with opioid dependence and withdrawal have documented changes in mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase 1/2 (ERK1/2) cascades, as well as

changes in transcription factors such as phosphorylated cAMP response element-binding protein (pCREB) and DeltaFosB, which have been linked to changes in the reward system ([Al-Hasani and Bruchas 2011](#)).

The continued study of the opioid system and the second-messenger changes brought about by the chronic administration of opioids has greatly facilitated our understanding of the molecular and cellular effects of drugs of abuse and the potential to develop novel therapeutics ([Nestler et al. 2015](#)). In response to the worldwide heroin epidemic, the medication buprenorphine, a partial agonist of the  $\mu$  opioid receptor and an antagonist of the  $\delta$  and  $\kappa$  opioid receptors, has become one of the most widely prescribed medications in the world to treat opioid use disorders, perhaps because it can be prescribed from an outpatient office setting.

---

## Conclusion

---

We have provided an overview of some fundamental aspects of neurotransmitters and brain receptor classes. For most psychiatrists, molecular and cellular biology have not traditionally played a major role in day-to-day clinical practice. However, new insights into the molecular and cellular basis of disease and drug action are being generated at an ever-increasing rate and will ultimately result in a transformation of our understanding and management of diseases. The “molecular medicine revolution” has used the power of sophisticated cellular and molecular biological methodologies to tackle many of society’s most devastating illnesses. The rate of progress

has been exciting indeed, and hundreds of GPCRs and their effectors have now been identified and characterized at the molecular and cellular levels. These efforts have allowed the study of a variety of human diseases that are caused by abnormalities in cell-to-cell communication. Studies of such diseases are offering unique insights into the physiological and pathophysiological functioning of many cellular transmembrane signaling pathways.

Psychiatry, like much of the rest of medicine, has entered a new and exciting age demarcated by the rapid advances and the promise of molecular and cellular biology and neuroimaging. There is a growing appreciation that severe psychiatric disorders arise from abnormalities in cellular plasticity cascades, leading to aberrant information processing in synapses and circuits mediating affective, cognitive, motoric, and neurovegetative functions. Thus, these illnesses can be best conceptualized as genetically influenced disorders of synapses and circuits rather than simply as deficits or excesses in individual neurotransmitters. Furthermore, many of these pathways play critical roles not only in synaptic and behavioral plasticity but also in long-term atrophic processes. Targeting these pathways in treatment may stabilize the underlying disease process by reducing the frequency and severity of the profound mood cycling that contributes to morbidity and mortality.



---

# References

---

- Adhikarla V, Zeng F, Votaw JR, et al: Compartmental modeling of [(11)C]MENET binding to the norepinephrine transporter in the healthy human brain. *Nucl Med Biol* 43(5):318-323, 2016 27150035
- Aghajanian GK, Marek GJ: Serotonin and hallucinogens. *Neuropsychopharmacology* 21 (2 suppl):16S-23S, 1999 10432484
- Ahlquist RP: A study of the adrenotropic receptors. *Am J Physiol* 153(3):586-600, 1948 18882199
- AhnAllen CG, Bidwell LC, Tidey JW: Cognitive effects of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. *Nicotine Tob Res* 17(5): 510-514, 2015 25143294
- Akil M, Kolachana BS, Rothmond DA, et al: Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. *J Neurosci* 23(6):2008-2013, 2003 12657658
- Al-Hasani R, Bruchas MR: Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology* 115(6):1363-1381, 2011 22020140
- Alexander SP, Benson HE, Faccenda E, et al; CGTP Collaborators: The Concise Guide to PHARMACOLOGY 2013/14: enzymes. *Br J Pharmacol* 170(8):1797-1867, 2013a 24528243
- Alexander SP, Benson HE, Faccenda E, et al; CGTP Collaborators: The Concise Guide to PHARMACOLOGY 2013/14: G protein-coupled receptors. *Br J Pharmacol* 170(8):1459-1581, 2013b 24517644
- Alexander SP, Benson HE, Faccenda E, et al; CGTP Collaborators: The Concise Guide to PHARMACOLOGY

- 2013/14: ion channels. Br J Pharmacol 170(8):1607-1651, 2013c 24528239
- Alexander SP, Benson HE, Faccenda E, et al; CGTP Collaborators: The Concise Guide to PHARMACOLOGY 2013/14: ligand-gated ion channels. Br J Pharmacol 170(8):1582-1606, 2013d 24528238
- Alexander SP, Benson HE, Faccenda E, et al; CGTP Collaborators: The Concise Guide to PHARMACOLOGY 2013/14: nuclear hormone receptors. Br J Pharmacol 170(8):1652-1675, 2013e 24528240
- Alexander SP, Benson HE, Faccenda E, et al; CGTP Collaborators: The Concise Guide to PHARMACOLOGY 2013/14: overview. Br J Pharmacol 170(8):1449-1458, 2013f 24528237
- Altier C, Zamponi GW: Opioid, cheating on its receptors, exacerbates pain. Nat Neurosci 9(12):1465-1467, 2006 17128281
- Altınbaş K, Guloksuz S, Oral ET: Clinical potential of cariprazine in the treatment of acute mania. Psychiatr Danub 25(3):207-213, 2013 24048386
- Amat J, Baratta MV, Paul E, et al: Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat Neurosci 8(3):365-371, 2005 15696163
- Anand A, Barkay G, Dziedzic M, et al: Striatal dopamine transporter availability in unmedicated bipolar disorder. Bipolar Disord 13(4):406-413, 2011 21843280
- Andén NE, Magnusson T, Rosengren E: On the presence of dihydroxyphenylalanine decarboxylase in nerves. Experientia 20(6):328-329, 1964 5216334
- Andrade R, Malenka RC, Nicoll RA: A G protein couples serotonin and GABAB receptors to the same channels in hippocampus. Science 234(4781):1261-1265, 1986 2430334
- Andreotta F, Carboni L, Grafton G, et al: Hippocampal 5-HT<sub>7</sub> receptors signal phosphorylation of the GluA1

- subunit to facilitate AMPA receptor mediated-neurotransmission in vitro and in vivo. *Br J Pharmacol* 173(9):1438–1451, 2016 26773257
- Ansorge MS, Zhou M, Lira A, et al: Early life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science* 306(5697):879–881, 2004 15514160
- Argolo FC, Cavalcanti-Ribeiro P, Netto LR, et al: Prevention of posttraumatic stress disorder with propranolol: a meta-analytic review. *J Psychosom Res* 79(2):89–93, 2015 25972056
- Arnsten AF, Girgis RR, Gray DL, et al: Novel dopamine therapeutics for cognitive deficits in schizophrenia. *Biol Psychiatry* 81(1):67–77, 2017 26946382
- Ayalon G, Stern-Bach Y: Functional assembly of AMPA and kainate receptors is mediated by several discrete protein-protein interactions. *Neuron* 31(1):103–113, 2001 11498054
- Ballard ED, Luckenbaugh DA, Richards EM, et al: Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. *J Psychiatr Res* 68:68–73, 2015 26228403
- Bangasser DA, Wiersielis KR, Khantsis S: Sex differences in the locus coeruleus-norepinephrine system and its regulation by stress. *Brain Res* 1641(pt B):177–188, 2016 26607253
- Barria A, Malinow R: NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. *Neuron* 48(2):289–301, 2005 16242409
- Bauman AL, Apparsundaram S, Ramamoorthy S, et al: Cocaine and antidepressant-sensitive biogenic amine transporters exist in regulated complexes with protein phosphatase 2A. *J Neurosci* 20(20):7571–7578, 2000 11027216
- Beaulieu JM, Sotnikova TD, Yao WD, et al: Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade.

- Proc Natl Acad Sci U S A 101(14):5099-5104, 2004  
15044694
- Bekkers JM, Stevens CF: NMDA and non-NMDA receptors are co-localized at individual excitatory synapses in cultured rat hippocampus. *Nature* 341(6239):230-233, 1989 2571090
- Bell C, Abrams J, Nutt D: Tryptophan depletion and its implications for psychiatry. *Br J Psychiatry* 178:399-405, 2001 11331552
- Ben Mamou C, Gamache K, Nader K: NMDA receptors are critical for unleashing consolidated auditory fear memories. *Nat Neurosci* 9(10):1237-1239, 2006 16998481
- Beneyto M, Kristiansen LV, Oni-Orisan A, et al: Abnormal glutamate receptor expression in the medial temporal lobe in schizophrenia and mood disorders. *Neuropsychopharmacology* 32(9):1888-1902, 2007 17299517
- Berman RM, Cappiello A, Anand A, et al: Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47(4):351-354, 2000 10686270
- Berry CB, Bubser M, Jones CK, et al: Discovery and characterization of ML398, a potent and selective antagonist of the D4 receptor with in vivo activity. *ACS Med Chem Lett* 5(9):1060-1064, 2014 25221667
- Blier P, Piñeyro G, el Mansari M, et al: Role of somatodendritic 5-HT autoreceptors in modulating 5-HT neurotransmission. *Ann N Y Acad Sci* 861:204-216, 1998 9928258
- Bogdanski DF, Pletscher A, Brodie BB, et al: Identification and assay of serotonin in brain. *J Pharmacol Exp Ther* 117(1):82-88, 1956 13320304
- Booker SA, Pires N, Cobb S, et al: Carbamazepine and oxcarbazepine, but not eslicarbazepine, enhance excitatory synaptic transmission onto hippocampal CA1 pyramidal cells through an antagonist action at

- adenosine A1 receptors. *Neuropharmacology* 93:103–115, 2015 25656478
- Bortolato M, Pivac N, Muck Seler D, et al: The role of the serotonergic system at the interface of aggression and suicide. *Neuroscience* 236:160–185, 2013 23333677
- Bourne HR, Nicoll R: Molecular machines integrate coincident synaptic signals. *Cell* 72 (suppl):65–75, 1993 8094038
- Bouvier M: Oligomerization of G-protein-coupled transmitter receptors. *Nat Rev Neurosci* 2(4):274–286, 2001 11283750
- Brambilla D, Chapman D, Greene R: Adenosine mediation of presynaptic feedback inhibition of glutamate release. *Neuron* 46(2):275–283, 2005 15848805
- Brodie TG: The immediate action of an intravenous injection of blood-serum. *J Physiol* 26(1-2):48–71, 1900 16992567
- Bruinvels AT, Palacios JM, Hoyer D: 5-hydroxytryptamine1 recognition sites in rat brain: heterogeneity of non-5-hydroxytryptamine1A/1C binding sites revealed by quantitative receptor autoradiography. *Neuroscience* 53(2):465–473, 1993 8492913
- Bruno V, Battaglia G, Copani A, et al: An activity-dependent switch from facilitation to inhibition in the control of excitotoxicity by group I metabotropic glutamate receptors. *Eur J Neurosci* 13(8):1469–1478, 2001 11328342
- Brüss M, Pörzgen P, Bryan-Lluka LJ, et al: The rat norepinephrine transporter: molecular cloning from PC12 cells and functional expression. *Brain Res Mol Brain Res* 52(2):257–262, 1997 9495547
- Brüss M, Bönisch H, Bühlen M, et al: Modified ligand binding to the naturally occurring Cys-124 variant of the human serotonin 5-HT1B receptor. *Pharmacogenetics* 9(1):95–102, 1999 10208648
- Bylund DB, Eikenberg DC, Hieble JP, et al: International Union of Pharmacology nomenclature of adrenoceptors.

- Pharmacol Rev 46(2):121-136, 1994 7938162
- Cahill L, Prins B, Weber M, et al: Beta-adrenergic activation and memory for emotional events. *Nature* 371(6499):702-704, 1994 7935815
- Camardese G, De Risio L, Di Nicola M, et al: Changes of dopamine transporter availability in depressed patients with and without anhedonia: a 123I-N- $\omega$ -fluoropropyl-carbomethoxy-3 $\beta$ -(4-Iodophenyl)tropane SPECT study. *Neuropsychobiology* 70(4):235-243, 2014a 25613182
- Camardese G, Di Giuda D, Di Nicola M, et al: Imaging studies on dopamine transporter and depression: a review of literature and suggestions for future research. *J Psychiatr Res* 51:7-18, 2014b 24433847
- Cannon DM, Klaver JK, Gandhi SK, et al: Genetic variation in cholinergic muscarinic-2 receptor gene modulates M2 receptor binding in vivo and accounts for reduced binding in bipolar disorder. *Mol Psychiatry* 16(4):407-418, 2011 20351719
- Carlezon WA Jr, Nestler EJ: Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? *Trends Neurosci* 25(12):610-615, 2002 12446127
- Carman CV, Benovic JL: G-protein-coupled receptors: turn-ons and turn-offs. *Curr Opin Neurobiol* 8(3):335-344, 1998 9687355
- Carter CS: Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology* 23(8):779-818, 1998 9924738
- Casado M, Bendahan A, Zafra F, et al: Phosphorylation and modulation of brain glutamate transporters by protein kinase C. *J Biol Chem* 268(36):27313-27317, 1993 7903307
- Caspi A, Sugden K, Moffitt TE, et al: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301(5631):386-389, 2003 12869766
- Catapano LA, Manji HK: G protein-coupled receptors in major psychiatric disorders. *Biochim Biophys Acta*

1768(4):976-993, 2007 17078926

Chan E, Fogler JM, Hammerness PG: Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. *JAMA* 315(18):1997-2008, 2016 27163988

Chandley MJ, Szebeni A, Szebeni K, et al: Elevated gene expression of glutamate receptors in noradrenergic neurons from the locus coeruleus in major depression. *Int J Neuropsychopharmacol* 17(10):1569-1578, 2014 24925192

Chávez AE, Singer JH, Diamond JS: Fast neurotransmitter release triggered by Ca influx through AMPA-type glutamate receptors. *Nature* 443(7112):705-708, 2006 17036006

Chen G, Hasanat KA, Bebchuk JM, et al: Regulation of signal transduction pathways and gene expression by mood stabilizers and antidepressants. *Psychosom Med* 61(5):599-617, 1999 10511011

Chen R, Lewis KA, Perrin MH, Vale WW: Expression cloning of a human corticotropin-releasing-factor receptor. *Proc Natl Acad Sci U S A* 90(19):8967-8971, 1993 7692441

Chiuccariello L, Houle S, Miler L, et al: Elevated monoamine oxidase a binding during major depressive episodes is associated with greater severity and reversed neurovegetative symptoms. *Neuropsychopharmacology* 39(4):973-980, 2014 24154665

Clark D, White FJ: D1 dopamine receptor—the search for a function: a critical evaluation of the D1/D2 dopamine receptor classification and its functional implications. *Synapse* 1(4):347-388, 1987 2971273

Conn PJ, Pin JP: Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev Pharmacol Toxicol* 37:205-237, 1997 9131252

Conn PJ, Sanders-Bush E: Central serotonin receptors: effector systems, physiological roles and regulation.

- Psychopharmacology (Berl) 92(3):267-277, 1987  
2819915
- Conradt M, Stoffel W: Inhibition of the high-affinity brain glutamate transporter GLAST-1 via direct phosphorylation. J Neurochem 68(3):1244-1251, 1997  
9048771
- Cooper JR, Bloom FE, Roth RH: The Biochemical Basis of Neuropharmacology, 8th Edition. New York, Oxford University Press, 2003
- Costa A, Riedel M, Müller U, et al: Relationship between SLC6A3 genotype and striatal dopamine transporter availability: a meta-analysis of human single photon emission computed tomography studies. Synapse 65(10):998-1005, 2011 21404331
- Coupland N, Zedkova L, Sanghera G, et al: Response to pentagastrin after acute phenylalanine and tyrosine depletion in healthy men: a pilot study. J Psychiatry Neurosci 26(3):247-251, 2001 11394194
- Coyle JT, Tsai G, Goff DC: Ionotropic glutamate receptors as therapeutic targets in schizophrenia. Curr Drug Targets CNS Neurol Disord 1(2):183-189, 2002 12769626
- Dahlström A: Regional distribution of brain catecholamines and serotonin. Neurosci Res Program Bull 9(2):197-205, 1971 5164695
- D'Amato RJ, Largent BL, Snowman AM, et al: Selective labeling of serotonin uptake sites in rat brain by [3H]citalopram contrasted to labeling of multiple sites by [3H]imipramine. J Pharmacol Exp Ther 242(1):364-371, 1987 3475452
- Darcet F, Gardier AM, David DJ, et al: Chronic 5-HT<sub>4</sub> receptor agonist treatment restores learning and memory deficits in a neuroendocrine mouse model of anxiety/depression. Neurosci Lett 616:197-203, 2016 26850572
- David SP, Murthy NV, Rabiner EA, et al: A functional genetic variation of the serotonin (5-HT) transporter affects 5-



- HT1A receptor binding in humans. *J Neurosci* 25(10):2586-2590, 2005 15758168
- De Vivo M, Maayani S: Stimulation and inhibition of adenylyl cyclase by distinct 5-hydroxytryptamine receptors. *Biochem Pharmacol* 40(7):1551-1558, 1990 2222510
- Descarries L, Watkins KC, Garcia S, et al: The serotonin neurons in nucleus raphe dorsalis of adult rat: a light and electron microscope radioautographic study. *J Comp Neurol* 207(3):239-254, 1982 7107985
- Deschwenden A, Karolewicz B, Feyissa AM, et al: Reduced metabotropic glutamate receptor 5 density in major depression determined by [(11)C]ABP688 PET and postmortem study. *Am J Psychiatry* 168(7):727-734, 2011 21498461
- Diazgranados N, Ibrahim L, Brutsche NE, et al: A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 67(8):793-802, 2010 20679587
- Ding YS, Naganawa M, Gallezot JD, et al: Clinical doses of atomoxetine significantly occupy both norepinephrine and serotonin transports: implications on treatment of depression and ADHD. *Neuroimage* 86:164-171, 2014 23933039
- Donaldson ZR, le Francois B, Santos TL, et al: The functional serotonin 1a receptor promoter polymorphism, rs6295, is associated with psychiatric illness and differences in transcription. *Transl Psychiatry* 6:e746, 2016 26926882
- Drevets WC, Bogers W, Raichle ME: Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol* 12(6):527-544, 2002 12468016
- Drevets WC, Zarate CA Jr, Furey ML: Antidepressant effects of the muscarinic cholinergic receptor antagonist

- scopolamine: a review. *Biol Psychiatry* 73(12):1156-1163, 2013 23200525
- Drury AN, Szent-Györgyi A: The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. *J Physiol* 68(3):213-237, 1929 16994064
- Du J, Gould T, Manji H: Neurotrophic signaling in mood disorders, in *Signal Transduction and Human Disease*. Edited by Finkel T, Gutkind JS. Hoboken, NJ, Wiley-Interscience, 2003, pp 411-445
- Du J, Suzuki K, Wei Y, et al: The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. *Neuropsychopharmacology* 32(4):793-802, 2007 16936714
- Duman RS: Synaptic plasticity and mood disorders. *Mol Psychiatry* 7 (suppl 1): S29-S34, 2002 11986993
- Dunlop BW, Nemeroff CB: The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry* 64(3):327-337, 2007 17339521
- Ebstein RP, Knafo A, Mankuta D, et al: The contributions of oxytocin and vasopressin pathway genes to human behavior. *Horm Behav* 61(3):359-379, 2012 22245314
- Emeson RB, Morabito MV: Food fight: the NPY-serotonin link between aggression and feeding behavior. *Sci STKE* 2005(277): pe12, 2005 15798100
- Encinas JM, Vaahtokari A, Enikolopov G: Fluoxetine targets early progenitor cells in the adult brain. *Proc Natl Acad Sci U S A* 103(21):8233-8238, 2006 16702546
- Faden AI, Demediuk P, Panter SS, et al: The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* 244(4906):798-800, 1989 2567056
- Farber NB, Kim SH, Dikranian K, et al: Receptor mechanisms and circuitry underlying NMDA antagonist neurotoxicity. *Mol Psychiatry* 7(1):32-43, 2002 11803444

- Feyissa AM, Chandran A, Stockmeier CA, et al: Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 33(1):70-75, 2009 18992785
- Feyissa AM, Woolverton WL, Miguel-Hidalgo JJ, et al: Elevated level of metabotropic glutamate receptor 2/3 in the prefrontal cortex in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 34(2):279-283, 2010 19945495
- Fields RD, Stevens-Graham B: New insights into neuron-glia communication. *Science* 298(5593):556-562, 2002 12386325
- Foote SL, Bloom FE, Aston-Jones G: Nucleus locus ceruleus: new evidence of anatomical and physiological specificity. *Physiol Rev* 63(3):844-914, 1983 6308694
- Fountoulakis KN, Gazouli M, Kelsoe J, et al: The pharmacodynamic properties of lurasidone and their role in its antidepressant efficacy in bipolar disorder. *Eur Neuropsychopharmacol* 25(3):335-342, 2015 25596883
- Frankle WG, Cho RY, Prasad KM, et al: In vivo measurement of GABA transmission in healthy subjects and schizophrenia patients. *Am J Psychiatry* 172(11):1148-1159, 2015 26133962
- Freedman R, Coon H, Myles-Worsley M, et al: Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci U S A* 94(2):587-592, 1997 9012828
- Gaddum JH, Picarelli ZP: Two kinds of tryptamine receptor. *Br Pharmacol Chemother* 12(3):323-328, 1957 13460238
- Galli A, DeFelice LJ, Duke BJ, et al: Sodium-dependent norepinephrine-induced currents in norepinephrine-transporter-transfected HEK-293 cells blocked by cocaine and antidepressants. *J Exp Biol* 198(pt 10):2197-2212, 1995 7500004

- Galli A, Blakely RD, DeFelice LJ: Norepinephrine transporters have channel modes of conduction. *Proc Natl Acad Sci U S A* 93(16):8671–8676, 1996 8710929
- Gardner AJ, Griffiths J: Propranolol, post-traumatic stress disorder, and intensive care: incorporating new advances in psychiatry into the ICU. *Crit Care* 18(6):698, 2014 25673425
- Gimpl G, Fahrenholz F: The oxytocin receptor system: structure, function, and regulation. *Physiol Rev* 81(2):629–683, 2001 11274341
- Glykys J, Peng Z, Chandra D, et al: A new naturally occurring GABA(A) receptor subunit partnership with high sensitivity to ethanol. *Nat Neurosci* 10(1):40–48, 2007 17159992
- González-Maeso J, Weisstaub NV, Zhou M, et al: Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 53(3):439–452, 2007 17270739
- Goodwin FK, Jamison KR, Ghaemi SN: Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression, 2nd Edition. New York, Oxford University Press, 2007
- Gould TD, Chen G, Manji HK: Mood stabilizer psychopharmacology. *Clin Neurosci Res* 2(3–4):193–212, 2002 22707923
- Gould T, Gray N, Manji H: Cellular neurobiology of severe mood and anxiety disorders: implications for the development of novel therapeutics, in *Molecular Neurobiology for the Clinician*. Edited by Charney D (Review of Psychiatry Series, Vol 22; Oldham JM and Riba MB, series editors). Washington, DC, American Psychiatric Publishing, 2003, pp 123–228
- Grailhe R, Grabtree GW, Hen R: Human 5-HT(5) receptors: the 5-HT(5A) receptor is functional but the 5-HT(5B) receptor was lost during mammalian evolution. *Eur J Pharmacol* 418(3):157–167, 2001 11343685

- Grammatopoulos DK, Randeva HS, Levine MA, et al: Rat cerebral cortex corticotropin-releasing hormone receptors: evidence for receptor coupling to multiple G-proteins. *J Neurochem* 76(2):509–519, 2001 11208914
- Gross C, Zhuang X, Stark K, et al: Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* 416(6879):396–400, 2002 11919622
- Gu S, Wang W, Wang F, et al: Neuromodulator and emotion biomarker for stress induced mental disorders. *Neural Plast* 2016:2609128, 2016 27051536
- Guillin O, Diaz J, Carroll P, et al: BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature* 411(6833):86–89, 2001 11333982
- Haass-Koffler CL, Leggio L, Kenna GA: Pharmacological approaches to reducing craving in patients with alcohol use disorders. *CNS Drugs* 28(4):343–360, 2014 24573997
- Habert E, Graham D, Tahraoui L, et al: Characterization of [3H]paroxetine binding to rat cortical membranes. *Eur J Pharmacol* 118(1-2):107–114, 1985 2935409
- Hammer H, Bader BM, Ehnert C, et al: A multifaceted GABAA receptor modulator: functional properties and mechanism of action of the sedative-hypnotic and recreational drug methaqualone (Quaalude). *Mol Pharmacol* 88(2):401–420, 2015 26056160
- Harder R, Bönisch H: Effects of monovalent ions on the transport of noradrenaline across the plasma membrane of neuronal cells (PC-12 cells). *J Neurochem* 45(4):1154–1162, 1985 4031884
- Henley JM, Wilkinson KA: Synaptic AMPA receptor composition in development, plasticity and disease. *Nat Rev Neurosci* 17(6):337–350, 2016 27080385
- Henry LK, DeFelice LJ, Blakely RD: Getting the message across: a recent transporter structure shows the way. *Neuron* 49(6): 791–796, 2006 16543127

- Heurteaux C, Lucas G, Guy N, et al: Deletion of the background potassium channel TREK-1 results in a depression-resistant phenotype. *Nat Neurosci* 9(9):1134-1141, 2006 16906152
- Hillhouse EW, Grammatopoulos DK: The molecular mechanisms underlying the regulation of the biological activity of corticotropin-releasing hormone receptors: implications for physiology and pathophysiology. *Endocr Rev* 27(3):260-286, 2006 16484629
- Hoffman BJ, Mezey E: Distribution of serotonin 5-HT<sub>1C</sub> receptor mRNA in adult rat brain. *FEBS Lett* 247(2):453-462, 1989 2714444
- Hollmann M, Maron C, Heinemann S: N-glycosylation site tagging suggests a three transmembrane domain topology for the glutamate receptor GluR1. *Neuron* 13(6):1331-1343, 1994 7993626
- Horti AG, Kuwabara H, Holt DP, et al: Recent PET radioligands with optimal brain kinetics for imaging nicotinic acetylcholine receptors. *J Labelled Comp Radiopharm* 56(3-4):159-166, 2013 24285321
- Hoyer D, Bartfai T: Neuropeptides and neuropeptide receptors: drug targets, and peptide and non-peptide ligands: a tribute to Prof. Dieter Seebach. *Chem Biodivers* 9(11):2367-2387, 2012 23161624
- Hoyer D, Pazos A, Probst A, et al: Serotonin receptors in the human brain, II: characterization and autoradiographic localization of 5-HT<sub>1C</sub> and 5-HT<sub>2</sub> recognition sites. *Brain Res* 376(1):97-107, 1986 2941113
- Hoyer D, Hannon JP, Martin GR: Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* 71(4):533-554, 2002 11888546
- Hrdina PD, Pappas BA, Roberts DC, et al: Relationship between levels and uptake of serotonin and high affinity [3H]imipramine recognition sites in the rat brain. *Can J Physiol Pharmacol* 63(10):1239-1244, 1985 3000552

- Humphrey PP, Hartig P, Hoyer D: A proposed new nomenclature for 5-HT receptors. *Trends Pharmacol Sci* 14(6):233-236, 1993 8372403
- Innocenti B, Parpura V, Haydon PG: Imaging extracellular waves of glutamate during calcium signaling in cultured astrocytes. *J Neurosci* 20(5):1800-1808, 2000 10684881
- Inoue E, Mochida S, Takagi H, et al: SAD: a presynaptic kinase associated with synaptic vesicles and the active zone cytomatrix that regulates neurotransmitter release. *Neuron* 50(2):261-275, 2006 16630837
- Iwata Y, Nakajima S, Suzuki T, et al: Effects of glutamate positive modulators on cognitive deficits in schizophrenia: a systematic review and meta-analysis of double-blind randomized controlled trials. *Mol Psychiatry* 20(10):1151-1160, 2015 26077694
- Jacobs BL, Abercrombie ED, Fornal CA, et al: Single-unit and physiological analyses of brain norepinephrine function in behaving animals. *Prog Brain Res* 88:159-165, 1991 1813921
- Jacobs BL, van Praag H, Gage FH: Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry* 5(3):262-269, 2000 10889528
- Kandel ER: *Principles of Neural Science*, 5th Edition. New York, McGraw-Hill, 2013
- Kaupmann K, Huggel K, Heid J, et al: Expression cloning of GABA(B) receptors uncovers similarity to metabotropic glutamate receptors. *Nature* 386(6622):239-246, 1997 9069281
- Kellendonk C, Simpson EH, Polan HJ, et al: Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron* 49(4):603-615, 2006 16476668
- Kim SF, Huang AS, Snowman AM, et al: From the cover: antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic

- AMP-kinase. *Proc Natl Acad Sci U S A* 104(9):3456–3459, 2007 17360666
- Kimelberg HK, Katz DM: High-affinity uptake of serotonin into immunocytochemically identified astrocytes. *Science* 228(4701):889–891, 1985 3890180
- Kish SJ, Furukawa Y, Chang LJ, et al: Regional distribution of serotonin transporter protein in postmortem human brain: is the cerebellum a SERT-free brain region? *Nucl Med Biol* 32(2):123–128, 2005 15721757
- Klimek V, Schenck JE, Han H, et al: Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. *Biol Psychiatry* 52(7):740–748, 2002 12372665
- Krügel U: Purinergic receptors in psychiatric disorders. *Neuropharmacology* 104:212–225, 2016 26518371
- Krystal JH, Anand A, Moghaddam B: Effects of NMDA receptor antagonists: implications for the pathophysiology of schizophrenia. *Arch Gen Psychiatry* 59(7):663–664, 2002 12090822
- Kumar JS, Mann JJ: PET tracers for serotonin receptors and their applications. *Cent Nerv Syst Agents Med Chem* 14(2):96–112, 2014 25360773
- Labrie V, Roder JC: The involvement of the NMDA receptor D-serine/glycine site in the pathophysiology and treatment of schizophrenia. *Neurosci Biobehav Rev* 34(3):351–372, 2010 19695284
- Lacerda-Pinheiro SF, Pinheiro Junior RF, Pereira de Lima MA, et al: Are there depression and anxiety genetic markers and mutations? A systematic review. *J Affect Disord* 168:387–398, 2014 25106036
- Laeng P, Pitts RL, Lemire AL, et al: The mood stabilizer valproic acid stimulates GABA neurogenesis from rat forebrain stem cells. *J Neurochem* 91(1):238–251, 2004 15379904
- Lambert GA: Preclinical neuropharmacology of naratriptan. *CNS Drug Rev* 11(3):289–316, 2005 16389295



- Langer SZ, Moret C, Raisman R, et al: High-affinity [3H]imipramine binding in rat hypothalamus: association with uptake of serotonin but not of norepinephrine. *Science* 210(4474):1133-1135, 1980 7444441
- Laporte AM, Koscielniak T, Ponchant M, et al: Quantitative autoradiographic mapping of 5-HT<sub>3</sub> receptors in the rat CNS using [125I]iodo-zacopride and [3H]zacopride as radioligands. *Synapse* 10(4):271-281, 1992 1585260
- Lawrence JA, Charters AR, Butcher SP, et al: 5-HT transporter antibodies as a tool in serotonergic synaptosomal isolation. *Biochem Soc Trans* 23(1):115S, 1995a 7758676
- Lawrence JA, Charters AR, Butcher SP, et al: Recognition of 5-HT transporter by antipeptide antibodies. *Biochem Soc Trans* 23(3):473S, 1995b 8566369
- Lee BH, Kim YK: Potential peripheral biological predictors of suicidal behavior in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 35(4):842-847, 2011 20708058
- Lee JL, Di Ciano P, Thomas KL, et al: Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. *Neuron* 47(6):795-801, 2005 16157275
- Leung LY, Baillie TA: Comparative pharmacology in the rat of ketamine and its two principal metabolites, norketamine and (Z)-6-hydroxynorketamine. *J Med Chem* 29(11):2396-2399, 1986 3783598
- Lewis DA, Hashimoto T, Volk DW: Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci* 6(4):312-324, 2005 15803162
- Liaw CW, Lovenberg TW, Barry G, et al: Cloning and characterization of the human corticotropin-releasing factor-2 receptor complementary deoxyribonucleic acid. *Endocrinology* 137(1):72-77, 1996 8536644
- Lilley BN, Krishnaswamy A, Wang Z, et al: SAD kinases control the maturation of nerve terminals in the

- mammalian peripheral and central nervous systems. Proc Natl Acad Sci U S A 111(3):1138-1143, 2014 24395778
- Lisman JE, McIntyre CC: Synaptic plasticity: a molecular memory switch. Curr Biol 11(19):R788-R791, 2001 11591339
- Liu QS, Pu L, Poo MM: Repeated cocaine exposure in vivo facilitates LTP induction in midbrain dopamine neurons. Nature 437(7061):1027-1031, 2005 16222299
- Liu YF, Albert PR: Cell-specific signaling of the 5-HT1A receptor: modulation by protein kinases C and A. J Biol Chem 266(35):23689-23697, 1991 1660881
- López-Giménez JF, Mengod G, Palacios JM, et al: Selective visualization of rat brain 5-HT2A receptors by autoradiography with [3H]MDL 100,907. Naunyn Schmiedeberg's Arch Pharmacol 356(4):446-454, 1997 9349630
- Lothe A, Boni C, Costes N, et al: 5-HT1A gene promoter polymorphism and [18F]MPPF binding potential in healthy subjects: a PET study. Behav Brain Funct 6:37, 2010 20609217
- Lovejoy DA, Chang BS, Lovejoy NR, et al: Molecular evolution of GPCRs: CRH/CRH receptors. J Mol Endocrinol 52(3):T43-T60, 2014 24711645
- Lummis SC, Beene DL, Lee LW, et al: Cis-trans isomerization at a proline opens the pore of a neurotransmitter-gated ion channel. Nature 438(7065):248-252, 2005 16281040
- Maciag D, Hughes J, O'Dwyer G, et al: Reduced density of calbindin immunoreactive GABAergic neurons in the occipital cortex in major depression: relevance to neuroimaging studies. Biol Psychiatry 67(5):465-470, 2010 20004363
- Madden DR: The structure and function of glutamate receptor ion channels. Nat Rev Neurosci 3(2):91-101, 2002 11836517

- Maeng S, Zarate CA Jr, Du J, et al: Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry* 63(4):349-352, 2008 17643398
- Malberg JE, Eisch AJ, Nestler EJ, et al: Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* 20(24):9104-9110, 2000 11124987
- Malenka RC, Nicoll RA: Long-term potentiation—a decade of progress? *Science* 285(5435):1870-1874, 1999 10489359
- Malinow R, Malenka RC: AMPA receptor trafficking and synaptic plasticity. *Annu Rev Neurosci* 25:103-126, 2002 12052905
- Mangelsdorf DJ, Thummel C, Beato M, et al: The nuclear receptor superfamily: the second decade. *Cell* 83(6):835-839, 1995 8521507
- Manji HK, Lenox RH: Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry* 46(10):1328-1351, 1999 10578449
- Manji HK, Drevets WC, Charney DS: The cellular neurobiology of depression. *Nat Med* 7(5):541-547, 2001 11329053
- Manto M, Dalmau J, Didelot A, et al: In vivo effects of antibodies from patients with anti-NMDA receptor encephalitis: further evidence of synaptic glutamatergic dysfunction. *Orphanet J Rare Dis* 5:31, 2010 21110857
- Masdeu JC, Dalmau J, Berman KF: NMDA receptor internalization by autoantibodies: a reversible mechanism underlying psychosis? *Trends Neurosci* March 22, 2016 [Epub ahead of print] 27130657
- McCann UD, Thorne D, Hall M, et al: The effects of L-dihydroxyphenylalanine on alertness and mood in alpha-

methyl-para-tyrosine-treated healthy humans: further evidence for the role of catecholamines in arousal and anxiety. *Neuropsychopharmacology* 13(1):41-52, 1995 8526970

McKeon A: Autoimmune encephalopathies and dementias. *Continuum (Minneapolis)* 22(2 Dementia):538-558, 2016 27042907

McMahon FJ, Buervenich S, Charney D, et al: Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet* 78(5):804-814, 2006 16642436

Meltzer HY: Action of atypical antipsychotics. *Am J Psychiatry* 159(1):153-154, author reply 154-155, 2002 11772718

Meyer JH, Krüger S, Wilson AA, et al: Lower dopamine transporter binding potential in striatum during depression. *Neuroreport* 12(18):4121-4125, 2001 11742250

Meyer JH, Goulding VS, Wilson AA, et al: Bupropion occupancy of the dopamine transporter is low during clinical treatment. *Psychopharmacology (Berl)* 163(1): 102-105, 2002 12185406

Meyer JH, McNeely HE, Sagrati S, et al: Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [11C]raclopride positron emission tomography study. *Am J Psychiatry* 163(9):1594-1602, 2006 16946186

Millar RP, Newton CL: The year in G protein-coupled receptor research. *Mol Endocrinol* 24(1):261-274, 2010 20019124

Miller JM, Hesselgrave N, Ogden RT, et al: Positron emission tomography quantification of serotonin transporter in suicide attempters with major depressive disorder. *Biol Psychiatry* 74(4):287-295, 2013 23453288

Mishina M, Ishiwata K: Adenosine receptor PET imaging in human brain. *Int Rev Neurobiol* 119:51-69, 2014

25175960

- Miwa JM, Stevens TR, King SL, et al: The prototoxin lynx1 acts on nicotinic acetylcholine receptors to balance neuronal activity and survival in vivo. *Neuron* 51(5):587-600, 2006 16950157
- Moberg T, Nordström P, Forslund K, et al: CSF 5-HIAA and exposure to and expression of interpersonal violence in suicide attempters. *J Affect Disord* 132(1-2):173-178, 2011 21356560
- Moghaddam B, Krystal JH: Capturing the angel in “angel dust”: twenty years of translational neuroscience studies of NMDA receptor antagonists in animals and humans. *Schizophr Bull* 38(5):942-949, 2012 22899397
- Möhler H, Fritschy JM, Rudolph U: A new benzodiazepine pharmacology. *J Pharmacol Exp Ther* 300(1):2-8, 2002 11752090
- Møllerud S, Frydenvang K, Pickering DS, et al: Lessons from crystal structures of kainate receptors. *Neuropharmacology* 112(Pt A):16-28, 2017 27236079
- Montecucchi PC, Anastasi A, de Castiglione R, et al: Isolation and amino acid composition of sauvagine: an active polypeptide from methanol extracts of the skin of the South American frog *Phyllomedusa sauvagei*. *Int J Pept Protein Res* 16(3):191-199, 1980 7461901
- Moses-Kolko EL, Price JC, Shah N, et al: Age, sex, and reproductive hormone effects on brain serotonin-1A and serotonin-2A receptor binding in a healthy population. *Neuropsychopharmacology* 36(13):2729-2740, 2011 21849982
- Mukherjee J, Baranwal A, Schade KN: Classification of therapeutic and experimental drugs for brown adipose tissue activation: potential treatment strategies for diabetes and obesity. *Curr Diabetes Rev* 12(4):414-428, 2016 27183844
- Mulligan SJ, MacVicar BA: VRACs CARVe a path for novel mechanisms of communication in the CNS. *Sci STKE*

2006(357): pe42, 2006 17047222

Murase S, Mathé JM, Grenhoff J, et al: Effects of dizocilpine (MK-801) on rat midbrain dopamine cell activity: differential actions on firing pattern related to anatomical localization. *J Neural Transm* 91(1):13-25, 1993 8452684

Navarria A, Wohleb ES, Voleti B, et al: Rapid antidepressant actions of scopolamine: role of medial prefrontal cortex and M1-subtype muscarinic acetylcholine receptors. *Neurobiol Dis* 82:254-261, 2015 26102021

Nestler EJ, Hyman SE, Malenka RC: *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*. New York, McGraw-Hill, 2001

Nestler EJ, Hyman SE, Holtzman DM, et al: *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*, 3rd Edition. New York, McGraw-Hill, 2015

Neumann ID, Landgraf R: Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci* 35(11):649-659, 2012 22974560

Newport DJ, Carpenter LL, McDonald WM, et al; APA Council of Research Task Force on Novel Biomarkers and Treatments: Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry* 172(10):950-966, 2015 26423481

Niswender CM, Sanders-Bush E, Emeson RB: Identification and characterization of RNA editing events within the 5-HT<sub>2C</sub> receptor. *Ann N Y Acad Sci* 861:38-48, 1998 9928237

Nutt D, Wilson S, Lingford-Hughes A, et al: Differences between magnetoencephalographic (MEG) spectral profiles of drugs acting on GABA at synaptic and extrasynaptic sites: a study in healthy volunteers. *Neuropharmacology* 88:155-163, 2015 25195191

- Oo KZ, Aung YK, Jenkins MA, Win AK: Associations of 5HTTLPR polymorphism with major depressive disorder and alcohol dependence: a systematic review and meta-analysis. *Aust N Z J Psychiatry* 50(9):842-857, 2016 26979101
- Ortiz R, Ulrich H, Zarate CA Jr, et al: Purinergic system dysfunction in mood disorders: a key target for developing improved therapeutics. *Prog Neuropsychopharmacol Biol Psychiatry* 57:117-131, 2015 25445063
- Owens MJ, Nemeroff CB: The serotonin transporter and depression. *Depress Anxiety* 8 (suppl 1):5-12, 1998 9809208
- Pacholczyk T, Blakely RD, Amara SG: Expression cloning of a cocaine- and antidepressant-sensitive human noradrenaline transporter. *Nature* 350(6316):350-354, 1991 2008212
- Panatier A, Theodosis DT, Mothet JP, et al: Glia-derived D-serine controls NMDA receptor activity and synaptic memory. *Cell* 125(4):775-784, 2006 16713567
- Papageorgiou A, Denef C: Estradiol induces expression of 5-hydroxytryptamine (5-HT) 4, 5-HT5, and 5-HT6 receptor messenger ribonucleic acid in rat anterior pituitary cell aggregates and allows prolactin release via the 5-HT4 receptor. *Endocrinology* 148(3):1384-1395, 2007 17122082
- Parker CA, Rabiner EA, Gunn RN, et al: Human kinetic modeling of the 5HT6 PET radioligand 11C-GSK215083 and its utility for determining occupancy at both 5HT6 and 5HT2A receptors by SB742457 as a potential therapeutic mechanism of action in Alzheimer disease. *J Nucl Med* 56(12):1901-1909, 2015 26383152
- Patapoutian A, Reichardt LF: Trk receptors: mediators of neurotrophin action. *Curr Opin Neurobiol* 11(3):272-280, 2001 11399424

- Paterson NE, Vocci F, Sevak RJ, et al: Dopamine D3 receptors as a therapeutic target for methamphetamine dependence. *Am J Drug Alcohol Abuse* 40(1):1-9, 2014 24359505
- Pazos A, Cortés R, Palacios JM: Quantitative autoradiographic mapping of serotonin receptors in the rat brain, II: serotonin-2 receptors. *Brain Res* 346(2):231-249, 1985 4052777
- Pessiglione M, Seymour B, Flandin G, et al: Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* 442(7106):1042-1045, 2006 16929307
- Piñeyro G, Blier P: Autoregulation of serotonin neurons: role in antidepressant drug action. *Pharmacol Rev* 51(3):533-591, 1999 10471417
- Pisano P, Samuel D, Nieoullon A, et al: Activation of the adenylate cyclase-dependent protein kinase pathway increases high affinity glutamate uptake into rat striatal synaptosomes. *Neuropharmacology* 35(5):541-547, 1996 8887962
- Pollak TA, McCormack R, Peakman M, et al: Prevalence of anti-N-methyl-D-aspartate (NMDA) receptor [corrected] antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis. *Psychol Med* 44(12):2475-2487, 2014 24330811
- Prabhakaran J, Underwood MD, Kumar JS, et al: Synthesis and in vitro evaluation of [18F]FECIMBI-36: a potential agonist PET ligand for 5-HT<sub>2A/2C</sub> receptors. *Bioorg Med Chem Lett* 25(18):3933-3936, 2015 26253634
- Przybylski J, Roulet P, Sara SJ: Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. *J Neurosci* 19(15):6623-6628, 1999 10414990
- Purselle DC, Nemeroff CB: Serotonin transporter: a potential substrate in the biology of suicide.



- Neuropsychopharmacology 28(4):613-619, 2003  
12655305
- Rajkowska G: Cell pathology in mood disorders. *Semin Clin Neuropsychiatry* 7(4): 281-292, 2002 12382210
- Rapport MM, Green AA, Page IH: Serum vasoconstrictor, serotonin; isolation and characterization. *J Biol Chem* 176(3): 1243-1251, 1948 18100415
- Rashid AJ, So CH, Kong MM, et al: D1-D2 dopamine receptor heterooligomers with unique pharmacology are coupled to rapid activation of Gq/11 in the striatum. *Proc Natl Acad Sci U S A* 104(2): 654-659, 2007 17194762
- Rasmussen K, Jacobs BL: Single unit activity of locus coeruleus neurons in the freely moving cat, II: conditioning and pharmacologic studies. *Brain Res* 371(2):335-344, 1986 3697762
- Rasmussen K, Strecker RE, Jacobs BL: Single unit response of noradrenergic, serotonergic and dopaminergic neurons in freely moving cats to simple sensory stimuli. *Brain Res* 369(1-2):336-340, 1986 3697750
- Ravid R, Van Zwieten EJ, Swaab DF: Brain banking and the human hypothalamus—factors to match for, pitfalls and potentials. *Prog Brain Res* 93:83-95, 1992 1480765
- Reader TA: Microiontophoresis of biogenic amines on cortical neurons: amounts of NA, DA and 5-HT ejected, compared with tissue content. *Acta Physiol Lat Am* 30(4):291-304, 1980 6152846
- Ressler KJ, Bradley B, Mercer KB, et al: Polymorphisms in CRHR1 and the serotonin transporter loci: gene x gene x environment interactions on depressive symptoms. *Am J Med Genet B Neuropsychiatr Genet* 153B(3):812-824, 2010 20029939
- Risinger R, Bhagwagar Z, Luo F, et al: Evaluation of safety and tolerability, pharmacokinetics, and pharmacodynamics of BMS-820836 in healthy subjects: a placebo-controlled, ascending single-dose study.

- Psychopharmacology (Berl) 231(11):2299–2310, 2014 24337079
- Robinson MB, Jackson JG: Astroglial glutamate transporters coordinate excitatory signaling and brain energetics. *Neurochem Int* 98:56–71, 2016 27013346
- Roman T, Schmitz M, Polanczyk G, et al: Attention-deficit hyperactivity disorder: a study of association with both the dopamine transporter gene and the dopamine D4 receptor gene. *Am J Med Genet* 105(5):471–478, 2001 11449401
- Roth BL, McLean S, Zhu XZ, et al: Characterization of two [3H]ketanserin recognition sites in rat striatum. *J Neurochem* 49(6):1833–1838, 1987 2960784
- Roth BL, Craig SC, Choudhary MS, et al: Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. *J Pharmacol Exp Ther* 268(3):1403–1410, 1994 7908055
- Roybal K, Theobald D, Graham A, et al: Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci U S A* 104(15):6406–6411, 2007 17379666
- Ruljancic N, Mihanovic M, Cepelak I: Thrombocyte serotonin and serum cholesterol concentration in suicidal and non-suicidal depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 35(5):1261–1267, 2011 21338651
- Ruljancic N, Mihanovic M, Cepelak I, et al: Platelet serotonin and magnesium concentrations in suicidal and non-suicidal depressed patients. *Magnes Res* 26(1):9–17, 2013 23614979
- Sakaba T, Stein A, Jahn R, et al: Distinct kinetic changes in neurotransmitter release after SNARE protein cleavage. *Science* 309(5733):491–494, 2005 16020741
- Salerno S, Da Settimo F, Taliani S, et al: Medicinal chemistry of indolylglyoxylamide GABAA/BzR high affinity ligands: identification of novel anxiolytic/non

- sedative agents. *Curr Top Med Chem* 12(4): 286–311, 2012 22204484
- Sanchez C, Asin KE, Artigas F: Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol Ther* 145:43–57, 2015 25016186
- Sanders J, Nemeroff C: The CRF system as a therapeutic target for neuropsychiatric disorders. *Trends Pharmacol Sci* 37(12): 1045–1054, 2016 27717506
- Savitz JB, Drevets WC: Neuroreceptor imaging in depression. *Neurobiol Dis* 52:49–65, 2013 22691454
- Savitz J, Lucki I, Drevets WC: 5-HT(1A) receptor function in major depressive disorder. *Prog Neurobiol* 88(1):17–31, 2009 19428959
- Saxena PR, De Vries P, Villalón CM: 5-HT<sub>1</sub>-like receptors: a time to bid goodbye. *Trends Pharmacol Sci* 19(8):311–316, 1998 9745358
- Schoeffter P, Bobirnac I: 5-Hydroxytryptamine 5-HT<sub>1D</sub> receptors mediating inhibition of cyclic AMP accumulation in Madin-Darby canine kidney (MDCK) cells. *Naunyn Schmiedeberg's Arch Pharmacol* 352(3):256–262, 1995 8584040
- Schoepp DD: Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *J Pharmacol Exp Ther* 299(1):12–20, 2001 11561058
- Scott JA, Crews FT: Down-regulation of serotonin<sub>2</sub>, but not of beta-adrenergic receptors during chronic treatment with amitriptyline is independent of stimulation of serotonin<sub>2</sub> and beta-adrenergic receptors. *Neuropharmacology* 25(12): 1301–1306, 1986 3031528
- Scott MM, Marcus JN, Elmquist JK: Orexin neurons and the TASK of glucosensing. *Neuron* 50(5):665–667, 2006 16731504
- Shaltiel G, Chen G, Manji HK: Neurotrophic signaling cascades in the pathophysiology and treatment of

- bipolar disorder. *Curr Opin Pharmacol* 7(1):22–26, 2007 17055337
- Sihra TS, Rodríguez-Moreno A: Presynaptic kainate receptor-mediated bidirectional modulatory actions: mechanisms. *Neurochem Int* 62(7):982–987, 2013 23538266
- Sleight AJ, Carolo C, Petit N, et al: Identification of 5-hydroxytryptamine<sub>7</sub> receptor binding sites in rat hypothalamus: sensitivity to chronic antidepressant treatment. *Mol Pharmacol* 47(1):99–103, 1995 7838138
- Smith DF, Jakobsen S: Molecular tools for assessing human depression by positron emission tomography. *Eur Neuropsychopharmacol* 19(9):611–628, 2009 19502013
- Smith RC, Amiaz R, Si TM, et al: Varenicline effects on smoking, cognition, and psychiatric symptoms in schizophrenia: a double-blind randomized trial. *PLoS One* 11(1):e0143490, 2016 26730716
- Sobczak S, Schruers K: Can formulation affect tryptophan depletion results? Hints from studies in experimental panic. *J Psychopharmacol* 28(5):486–490, 2014 24429220
- Soltesz I, Staley K: High times for memory: cannabis disrupts temporal coordination among hippocampal neurons. *Nat Neurosci* 9(12):1461–1463, 2006 17128279
- Spreux-Varoquaux O, Alvarez JC, Berlin I, et al: Differential abnormalities in plasma 5-HIAA and platelet serotonin concentrations in violent suicide attempters: relationships with impulsivity and depression. *Life Sci* 69(6):647–657, 2001 11476186
- Squire LR: *Fundamental Neuroscience*, 4th Edition. Boston, MA, Elsevier/Academic Press, 2013
- Stoof JC, Kebabian JW: Two dopamine receptors: biochemistry, physiology and pharmacology. *Life Sci* 35(23):2281–2296, 1984 6390056

- Szabo ST, Blier P: Response of the norepinephrine system to antidepressant drugs. *CNS Spectr* 6(8):679-684, 2001 15520619
- Szabo S, Machado-Vieira R, Yuan P, et al: Glutamate receptors as targets of protein kinase C in the pathophysiology and treatment of animal models of mania. *Neuropharmacology* 56(1):47-55, 2009 18789340
- Taber MT, Fibiger HC: Electrical stimulation of the medial prefrontal cortex increases dopamine release in the striatum. *Neuropsychopharmacology* 9(4):271-275, 1993 8305127
- Taliani S, Cosimelli B, Da Settimo F, et al: Identification of anxiolytic/nonsedative agents among indol-3-ylglyoxylamides acting as functionally selective agonists at the gamma-aminobutyric acid-A (GABAA) alpha2 benzodiazepine receptor. *J Med Chem* 52(12):3723-3734, 2009 19469479
- Tatsch K, Poepperl G: Nigrostriatal dopamine terminal imaging with dopamine transporter SPECT: an update. *J Nucl Med* 54(8):1331-1338, 2013 23864718
- Tejani-Butt SM, Ordway GA: Effect of age on [3H]nisoxetine binding to uptake sites for norepinephrine in the locus coeruleus of humans. *Brain Res* 583(1-2):312-315, 1992 1504838
- Tejani-Butt SM, Brunswick DJ, Frazer A: [3H] Nisoxetine: a new radioligand for norepinephrine uptake sites in brain. *Eur J Pharmacol* 191(2):239-243, 1990 2086242
- Truss M, Beato M: Steroid hormone receptors: interaction with deoxyribonucleic acid and transcription factors. *Endocr Rev* 14(4):459-479, 1993 8223341
- Tsao P, von Zastrow M: Downregulation of G protein-coupled receptors. *Curr Opin Neurobiol* 10(3):365-369, 2000 10851176
- Ungerstedt U: Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta Physiol Scand Suppl*

367:1-48, 1971 4109331

- van Donkelaar EL, Blokland A, Ferrington L, et al: Mechanism of acute tryptophan depletion: is it only serotonin? *Mol Psychiatry* 16(7):695-713, 2011 21339754
- Van Sickle MD, Duncan M, Kingsley PJ, et al: Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science* 310(5746):329-332, 2005 16224028
- Van Tol HH, Wu CM, Guan HC, et al: Multiple dopamine D4 receptor variants in the human population. *Nature* 358(6382):149-152, 1992 1319557
- Vo L, Drummond PD: Involvement of  $\alpha_2$ -adrenoceptors in inhibitory and facilitatory pain modulation processes. *Eur J Pain* 20(3):386-398, 2016 26032281
- Voineskos AN, Wilson AA, Boovariwala A, et al: Serotonin transporter occupancy of high-dose selective serotonin reuptake inhibitors during major depressive disorder measured with [11C]DASB positron emission tomography. *Psychopharmacology (Berl)* 193(4):539-545, 2007 17497139
- Volkow ND, Morales M: The brain on drugs: from reward to addiction. *Cell* 162(4):712-725, 2015 26276628
- Weinshenker D, Holmes PV: Regulation of neurological and neuropsychiatric phenotypes by locus coeruleus-derived galanin. *Brain Res* 1641(pt B):320-337, 2016 26607256
- Weisstaub NV, Zhou M, Lira A, et al: Cortical 5-HT<sub>2A</sub> receptor signaling modulates anxiety-like behaviors in mice. *Science* 313(5786):536-540, 2006 16873667
- Wentworth BA, Stein MB, Redwine LS, et al: Post-traumatic stress disorder: a fast track to premature cardiovascular disease? *Cardiol Rev* 21(1):16-22, 2013 22717656
- Westphal RS, Sanders-Bush E: Reciprocal binding properties of 5-hydroxytryptamine type 2C receptor

- agonists and inverse agonists. *Mol Pharmacol* 46(5):937-942, 1994 7969083
- Whitaker-Azmitia PM, Shemer AV, Caruso J, et al: Role of high affinity serotonin receptors in neuronal growth. *Ann N Y Acad Sci* 600:315-330, 1990 2252318
- Wiklund L, Björklund A: Mechanisms of regrowth in the bulbospinal serotonin system following 5,6-dihydroxytryptamine induced axotomy, II: fluorescence histochemical observations. *Brain Res* 191(1): 109-127, 1980 7378747
- Wisner A, Dufour E, Messaoudi M, et al: Human opiorphin, a natural antinociceptive modulator of opioid-dependent pathways. *Proc Natl Acad Sci U S A* 103(47):17979-17984, 2006 17101991
- Wiste AK, Arango V, Ellis SP, et al: Norepinephrine and serotonin imbalance in the locus coeruleus in bipolar disorder. *Bipolar Disord* 10(3):349-359, 2008 18402623
- Wolf WA, Bobik A: Effects of 5,6-dihydroxytryptamine on the release, synthesis, and storage of serotonin: studies using rat brain synaptosomes. *J Neurochem* 50(2):534-542, 1988 2447243
- Xia Y, Zheng MQ, Holden D, et al: Measurement of Bmax and Kd with the glycine transporter 1 radiotracer <sup>18</sup>F-MK6577 using a novel multi-infusion paradigm. *J Cereb Blood Flow Metab* 35(12):2001-2009, 2015 26198176
- Yamashita A, Singh SK, Kawate T, et al: Crystal structure of a bacterial homologue of Na<sup>+</sup>/Cl<sup>-</sup>-dependent neurotransmitter transporters. *Nature* 437(7056):215-223, 2005 16041361
- Yau JL, Noble J, Seckl JR: Acute restraint stress increases 5-HT<sub>7</sub> receptor mRNA expression in the rat hippocampus. *Neurosci Lett* 309(3):141-144, 2001 11514061
- Ye ZC, Oberheim N, Kettenmann H, Ransom BR: Pharmacological "cross-inhibition" of connexin

- hemichannels and swelling activated anion channels. *Glia* 57(3):258-269, 2009 18837047
- Yun HM, Rhim H: The serotonin-6 receptor as a novel therapeutic target. *Exp Neurobiol* 20(4):159-168, 2011 22355260
- Zanos P, Moaddel R, Morris PJ, et al: NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 533(7604):481-486, 2016 27144355
- Zarate CA Jr, Singh JB, Carlson PJ, et al: A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63(8):856-864, 2006a 16894061
- Zarate CA Jr, Singh J, Manji HK: Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry* 59(11):1006-1020, 2006b 16487491
- Zhang J, McDonald AJ: Light and electron microscopic analysis of enkephalin-like immunoreactivity in the basolateral amygdala, including evidence for convergence of enkephalin-containing axon terminals and norepinephrine transporter-containing axon terminals onto common targets. *Brain Res* 1636:62-73, 2016 26835559
- Zuckerman M: Sensation seeking, mania, and monoamines. *Neuropsychobiology* 13(3):121-128, 1985 4047373



# CHAPTER 3

## Genetics and Genomics

Jessica Keverne, Ph.D.

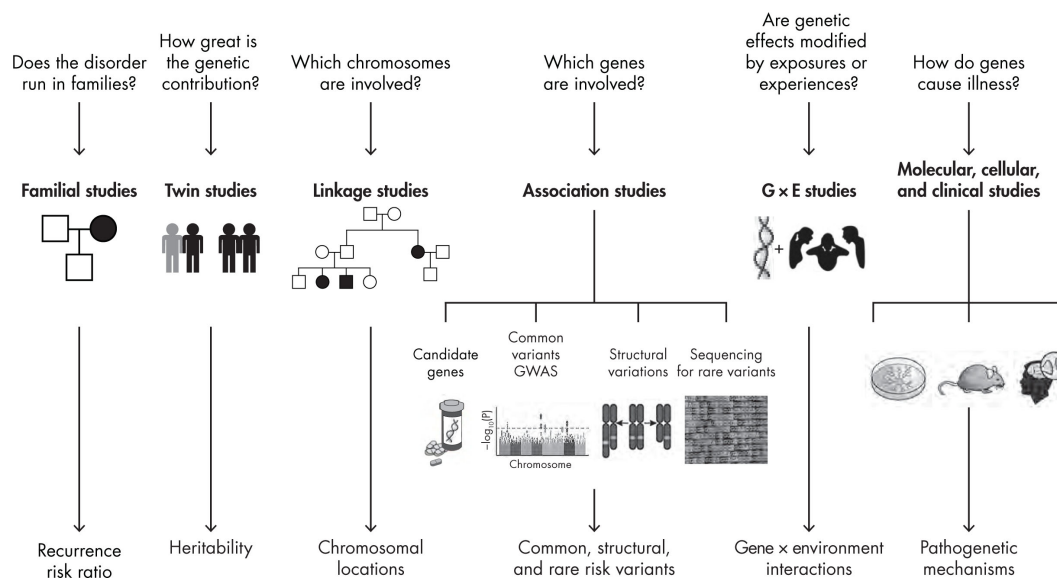
Darina Czamara, Ph.D.

Joseph F. Cubells, M.D., Ph.D.

Elisabeth B. Binder, M.D., Ph.D.

Genetics and genomics are among the most important tools in modern psychiatric research. Spurred by the completion of the human genome sequence in 2001, the number of psychiatric genetic studies has increased dramatically in the last two decades ([Lander et al. 2001](#); [Venter et al. 2001](#)). In this chapter, we cover the basic methodologies and concepts and define key terms currently used in psychiatric genetics and genomics. [Figure 3-1](#) illustrates the genetic methods available in psychiatric research today. Our goal is to facilitate interpretation by physicians and scientists in the field of psychopharmacology of the avalanche of genetic and genomic data accumulating in the human neuropsychiatric literature. Throughout this

chapter, terms in common use in the genetics and genomics literature are italicized on first use and are defined.



**FIGURE 3-1.** Overview of genetic methods available for psychiatry research.

*See Plate 12 to view this figure in color.*

G x E=genex environment; GWAS=genomewide association studies.

*Source.* Adapted from Smoller JW: "The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders." *Neuropsychopharmacology* 41(1):297-319, 2016. Copyright 2016, American College of Neuropsychopharmacology. Used with permission.

## Epidemiological Basis for Genetic Contributions to Neurobehavioral Disorders

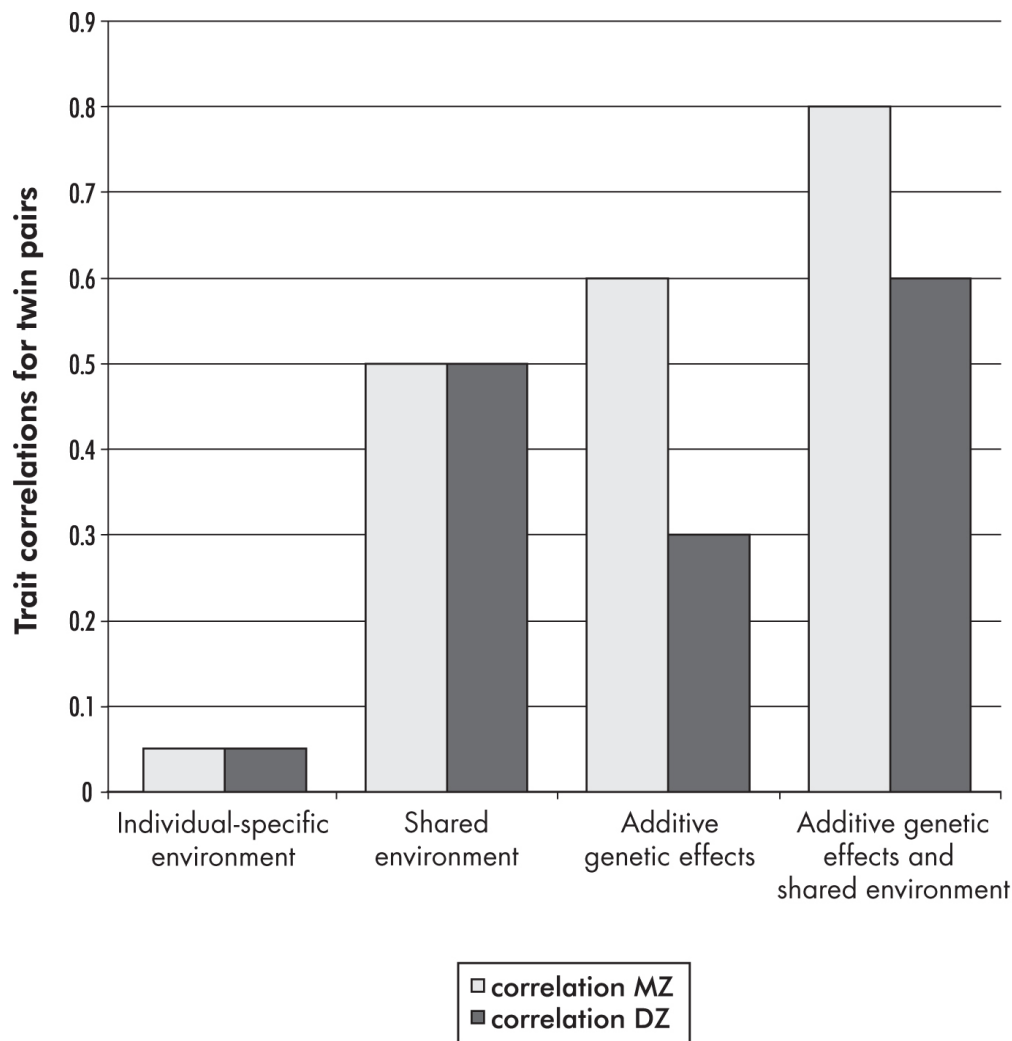
# Insights From Adoption and Twin Studies

Genetic epidemiological studies have established that most psychiatric disorders, as well as many nonpathological human behavioral traits, have a substantial genetic component. Investigations in genetic epidemiology have provided the scientific foundation for molecular genetic and genomic studies of human behavior and behavioral disorders (Kendler 1993, 2001; Plomin and Kosslyn 2001). Genetic epidemiology uses family, twin, and adoption studies to assess the contribution of familial, environmental, and genetic factors to a trait of interest. A family study uses a *pedigree* (a type of family tree) to establish whether a given disorder “runs in the family”; however, these studies cannot easily distinguish whether such familiarity is due to genetic or environmental factors. An everyday example of the distinction between *genetic* and *familial* (but environmental) traits is the difference between the ability to acquire language (a *genetic* trait that distinguishes humans from other species) and the native language spoken by a given person, which is *familial* but entirely environmentally determined.

Adoption and twin studies distinguish between genetic and environmental influences on traits by accounting for each separately. Adoption studies investigate whether an individual’s risk for a psychiatric disease depends on the mental health status of the biological or adoptive parents to disentangle genetic (i.e., similarity to biological parents, who have had little or no interaction with the adoptee) from environmental influence (i.e., similarity to adoptive parents, who have provided the adoptee with his or her family and

social environment) ([Cadoret 1986](#); [Tienari and Wynne 1994](#); [Tienari et al. 2004](#)). Practical, ethical, and legal obstacles make large-scale adoption studies very difficult to conduct. Twin studies, while also quite challenging, are more tractable, and large twin registries are now available globally ([Busjahn 2002](#)). These studies have provided the bulk of the strong evidence supporting genetic contributions to psychiatric disorders and human behavioral traits.

In twin studies, one determines the probability of one twin being affected with a given trait or disorder, given the affectation status of the co-twin. This degree of correlation between twins for the investigated trait is then compared between monozygotic (MZ) and dizygotic (DZ) twins to gain information on the degree of genetic and environmental influence on a certain trait. MZ twins result from a separation of the zygote to yield two genetically identical embryos. DZ twins result from the separate fertilization of two eggs in the same pregnancy. DZ twins thus share on average only 50% of their genes, similar to siblings born in separate pregnancies. Although neither the pre- nor the postnatal environments of twins are perfectly identical, to a first approximation MZ and DZ twins are equally correlated for relevant environmental exposures ([Kendler and Gardner 1998](#)). The trait correlation between MZ and DZ twins therefore allows estimation of the degree to which additive genetic effects or shared or individual-specific environmental effects contribute to the likelihood of a given trait. [Figure 3-2](#) summarizes the relative contributions of each factor, estimated from patterns of correlation between MZ and DZ twins (for a methodological review of this topic, see [Bulik et al. 2000](#)).



**FIGURE 3-2.** Patterns of intrapair correlations and source of variance implied.

Intrapair correlations around zero imply effects of individual-specific environment. Equal intrapair correlations that are greater than zero for monozygotic (MZ) and dizygotic (DZ) twins imply effects of shared environment. Correlations for MZ twins that are twice as great as those for DZ twins imply additive genetic effects. Correlations for MZ twins that are greater than—but not twice as great as—those for DZ twins imply additive genetic effects and shared environment effects. The correlations of less than 1.0 in the

last three examples are likely mediated by individual-specific environment effects.

Twin studies have firmly established important genetic contributions for all psychiatric disorders, with *heritability* estimates (i.e., the proportion of risk for a disorder attributable to the additive effects of genes) ranging from 30% to 80% for most common psychiatric disorders (Table 3-1).

**TABLE 3-1. Heritability scores for major psychiatric illnesses, with focus on results of meta-analyses**

Disorder	Heritability	<i>N</i> in meta-analysis	References
Autism spectrum disorder	>0.80	—	Bailey et al. 1995; Rutter 2000
Schizophrenia	0.81 (0.73–0.90)	12 studies (Sweden, United States, England, Norway, Denmark, Finland, Germany), <i>N</i> not available	Sullivan et al. 2003 (meta-analysis)

<b>Disorder</b>	<b>Heritability</b>	<b><i>N</i> in meta-analysis</b>	<b>References</b>
Bipolar disorder	0.79–0.85	—	<a href="#">Kendler et al. 1995b</a> ; <a href="#">McGuffin et al. 2003</a>
Major depressive disorder	0.37 (0.31–0.42)	5 studies (United Kingdom, Sweden, United States), <i>N</i> >21,000	<a href="#">Sullivan et al. 2000</a> (meta-analysis)
Panic disorder	0.43 (0.32–0.53)	3 studies, <i>N</i> >9,000	<a href="#">Hettema et al. 2001</a> (meta-analysis)
Generalized anxiety disorder	0.32 (0.24–0.39)	2 studies, <i>N</i> >12,000	<a href="#">Hettema et al. 2001</a> (meta-analysis)
Specific phobia	0.25–0.35	—	<a href="#">Kendler et al. 1992</a> , 2001b
Social phobia (social anxiety disorder)	0.20–0.30	—	<a href="#">Kendler et al. 1992</a> , 2001b
Agoraphobia	0.37–0.39	—	<a href="#">Kendler et al. 1992</a> , 2001b

<b>Disorder</b>	<b>Heritability</b>	<b><i>N</i> in meta-analysis</b>	<b>References</b>
Obsessive-compulsive disorder	0.45–0.65 (children) 0.27–0.47 (adults)	—	<a href="#">van Grootheest et al. 2005</a> (review)
Anorexia nervosa	0.56 (0.00–0.86)	Swedish twin registry, <i>N</i> >30,000	<a href="#">Bulik et al. 2006</a>
Bulimia nervosa	0.28–0.83	—	<a href="#">Bulik et al. 2000</a> (review)
Alcohol dependence	0.48–0.73 (men) 0.51–0.65 (women)	—	<a href="#">Tyndale 2003</a> (review)
Nicotine addiction	0.40–0.70	—	<a href="#">Li 2003</a> ; <a href="#">Tyndale 2003</a> (reviews)
Antisocial personality disorder	0.32	51 studies, <i>N</i> not available	<a href="#">Rhee and Waldman 2002</a> (meta-analysis)

In more recent research, twin studies are being used to investigate the influence of *epigenetics*. Epigenetics refers to the chemical modification of genes without alteration of the genome sequence. These modifications determine



whether a given gene is expressed (switched on) or not expressed (switched off) and are driven by the DNA sequence together with environmental stimuli. Large-scale twin studies are helping to reveal the contribution of epigenetic alterations in psychiatric disorders by allowing investigators to disentangle genetic versus environmental contributions in MZ and DZ twins.

Genetic epidemiology also can contribute to exploration of more complex questions, such as whether genetic risk factors are shared among different psychiatric disorders and between sexes and whether these genetic risk factors can moderate the effects of environmental risk factors ([Kendler 2001](#)) and can therefore lead the design of follow-up molecular genetic studies. For example, a twin study has suggested that genetic risk factors for major depressive disorder could in part act by increasing vulnerability to stressful life events ([Kendler 1995](#)). This suggestion has been corroborated by findings from a number of gene  $\times$  environment (G $\times$ E) interaction studies, including studies confirming the interaction of functional alleles of the locus encoding the serotonin transporter protein with stressful life events to predict risk of depression ([Caspi et al. 2003](#); [Karg et al. 2011](#); [Kaufman et al. 2004](#); [Kendler et al. 2005](#); [Sjöberg et al. 2006](#); [Surtees et al. 2006](#); [Wilhelm et al. 2006](#)) and the interaction of genetic polymorphisms at the gene for FK506 binding protein 5 (*FKBP5*) with childhood abuse to predict risk of posttraumatic stress disorder (PTSD; [Zannas et al. 2016](#)). Genetic epidemiological studies—and, more specifically, twin studies—therefore have been an important foundation of psychiatric genetics and are likely to continue to contribute more elaborate disease models for future molecular genetic analysis. The major limitation of these studies, however, is that the estimated

heritability with twin studies is only an estimate of the aggregate genetic effect. Heritability does not give any information about the contributions of specific genes to risk for a disorder. The answers to those questions, which will require deployment of an array of molecular genetic techniques, will ultimately shed light on the developmental neurobiology underlying psychiatric illness.

## Psychiatric Disorders Are Complex Genetic Disorders

Genetic epidemiological studies have established that psychiatric disorders are likely not single-gene disorders inherited in a *Mendelian* fashion (i.e., in a clear recessive, dominant, or X-linked fashion), although rare families in which psychiatric phenotypes are inherited this way have been reported ([Brunner et al. 1993](#)). A genetic disorder can be complex for several reasons:

- *Incomplete penetrance*: not every person carrying the disease allele(s) becomes ill.
- *Phenocopy occurrence*: nonheritable traits caused by environmental factors can resemble traits caused by a genetic mutation.
- *Locus heterogeneity*: variants in different genes can lead to similar or identical disease phenotypes.
- *Allelic heterogeneity*: different patterns of variation within the same gene or genes can lead to similar or identical disease phenotypes.
- *Polygenic inheritance*: additive or interactive effects of variation at multiple genes (i.e., *epistatic effects*) are necessary for an illness to manifest.

- *Gene–environment interaction*: a disorder manifests in response to environmental factors only in the context of predisposing genetic variants. An extreme example of such interaction is phenylketonuria, in which exposure to dietary phenylalanine causes severe neurobehavioral impairment in individuals carrying two mutant copies of the locus encoding phenylalanine hydroxylase; limitation of dietary phenylalanine prevents the neurobehavioral disorder.
- *High frequency of the disorder and the predisposing alleles*. It appears increasingly likely that common disorders such as schizophrenia, diabetes mellitus, stroke, and hypertension represent final common outcomes of a variety of combinations of environmental and genetic predisposing factors. Thus, two individuals, even within the same family, might manifest clinically indistinguishable disorders for different reasons.
- *Other genetic mechanisms of inheritance*: alternative genetic mechanisms—for example, mitochondrial inheritance or alteration of the genome across generations, such as occurs in trinucleotide-repeat-expansion disorders (e.g., Huntington’s disease and fragile X syndrome) or in epigenetic disorders—may be involved in producing a disorder. Epigenetic disorders result from alterations in the genetic material that do not involve changes in the base-pair sequence of DNA. Examples of epigenetic disease include the imprinted disorders Angelman syndrome and Prader-Willi syndrome, in which parent of origin–dependent chemical modification of DNA produces different phenotypic outcomes from the same chromosomal deletion.

From the cumulative evidence of psychiatric genetic studies thus far, one can conclude that psychiatric disorders deviate from the “common disease, common variant” hypothesis and instead fit a polygenic mode of inheritance, with many polymorphic loci contributing to these disorders ([Cross-Disorder Group of the Psychiatric Genomics Consortium 2013](#); [Geschwind and Flint 2015](#); [Smoller 2016](#); [Sullivan et al. 2012](#)), as has been found in studies of unipolar depression (i.e., major depressive disorder) ([Johansson et al. 2001](#); [Kendler et al. 2006](#); [Ripke et al. 2013b](#)), bipolar disorder ([Blackwood and Muir 2001](#); [Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011](#); [Ruderfer et al. 2014](#)), schizophrenia ([S.H. Lee et al. 2012](#); [Purcell et al. 2009](#); [Ripke et al. 2013a](#); [Ruderfer et al. 2014](#)), and autism spectrum disorder ([Carayol et al. 2014](#); [Folstein and Rosen-Sheidley 2001](#); [Gillis and Rouleau 2011](#)). For example, the largest genomewide association analysis to date identified 108 schizophrenia loci ([Ruderfer et al. 2014](#)), supporting the hypothesis that locus heterogeneity is an important factor in schizophrenia. Thus, [Bleuler \(1951\)](#) appears to have been correct when he referred to dementia praecox as “the group of schizophrenias.”

As already noted, susceptibility genes are likely to interact with environment, gender, and other genes, making the search for “genes for psychiatric disorders” even more complex ([Kendler and Greenspan 2006](#)). Twin studies have produced evidence that genetic interactions with stressful life events predict major depressive disorder ([Kendler et al. 1995a](#)) and that genetic interactions with early rearing environment predict schizophrenia, conduct disorder, and drug abuse ([Cadoret et al. 1995a, 1995b](#); [Tienari et al. 2004](#)). A key series of studies by [Caspi and](#)

[Moffitt \(2006\)](#) enriched our understanding of G×E interactions and led to increased momentum in research. Although most G×E studies look into detrimental environmental factors, their scope also should encompass positive or protective environmental factors ([Klengel and Binder 2015](#)). Furthermore, gender-specific predisposing genes for psychiatric disorders are likely. Data from twin studies suggest that the combined genetic factors conferring risk for major depressive disorder, phobias, and alcoholism may differ in some respects for men and women ([Kendler and Prescott 1999](#); [Kendler and Walsh 1995](#); [Kendler et al. 2001a, 2002, 2006](#); [Prescott and Kendler 2000](#); [Prescott et al. 2000](#)), and this theory has been supported in molecular genetic studies by the identification of gender-specific loci for anxiety and major depressive disorder, for example ([Quast et al. 2014](#); [Unschuld et al. 2010](#)). Finally, gene–gene interactions also may be relevant for these disorders ([Risch 1990](#)) but have not been studied in detail thus far.

## Genetic Modifiers of Response to Drug Treatment

In contrast to the profusion of genetic epidemiological studies on disease susceptibility, genetic epidemiological studies on responses to psychotropic drugs are rare. Some evidence from family studies suggests an important contribution of genetic factors in antidepressant response. Already in the early 1960s, studies on the effects of tricyclic antidepressants (TCAs) and later on lithium ([Grof and Alda 2000](#); [Smeraldi et al. 1984](#)) in patients and their first-degree relatives suggested that response to these drugs

was similar among family members ([Angst 1961](#); [Pare et al. 1962](#)). [O'Reilly et al. \(1994\)](#) reported a familial aggregation of response to tranylcypromine, a monoamine oxidase inhibitor, in a large family with major depressive disorder. These initial reports were followed by only a few systematic studies. [Franchini et al. \(1998\)](#) indicated a possible genetic basis of response to the selective serotonin reuptake inhibitor (SSRI) fluvoxamine in 45 pairs of relatives. In light of these data, some groups have used or proposed to use response to certain antidepressant drugs or mood stabilizers as an additional phenotype in classical linkage analyses for mood disorders in the hope of identifying genetically more homogeneous families ([Serretti et al. 1998](#); [Turecki et al. 2001](#)).

Nonetheless, family studies supporting a genetic basis for response to psychotropic drugs are sparse, certainly reflecting the extreme difficulties inherent in conducting well-controlled family studies of therapeutic response to medications. It has been proposed that genetic modifiers of response to treatment to psychotropic drugs may be easier to detect than associations with disease susceptibility, because the genetic contribution to these traits may be less complex ([Weinshilboum 2003](#)). The strongest molecular data exist for lithium response. The response of bipolar patients to lithium treatment has been associated with genetic variations with genomewide significance ([Alda 2015](#); [Chen et al. 2014](#); [Hou et al. 2016](#)).

Mounting evidence suggests that in addition to genetic variation, epigenetic mechanisms underlie some of the therapeutic effects of common psychotropic drugs ([Boks 2014](#)), including antidepressants ([Menke and Binder 2014](#)), valproic acid, and lithium ([Boyadjieva and Varadinova 2012](#); [R.S. Lee et al. 2015](#)).

---

# Human Genetic Variation

---

As mentioned previously, genetic epidemiological studies can indicate the presence of an aggregate genetic effect but cannot identify which type and how many variations contribute to the effect. A discrepancy exists between heritability estimates from family studies and those from population cohorts. For example, heritability estimates for schizophrenia from twin studies average about 0.8 ([Sullivan et al. 2003](#)), whereas population estimates are always lower, about 0.65 ([Lichtenstein et al. 2009](#)). In this section, we offer an overview of the types of variation that occur in the human genome and provide examples illustrating the implications of each variation type for psychiatric disorders.

## Variation on a Chromosomal Scale

### Variation in Chromosomal Number

The human genome has approximately 3 billion bases that are distributed over 23 chromosome pairs, with 22 pairs of autosomes and 1 pair of sex chromosomes, X and Y. The most obvious genetic variations can be observed at the light microscope level in the karyotype. This approach visualizes metaphase chromosomes using histological procedures, allowing identification of each specific pair of chromosomes and variations in the total number of chromosomes, such as unisomies and trisomies. Several of the known variations of total chromosome number have an associated psychiatric phenotype. For example, Down syndrome is a complex neurodevelopmental disorder that results in variable levels of intellectual disability and, in old age, dementia strikingly

similar to Alzheimer's disease ([Visootsak and Sherman 2007](#)). Down syndrome results from *trisomy 21* (i.e., inheritance of three copies of chromosome 21, caused by meiotic nondisjunction during oogenesis). Turner syndrome, in which the person has only a single X chromosome (i.e., an XO karyotype), is associated with nonverbal learning disabilities, particularly in arithmetic, certain visuospatial skills, and processing speed ([Sybert and McCauley 2004](#)).

## Translocations

Karyotypic examination and other cytogenetic techniques such as fluorescent in situ hybridization (FISH) can detect additional large-scale chromosomal abnormalities, such as translocations, deletions, or duplications of large regions of chromosomes. In a large Scottish pedigree, a balanced translocation between chromosomes 1 and 11 appears to be causally linked to a series of major psychiatric disorders, including schizophrenia, bipolar disorder, recurrent major depressive disorder, and conduct disorder ([St Clair et al. 1990](#)). This *balanced translocation* (which exchanged parts of chromosome 1 with parts of chromosome 11 to produce two abnormal chromosomes but no net loss of chromosomal material) disrupts two genes at the translocation breakpoint on chromosome 1, termed *disrupted in schizophrenia* (DISC) 1 and 2 ([Millar et al. 2000, 2001](#)). Subsequent molecular analysis has provided strong evidence that variation in *DISC1* can alter the risk for schizophrenia ([Porteous et al. 2006](#)). Although most still consider the *DISC1* translocation to be a confirmed schizophrenia risk factor ([Porteous et al. 2014](#)), this is hotly debated because of concerns about the standard of the evidence ([Sullivan 2013](#)).



## Deletions

Microdeletions occurring on the long arm of chromosome 22 have received considerable attention as cytogenetic risk factors for the development of schizophrenia ([Karayiorgou and Gogos 2004](#)). The 22q11 deletion syndrome, in which 1.5–3.0 million base pairs (bp) of DNA are missing on one copy of 22q, includes a spectrum of disorders affecting structures associated with development of the fourth branchial arch and migration of neural crest cells (e.g., the great vessels of the heart, the oropharynx, the facial midline, the thymus, the parathyroid glands). Originally described as distinct disease syndromes prior to the elucidation of their common molecular etiology, 22q11 deletion syndrome includes velocardiofacial syndrome (VCFS), DiGeorge syndrome, and conotruncal anomaly face syndrome. Following an initial report of early-onset psychosis in patients with VCFS ([Shprintzen et al. 1992](#)), [Pulver et al. \(1994\)](#) examined psychiatric symptoms in adults with VCFS and in a cohort of patients ascertained for schizophrenia ([Karayiorgou et al. 1995](#)). The latter study identified two previously undiagnosed cases in 200 patients, verified by FISH to carry 22q11 deletions ([Karayiorgou et al. 1995](#)). There is a reported 10–20 times higher prevalence of the 22q11 deletion in patients with schizophrenia ([Rees et al. 2014b](#)), and duplications of 22q11.2 might prove protective ([Rees et al. 2014a](#)). The deletion is thought to be one of the strongest risk factors for psychosis ([Schneider et al. 2014](#)), with early cognitive decline being a strong indicator of subsequent psychosis development ([Vorstman et al. 2015](#)).

## Duplications

Duplications of the long arm of chromosome 15 (15q11-13) are the most frequent cytogenetic anomalies in autism spectrum disorder, occurring in approximately 1%-2% of cases ([Cook 2001](#)). This duplication syndrome cannot be clinically differentiated from idiopathic autism ([Veenstra-VanderWeele and Cook 2004](#)), indicating that a complete workup of autism spectrum disorder should include testing for this cytogenetic abnormality as well as several others ([Martin and Ledbetter 2007](#)). Interestingly, deletion of this same region of 15q is associated with Angelman syndrome when the deletion occurs on the maternal copy of chromosome 15 and with Prader-Willi syndrome when the deletion occurs on the paternal chromosome (or, more rarely, when two maternal copies of chromosome 15 are present and the paternal chromosome is missing entirely, a condition known as *maternal disomy*). Both syndromes manifest as quite distinct but dramatic neurobehavioral disorders ([Nicholls and Knepper 2001](#); [Vogels and Fryns 2002](#)). Induced pluripotent stem cells are now being used to model copy number variations for individual patients. These models have the potential to help explain the underlying mechanisms of psychopathologies. For example, induced pluripotent stem cells taken from patients with 15q11 copy deletion show deficits in adherens junctions and apical polarity. The study pinpointed a haploinsufficiency at *CYFIP1*, one of the genes within the larger deletion ([Yoon et al. 2014](#)).

## Molecular Variation in the Genome

Most genetic and genomic studies in neuropsychiatry conducted to date have examined variation at the molecular

level, which would be undetectable with methods appropriate for the chromosomal-level variation described earlier. To introduce this section, we provide basic definitions of common terms.

## **Definition of Alleles, Genotypes, and Haplotypes**

Familiarity with the terms *allele*, *genotype*, and *haplotype* is fundamental to understanding the various types of polymorphisms discussed later in this section. An *allele* is a variation in DNA sequence that occurs at a particular *polymorphic* site on one chromosome. Every individual with a normal set of chromosomes has two alleles for each polymorphism on the *autosomes* (nonsex chromosomes, numbers 1-22). On the sex chromosomes, men have only one allele each for all polymorphisms located on the X and Y chromosome, whereas women carry two copies of each X-linked allele. A *genotype* is the combined description for the variation at a particular corresponding point on homologous chromosomes and is expressed as two alleles. When the alleles on both chromosomes are the same, it is a *homozygous* genotype. When the alleles differ, it is a *heterozygous* genotype. A *haplotype*, a term derived from the abbreviation of “haploid genotype,” is the sequence of alleles along an adjacent series of polymorphic sites on a single chromosome. When genotypic data are available from three generations, haplotypes in the third generation can be unambiguously deduced. In the absence of sufficient family-based data (e.g., in case-control studies of unrelated individuals), some haplotypes are ambiguous because the combination of genotypes at the polymorphic sites under study can be explained by more than one set of possible

chromosomal arrangements of the component alleles. In these cases, methods such as estimation maximization can be used to infer the most likely haplotype ([Hawley and Kidd 1995](#); [Long et al. 1995](#)).

## Copy Number Variation

Genome-scale investigations enabled by the sequencing of the human genome and the advent of array-based comparative genomic hybridization have identified a previously unappreciated form of polymorphic variation in the human genome: chromosomal regions containing one or more genes can sometimes be deleted or, alternatively, occur in multiple copies, with the number of copies differing among individuals ([Nadeau and Lee 2006](#); [Sebat et al. 2004](#)). Such *copy number variants* (CNVs) occur normally in human populations, and a map of such variants is available ([Zarrei et al. 2015](#)). CNVs have been associated with marked differences in gene expression ([Stranger et al. 2007](#)), and they also can be associated with predisposition to disease, including neurobehavioral disorders ([Sebat et al. 2007](#)).

CNV analysis in schizophrenia has shown that rare deletions and duplications increase risk ([International Schizophrenia Consortium 2008](#)) and has implicated the involvement of genes in neurodevelopmental pathways ([Walsh et al. 2008](#)) and postsynaptic signaling complexes ([Kirov et al. 2012](#)). CNVs also have been found to be associated with autism spectrum disorder ([Marshall et al. 2008](#)). Indeed, CNV studies have now shown the same genes to be disrupted or affected in schizophrenia, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder. This broad phenotypic spectrum suggests that these CNVs generally impair

neurodevelopment ([Rosenfeld et al. 2010](#)). Interestingly, a recent study in children with ADHD showed that in comparison with control subjects, children with large, rare CNVs had lower polygenic risk scores, whereas those without such CNVs had higher polygenic risk scores ([Martin et al. 2015](#)), indicating that risk is conferred by either rare (for lower scores) or common (for higher scores) variants. (Polygenic risk scores are discussed later in this chapter, in the section titled “Use of GWAS Data.”)

Copy number variation of the cytochrome P450 (CYP) gene *CYP2D6*, which is important for the metabolism of many antidepressants, antipsychotics, and mood stabilizers ([Kirchheiner et al. 2004](#)), provides a prominent example of the importance of CNVs to pharmacogenetics. The presence in the genome of copy number variation at the *CYP2D* locus was inferred through biochemical-genetic studies predating the molecular era and was subsequently confirmed by molecular studies. The reported range of copy numbers of *CYP2D6* is from 0 to 13. The number of functional *CYP2D6* gene copies directly correlates with plasma levels of metabolized drugs, such as the TCA nortriptyline ([Bertilsson et al. 2002](#)). In fact, the first trial examining the cost-effectiveness of screening for *CYP2D6* in patients initiating treatment with the antidepressant nortriptyline or venlafaxine has begun ([Berm et al. 2015](#)).

## Insertion/Deletion Polymorphisms

Microscopic insertions and deletions (much smaller than CNVs—on the order of one to hundreds of bp) are another important type of genetic variation. The most famous insertion/deletion polymorphism in psychiatric genetics is a common functional polymorphism in the promoter region of the serotonin transporter gene *SLC6A4*, referred to as the

serotonin transporter-linked promoter region (5HTTLPR). It consists of a repetitive region containing 16 imperfect repeat units of 22 bp, located approximately 1,000 bp upstream of the transcriptional start site (Heils et al. 1996; Lesch et al. 1996). The 5HTTLPR is polymorphic because of the insertion/deletion of the repeat units 6-8 (of the 16 repeats), which produces a short (S) allele that is 44 bp shorter than the long (L) allele. Although the 5HTTLPR was originally described as biallelic, rare (<5%) very-long and extra-long alleles have been described in Japanese and African Americans (Gelernter et al. 1999). Numerous additional variants within the repetitive region also occur (Nakamura et al. 2000). Thus, although most studies continue to treat this complex region as biallelic, this is an oversimplification that may be hiding additional genetic information.

The 5HTTLPR has been associated with altered basal activity of the transporter, most likely related to differential transcriptional activity (Heils et al. 1996; Lesch et al. 1996). The long variant (L allele) of this polymorphism has been shown to lead to a higher serotonin reuptake by the transporter in vitro. It is also noteworthy that the function of this insertion/deletion polymorphism may be influenced by a *single nucleotide polymorphism* (SNP) that occurs with the L allele (Hu et al. 2006). However, a positron emission tomography (PET) study was unable to identify differences in serotonin transporter binding potential by the 5HTTLPR genotype, even when including the information of the additional SNP, in healthy control subjects or patients with major depressive disorder (Parsey et al. 2006). This polymorphism has shown associations with a multitude of psychiatric disorders and related phenotypes. The best-established associations are with response to SSRI

antidepressants ([Porcelli et al. 2012](#); [Serretti et al. 2007](#)) and with moderation of the influence of life events on risk of depression ([Caspi et al. 2003](#)), although the latter finding remains controversial ([Karg et al. 2011](#); [Kaufman et al. 2004](#); [Kendler et al. 2005](#); [Munafò et al. 2009](#); [Risch et al. 2009](#); [Surtees et al. 2006](#); [Wilhelm et al. 2006](#); [Zalsman et al. 2006](#)).

---

## Microsatellites: STRs and VNTRs

---

A very important class of polymorphisms, on which molecular linkage studies and some association studies were based until very recently, is *microsatellite* markers, also called *short tandem repeats* (STRs) or *variable number of tandem repeats* (VNTRs). The polymorphisms consist of simple sequences, such as guanine-thymine (GT) or guanine-adenine-thymine-adenine (GATA), that are repeated a variable number of times. An individual thus may have five GT repeats at a specific locus on one chromosome and seven such repeats on the other. When these regions are amplified by *polymerase chain reaction* (PCR), a technique for producing many copies of a specific small portion of the genome based on DNA polymerase activity directed by specific DNA sequences, the difference in number of repeats results in differences in the length of the amplified fragments (a difference of 4 bp in the present example), allowing efficient genotyping of these polymorphisms by gel electrophoresis, which separates DNA fragments according to length. About 30,000 of these polymorphisms are now known in the human genome ([Kawashima et al. 2006](#); [Tamiya et al. 2005](#)), and they have

served as markers for genomewide linkage analysis (see “Linkage Studies” subsection later in this chapter for more detail).

VNTRs not only serve as genetic markers for linkage analysis but also may produce functional variation within genes. An important example of such functional variation is a VNTR in the 3′ untranslated region of the dopamine transporter (DAT) gene *SLC6A3*. The repeat element consists of a 40-bp sequence that can occur with 3–11 repeats, with 9 or 10 repeats being the most common ([Vandenbergh et al. 1992](#)). Different effects of the 9 or 10 repeats on gene expression and DAT binding using single photon emission computed tomography (SPECT) in humans have been reported, although the direction of these differences is controversial ([Greenwood and Kelsoe 2003](#); [Inoue-Murayama et al. 2002](#); [Martinez et al. 2001](#); [Mill et al. 2002, 2005](#); [van Dyck et al. 2005](#); [VanNess et al. 2005](#)), with the 9- and the 10-repeat alleles respectively associated with higher expression of the DAT gene and higher DAT binding in different studies. Another example of a functional VNTR (48-bp repeat) is a polymorphism in the third exon of the *DRD4* locus (the locus encoding the dopamine D<sub>4</sub> receptor), which results in a variable number of glutamine residues in the third intracellular loop of the dopamine D<sub>4</sub> receptor protein ([Van Tol et al. 1992](#)). The allelomorphic proteins differ in their ligand-binding affinities, but all couple to G proteins ([Van Tol et al. 1992](#)). Both polymorphisms have been associated with a multitude of behavioral and psychiatric phenotypes ([Gatt et al. 2015](#)), including bipolar disorder ([Seifuddin et al. 2012](#)), ADHD ([Wu et al. 2012](#)), and depression ([Opmeer et al. 2010](#)). In PET studies, the 9- or 10-repeat alleles have been



associated with decreased in vivo DAT activity (Faraone et al. 2014).

## Single Nucleotide Polymorphisms

The polymorphisms that have revolutionized (not only) psychiatric genetics are SNPs (Altshuler et al. 2000; Sachidanandam et al. 2001). SNPs consist of a single-base difference at a particular site in the genome—in two-thirds of the cases, a cytosine (C)-to-thymine (T) exchange. Although theoretically the presence of all four different bases at an SNP is possible, the vast majority of SNPs have only two alleles, but SNPs with three or four different alleles occasionally have been reported. As of September 2016, around 150 million human SNPs had been catalogued in public databases (such as dbSNP: e.g., [www.ncbi.nlm.nih.gov/projects/SNP](http://www.ncbi.nlm.nih.gov/projects/SNP)). SNPs are so far the most common type of genetic variation and may represent up to 90% of all genetic variations (although this estimate may need revision as knowledge about CNVs accumulates). Besides being very common (SNPs occur, on average, every 300 bases), they are also amenable to high-throughput genotyping methods (Kim and Misra 2007; Kwok 2000). Because SNPs are common (essentially every gene of interest has several known SNPs) and cheap to genotype, they are the markers of choice for complex trait genetic association studies.

Besides serving as genetic markers for chromosomal loci in association studies, SNPs also can have functional relevance themselves. SNPs in regulatory regions can alter the transcriptional regulation of a gene, SNPs in regions relevant for mRNA splicing can alter splice sites, and SNPs in protein-coding exons can encode differences in primary amino acid sequence. Interestingly, when one considers the

occurrence of SNPs across the genome, one observes that SNPs are most dense in intergenic and intronic regions but scarcer in putative regulatory regions and exons, suggesting selection against putatively functional variants ([Altshuler et al. 2000](#); [Sachidanandam et al. 2001](#)). Within exons, SNPs that will not cause an amino acid exchange due to the degenerate code are called *synonymous* SNPs as opposed to *nonsynonymous* SNPs, which lead to amino acid substitution. One nonsynonymous SNP that repeatedly has been associated with psychiatric phenotypes is a valine (Val)-to-methionine (Met) exchange at amino acid position 108/158 in the soluble or membrane-bound form of the catechol-*O*-methyltransferase (COMT) peptide sequence resulting from a guanine (G)-to-adenine (A) exchange at position 472 of exon 4. This amino acid exchange dramatically affects the temperature lability of this enzyme, with the Met allelomorphic protein having only one-fourth of the enzyme activity at 37°C of the Val allelomorph ([Lachman et al. 1996](#); [Lotta et al. 1995](#)). It is presumed that individuals with the Val/Val genotype have a more rapid inactivation of centrally released dopamine than individuals with the other genotypes, following an additive genetic model. This polymorphism seems to affect dopamine transmission—particularly in the frontal cortex, where expression of the dopamine transporter protein is relatively low—and has been associated with differences in executive cognition and functional activity of the prefrontal cortex during working-memory tasks ([Egan et al. 2001](#); [Goldberg et al. 2003](#); [Joober et al. 2002](#); [Mattay et al. 2003](#)). Although it was hypothesized that this polymorphism also could alter the risk for schizophrenia (particularly because COMT resides in the 22q11 region, the deletion of which has been associated with schizophrenia), larger association

studies and meta-analyses do not fully support that conclusion ([Fan et al. 2005](#); [Farrell et al. 2015](#); [Okochi et al. 2009](#)).

---

## Identification of Risk Loci for Psychiatric Disorders

---

In the following subsections, we focus on methods for identifying genetic psychiatric disease risk.

### Cytogenetic Studies

Disruption of chromosomal integrity by rare events such as balanced translocations has facilitated gene discovery in a variety of diseases and holds significant promise for similar applications in psychiatric illness ([Pickard et al. 2005](#)). Advances in techniques such as chromosome painting, high-resolution FISH, and, most recently, genomewide analysis of CNVs using microarrays have made it possible to identify disruptions in chromosomal architecture to single-base resolution, thus facilitating identification of specific genes in families cosegregating mental illness and cytogenetic abnormalities. Such data then may be used to generate testable hypotheses about the role of a particular gene in disease pathophysiology. The *DISC1* and *DISC2* genes provide clear examples of specific genes implicated in mental illness following their discovery through careful molecular analysis of a cytogenetic anomaly. Because much more work has been published on *DISC1*, we focus on that locus here.

As noted previously, *DISC1* was initially identified by cytogenetic studies in which a large Scottish family with numerous relatives affected by major psychiatric illness were shown to carry a balanced (1;11) (q42;q14.3) translocation that cosegregates with the presence of psychiatric illness. Linkage analysis using the psychiatric diagnosis as a phenotype and the translocation as a genetic marker yielded highly significant evidence supporting linkage of the translocation to psychiatric illness, and particularly to schizophrenia ([Blackwood et al. 2001](#); [St Clair et al. 1990](#)). The translocation was shown to disrupt *DISC1* and *DISC2* on chromosome 1 ([Millar et al. 2000, 2001](#)), whereas no known genes were disrupted on chromosome 11. *DISC1* was shown to encode a novel protein, with no known related proteins, that subsequently has been shown to play important roles in several key neuronal functions, including axonal transport and regulation of G-protein-mediated intracellular signaling ([Porteous et al. 2006, 2014](#)). Studies in induced pluripotent stem cell-derived forebrain neurons suggest that *DISC1* mutations are associated with disrupted synaptic vesicle release ([Wen et al. 2014](#)).

## Linkage Studies

In the 1980s and 1990s, many genes for Mendelian disorders were successfully identified with linkage analysis in large families. Linkage relies on the principle that, on average, chromosomes from parents differ from those of offspring by only one meiotic crossover event. During *meiosis*, the cell divisions that produce gametes by reducing the diploid genome (i.e., two chromosomes of each

pair per cell) to a haploid genome (one copy of each chromosome per spermatocyte or oocyte), homologous grandparental chromosomes (i.e., paternal and maternal to the parents of the offspring of interest), make physical contact and exchange homologous regions (referred to as *crossing over*) to give rise to a new set of chromosomes in which each gametic chromosome is a mix of grandparental sequences. This crossing-over process produces *recombination* that can then be tracked with molecular markers to delineate the ancestral origin of each chromosomal region in the offspring.

Classically, linkage studies use from several hundred to a few thousand microsatellite markers, evenly spaced across the genome. These markers are then genotyped in large families in which the disease of interest is common. To identify positions in the genome that may be involved in the disease, one tracks whether marker alleles are inherited by affected relatives more often than would be expected by chance (i.e., linkage tests whether a particular chromosomal region *cosegregates* with the disease). A quantitative measure of the likelihood of a particular pattern of marker-disease cosegregation is the *logarithm of odds (LOD) score*. As the name implies, the LOD score is logarithmic, with LOD=1 corresponding to 1:10 odds, LOD=2 to 1:100 odds, and so forth. Because of the high a priori probability that a given region is *not* linked to a given phenotype, a LOD score of 3.3 or greater is usually required before significant linkage is accepted ([Lander and Schork 1994](#)). The results of linkage analyses are usually presented as plots of LOD scores at each marker, which are arranged in their known order across individual chromosomes or the entire genome. These plots show a pattern of peaks and valleys. Linkage peaks identify

chromosomal regions (i.e., loci) where the LOD score is high, suggesting a high probability that a disease-linked variant resides nearby. Because of the spacing of the markers and their multiallelic properties, the identified regions are usually large, comprising up to tens of mega bases and harboring dozens of genes (which are then referred to as *positional candidates* because they reside under the linkage peak). Linkage peaks need to be followed up with additional *fine mapping* using denser marker maps, including SNPs, to hone in on the candidate gene(s) of interest.

Classical linkage approaches have been very successful in identifying monogenic diseases that follow clear, simple patterns of inheritance, but they have been far less successful in complex psychiatric disease. Parametric linkage analysis requires specification of an inheritance model (e.g., recessive or dominant), information we do not have for psychiatric disorders, as they clearly do not follow Mendelian inheritance. In addition, each family may have a different pattern of inheritance, so that specifying one model for several pedigrees may decrease the power to detect a signal in some of the families. Nonparametric linkage analyses that are mode-of-inheritance independent have been developed to address this problem. Also, linkage analysis requires that each person in a pedigree be designated as either affected or unaffected, so one must decide, for example, in which category to place individuals with a single major depressive episode in a bipolar pedigree. Linkage analysis studies therefore often run several different models and also may use different definitions of affected status and then report the best LOD score, but here the threshold for significance also has to be adjusted for additional multiple testing, so that even higher

LOD scores are required for statistical significance. Linkage analyses in psychiatric disorders are further complicated by the fact that they explore complex psychiatric diseases, with likely multiple (possibly additive or interacting) susceptibility genes and a strong environmental component, all of which cannot be modeled easily in these analyses. It is therefore not surprising that linkage analyses have yielded inconsistent results in the past.

## Association Studies

Association studies are usually performed in case-control studies of unrelated individuals. In such studies, allele frequencies of markers are compared between a case and a control population. Association has been shown to have more power than linkage studies to detect susceptibility genes that exert only a small effect on disease risk ([Risch and Merikangas 1996](#)). Considering the strong evidence supporting complex inheritance for most psychiatric disorders, it appears that association studies are the optimal study design to identify and/or test candidate genes for these disorders. To help interpret genetic association studies, we first want to introduce several key concepts, which are important for the design and understanding of association studies.

### Linkage Disequilibrium

Association studies rely on the principle that even unrelated individuals share very small stretches of chromosomal DNA derived from a distant common ancestor. In the case of a disease-predisposing mutation, some proportion of ill individuals will share that mutation arising from an original

common ancestor. As the variant is passed down from generation to generation, meiotic recombination events will shrink the size of the initial piece of ancestral chromosome that is inherited together with the disease mutation. On these small ancestral stretches of chromosome (perhaps several thousand to several hundred thousand bp in length), nonfunctional “marker” polymorphisms close to the disease mutation will “ride” through generations together with the disease variant. Such markers (SNPs, for example) thus can serve as surrogate “tags” for the disease mutation. Note, however, that as generations pass and individuals become ever more distant relatives (to a point when social/cultural “memory” of genetic relationship is usually lost), different families will produce recombination events at different points near the disease mutation. Therefore, at a population level, unrelated individuals carrying the disease marker will carry variable lengths of DNA on which markers linked to the disease variant ride. Stated another way, unrelated individuals carrying the disease variant will carry *haplotypes* that become more similar to one another as the boundaries of the haplotypes are moved closer to the disease variant. Thus, the closer a marker is to the disease variant, the more likely it is to be originally linked to the variant. When a marker is close enough to a disease marker that the number of recombination events in the population has not yet completely randomized, and the odds are high that it is on the same ancestral stretch of DNA (haplotype) as the disease variant, the marker and the disease variant are correlated and are said to be in *linkage disequilibrium* (LD). Knowing the allele of a marker variant in LD with a disease variant can therefore allow one to predict the allele of the disease variant (i.e., the marker and the disease variant are not statistically independent).



Several factors influence the length of DNA over which LD occurs. The most important are the geographic origins of the population from which an individual is drawn and the history of that population. For example, sub-Saharan African populations are ancient and reflect the greatest proportions of the total human pool of variation, because most of the human species' history predates migration of humans out of Africa. Therefore, on average, sub-Saharan African populations have undergone the greatest number of recombination events since a given pair of unrelated individuals shared a common ancestor. Those individuals thus share only short stretches of ancestral chromosomes (which are said to be *identical by descent*, or IBD). Non-African populations all derive from a relatively small number of migrants who left Africa within approximately the last 100,000 years. Thus, Europeans, Eastern Asians, or Native Americans share longer stretches of DNA IBD within their respective continental groups than do sub-Saharan Africans ([Daly et al. 2001](#); [Gabriel et al. 2002](#); [Patil et al. 2001](#); [Reich et al. 2001](#)). On the other extreme, individuals from reproductively isolated populations, in which a small recent founder population has expanded with little admixture (i.e., introduction of outside individuals into the mating pool), share longer blocks of ancestral chromosomes IBD ([Shifman and Darvasi 2001](#)). An example of such an isolate is the Icelandic population, which derives almost exclusively from a small number of migrants who arrived on the island only several hundred years ago ([Helgason et al. 2003](#)).

Another factor contributing to the complexity of patterns of LD is the fact that recombination events do not occur with the same likelihood across all parts of the genome ([Phillips et al. 2003](#); [Reich et al. 2002](#)). In addition to a

general pattern in which more telomeric regions of chromosomes are more likely to recombine than centromeric regions, specific “hot spots” of recombination have been identified that are spaced unevenly along chromosomes. This variation across the genome in the likelihood of recombination results in the observation that certain stretches in the genome (sometimes referred to as *blocks*) have undergone relatively little recombination over the generations and therefore show strong LD among SNPs in the region. Such regions of high LD can span millions of bases, whereas other regions in the same population have recombined more frequently, resulting in very short blocks of LD (e.g., <5,000 bp). It is important to note that the observed haplotypes formed by the SNPs within a given stretch of chromosome usually represent only a small proportion of all possible haplotypes (for SNPs, the number of possible haplotypes= $2^n$ , where  $n$ =the number of SNPs defining the haplotype). For this reason, such regions of high LD are also called *haplotype blocks* ([Daly et al. 2001](#); [Gabriel et al. 2002](#); [Patil et al. 2001](#); [Reich et al. 2001](#)).

### **Catalogues of human genetic variation.**

Originally, the HapMap (genotyping) and subsequently the 1,000 Genomes (next-generation sequencing) projects provided a high-resolution map of the landscape of human genetic variation. The HapMap project included 1.6 million SNPs from 11 different populations. However, in June 2016, the HapMap project was decommissioned, having been eclipsed by the 1,000 Genomes project. The 1,000 Genomes project aimed to discover the genetic variants with frequencies of at least 1% in the population by mapping 1,000 genomes. The pilot-phase milestone ([1000 Genomes Project Consortium et al. 2010](#)) and the successful

completion of 1,092 genomes in 2012 ([1000 Genomes Project Consortium et al. 2012](#)) continue to be improved (now overseen by the International Genome Sample Resource), with structural variations of 2,504 genomes from 26 populations now mapped ([Auton et al. 2015](#); [Sudmant et al. 2015](#)).

**LD and replication of association studies.** It is now general consensus that finding “true” genetic associations of SNPs in psychiatric disorders demands high-powered studies and replication in independent patient cohorts. As a result of varying founder effects, the verification of a specific SNP might fail in populations with different ancestry, in which case other SNPs in proximity can help to determine the universal significance of that given genetic association.

## Population Stratification

Frequencies of specific alleles can vary to a large degree among different populations. The frequency of the S allele of the 5HTTLPR, for example, is approximately 40%–50% in European, approximately 70%–80% in East Asian, and approximately 25% in African populations ([Gelernter et al. 1999](#)). Spurious associations can thus be found if subjects for a genetic association study are sampled from genetically different subpopulations (with different marker allele frequencies) in different proportions in case and control participants, for example. False-positive associations can also result if an outcome is more prevalent in one subpopulation, perhaps because of different environmental exposure, so that individuals from this subpopulation will be represented more frequently in the case as opposed to the control group. Differences in allele frequencies between

comparison groups can thus result from differences in the population structure of the sample alone, without any causal relationship to the outcome of interest. This problem is called *population stratification* and is exemplified by the hypothetical example of the “chopsticks gene” ([Hamer and Sirota 2000](#)).

Several methods have been developed to address population stratification in genetic association studies. Family-based approaches to genetic association studies, such as the transmission disequilibrium test (TDT; [Spielman et al. 1993](#)) and the haplotype-relative risk (HRR) method ([Knapp et al. 1993](#)), are robust to population stratification. In the TDT, rather than comparing allele frequencies between case and control subjects, genotypes are determined in *probands* (individuals who serve as the starting point for the study) and their parents. To be informative, at least one parent must be heterozygous at the marker of interest (this is one of the disadvantages of the method in its original form: in some cases, not all families can be used). The allele transmitted to the proband from each parent is recorded, as well as the nontransmitted allele. Under the null hypothesis of no linkage or association, the expected chance of each allele’s transmission is 50%. Significant deviations from that chance provide evidence for association (and linkage) between the trait and the marker. The HRR method is similar, except that the frequency of the nontransmitted alleles is compared with that of the transmitted alleles over a large number of families. Each family thus provides its own control, and because the proband is always matched for the population background of the parents, population stratification cannot arise.

Methods based on the TDT have been developed to allow transmission disequilibrium testing in larger family groups. Such family-based association tests offer the advantage of using more of the available genetic information from each family ([Horvath et al. 2001](#)). The major disadvantage of the family-based methods is that it is often impractical to gather families, especially in disorders such as schizophrenia or substance use disorder, which are often associated with familial estrangement, or in age-related disorders such as Alzheimer's disease, in which surviving relatives (especially parents) may not be available. An additional problem with family-based association studies is that they generally have less statistical power than case-control studies ([Risch and Merikangas 1996](#)).

To control for population stratification in case-control studies, several methods have been suggested. One approach is to estimate, and then correct for, the expected degree of stratification by typing a series of unlinked markers across the genome ([Devlin and Roeder 1999](#); [Pritchard et al. 2000](#)). The method of genomic control ([Devlin and Roeder 1999](#)) derives an inflation factor, the so-called  $\lambda$  value, by comparing observed with expected test statistics. This value is then used to rescale association results. One disadvantage of this approach is that  $\lambda$ , and hence inflation, is assumed to be constant across the genome.

Structured association ([Rosenberg et al. 2002](#)) involves the use of a clustering algorithm to assign samples to subpopulations. Association statistics are computed stratified by cluster.

Principal components analysis is another widely used method of detecting and correcting for spurious associations resulting from population stratification ([Price](#)

[et al. 2006](#)). In this approach, the main axes of variation, also called *principal components*, are plotted against each other to identify possible population outliers or clusters. These main (principal) components are also included as covariates in subsequent association analyses to correct for population admixture.

## Genomewide Association Studies

### New Possibilities From the Human Genome Project

Despite more than 40 years of intense research on a series of promising markers, none have thus far been validated as diagnostic tools or predictors of treatment response. In addition, most of the past approaches were hypothesis driven, relying on our limited knowledge of the pathophysiology of psychiatric disorders. With the sequence of the human genome being publicly available since 2001 ([Lander et al. 2001](#); [Venter et al. 2001](#)), a variety of novel research tools are now accessible that may yield unbiased, hypothesis-free insight into the pathophysiological underpinnings of certain psychiatric disorders. These new tools combine knowledge of the sequence of the human genome with miniaturized assays amenable to high-throughput processing or next-generation sequencing methods for a parallel analysis of the whole genome. One can use these tools to investigate the whole genome at the level of the DNA (genomics), all RNA (transcriptomics), and all protein/DNA and protein/RNA interactions (proteomics) in a single experiment. Additionally, similar “omic” approaches are possible at the level of the proteome, including posttranslational modifications. These approaches

have to deal with increasing levels of complexity, because the approximately 20,300 human genes are expected to give rise to at least 10 times as many protein isoforms with a multitude of posttranslational modifications, such as phosphorylation and glycosylation. In addition, the complexity of RNA analysis is massively increased because of differential splicing and noncoding RNAs. These unbiased whole-genome-based approaches can be used to identify novel pathways and molecules involved in the pathogenesis of psychiatric disorders.

In this chapter, we focus primarily on genomewide SNP association studies and their effect on psychiatric genetics. For additional information on the effects of omics on pathophysiological concepts in psychiatry, the reader is referred to the reviews of [Biesecker and Peay 2013](#); [Gratten et al. 2014](#); [Kato 2015](#); and [Schreiber et al. 2013](#).

## Genomewide SNP Arrays

**How many SNPs?** The presence of LD in the human genome allows the investigator to evaluate a large extent of the common genetic variation with selected markers. Estimates of the number of SNPs necessary to account for most of the common sequence variation across the genome (e.g., to account for SNPs with minor allele frequencies of 1% or greater) have varied over time, with estimates ranging from as few as 10,000–100,000 to more than a million SNPs. Thanks to the HapMap, 1,000 Genomes, and ENCyclopedia Of DNA Elements (ENCODE) resequencing projects ([Altshuler et al. 2010](#); [www.hapmap.org](http://www.hapmap.org)), we can efficiently cover the entire genome using SNP assays. Even though the cost for next-generation sequencing has decreased dramatically in the last decade, and the \$1,000

genome was made available in January 2014 by Illumina, array-based methods are still much more cost and time efficient, especially given the enormous sample sizes (10,000 cases and greater) required to identify disease loci in psychiatric traits. These massive genotyping and resequencing projects have confirmed the segments of long LD in the genome and thus the possibility of using tag SNPs (see discussion in “Linkage Disequilibrium” earlier in this chapter) for each of these segments. Using the data from several hundred thousand SNPs should be sufficient to cover most common variants in Caucasians; more SNPs will be necessary in African populations with shorter LD distances (for a review, see [Hirschhorn and Daly 2005](#)).

Certainly to date, genomewide association studies (GWAS) that use arrays have been the most common approach to identifying disease associations across the whole genome. However, next-generation sequencing methods are the most comprehensive, able to interrogate all 3.2 billion bases of the human genome, including rare and private mutations. This unbiased detection of changes at bp resolution makes next-generation sequencing attractive ([Precone et al. 2015](#)). Cost of sequencing depends on both the length of the genome and the depth of sequencing (i.e., the coverage, defined as the number of times a genomic region is read in the sequencing process). Next-generation sequencing typically allows *deeper sequencing* (i.e., at a coverage of  $>10\times$  ).

Reduced cost for more focused approaches can be achieved by preselecting (i.e., targeting) only parts of the genome. The most common targeted next-generation sequencing method is *whole-exome sequencing*. The *exome* makes up less than 2% of the genome but contains many known disease-causing rare variants ([Tennesen et al.](#)



2012). This narrower focus makes whole-exome sequencing a cost-effective targeted method with high coverage. The higher coverage possible with whole-exome sequencing allows identification of rare variants that currently would be too expensive with whole-genome sequencing.

The last few years have yielded a profusion of published studies in which whole-exome sequencing was used, some of which apply to psychiatry; for comprehensive reviews, the reader is referred to [Kato \(2015\)](#) and [Schreiber et al. \(2013\)](#). Some of the most notable findings in psychiatric research from whole-exome sequencing have been in autism spectrum disorder ([Chapman et al. 2015](#); [Toma et al. 2014](#)). It should be noted that in the future, communicating the results of whole-genome sequencing to patients will almost certainly raise ethical questions ([Biesecker and Peay 2013](#)), given that information beyond genetic risk for the interrogated disease will be available.

A major drawback of whole-genome LD-based approaches to association testing, such as those just outlined, is that most sequence variation in the genome is *rare*, with minor allele frequencies too small to be detected with any power by even very dense maps of SNPs. Thus, to the degree that the genetic underpinnings of complex disease deviate from the “common disease, common variant” hypothesis, whole-genome SNP scans will be inadequate to detect associated genes ([Zwick et al. 2000](#)). This concern is not merely theoretical. Thus, it is abundantly clear that in Mendelian diseases, such as cystic fibrosis, in which variation at only one *locus* accounts for the disease, a multitude of very rare *sequence variants* are causal in different families. Rare variation also clearly contributes to complex disease—most notably, autism spectrum disorder ([Levy et al. 2011](#); [Merikangas et al. 2015](#); [Sanders et al. 2011](#)). In all

likelihood, complex disorders will represent a mixture of contributions from rare and common variants, so that methods appropriate for both types of variation will need to be developed and implemented.

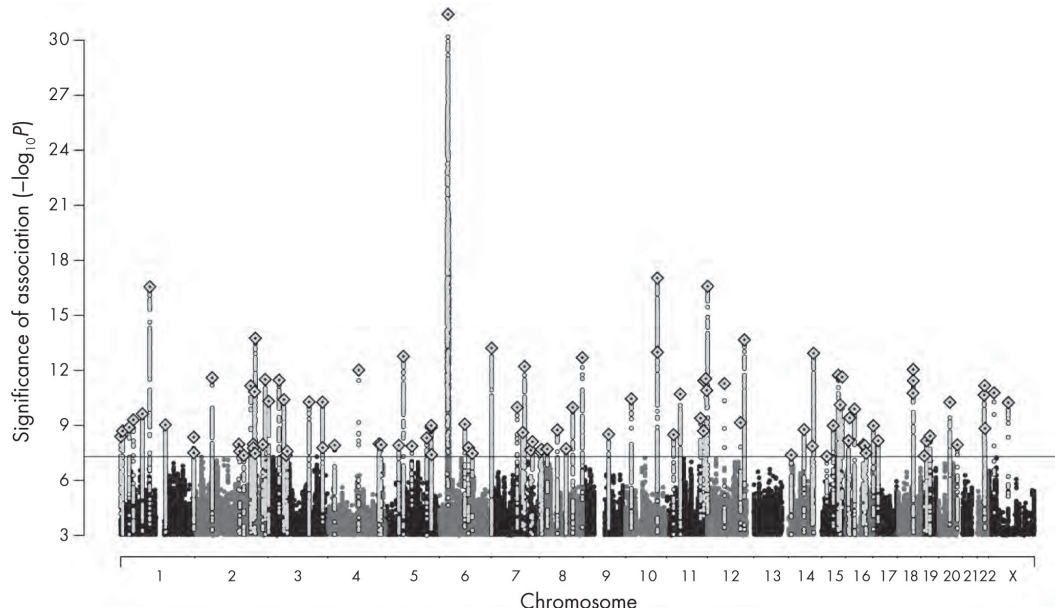
**How many individuals?** Genomewide associations require massive correction for multiple testing so that genomewide significant  $P$  values less than  $5 \times 10^{-8}$  can be achieved. These necessarily low alpha levels, together with the expected low odds ratios (ORs) associated with identified susceptibility variants, require large sample sizes for adequate power. When one surveys genomewide association discoveries over time, it can be seen that the larger the sample size, the more genomewide association hits are found (see Figure 2 in [Visscher et al. 2012](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257326/figure/figure2); available at: [www.ncbi.nlm.nih.gov/pmc/articles/PMC3257326/figure/figure2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257326/figure/figure2)).

Power (i.e., the probability of obtaining a true positive result) is determined by sample size, allele frequency, effect size, and significance level. For example, to detect the effect of a susceptibility allele that has a frequency of 20% and an OR of 1.3 with a power of at least 80% and an even more liberal alpha level of  $10^{-6}$ , more than 2,500 cases are necessary. If the allele is rarer (e.g., 10% carriers), at least 6,000 cases would be required ([Wang et al. 2005](#)). Considering a quantitative trait and setting the alpha level to  $5 \times 10^{-8}$ , to detect a variant that explains 0.2% of the variance with a power of at least 80%, more than 10,000 individuals would be needed ([Visscher 2008](#)). Often, these high sample sizes can be reached only within consortia that combine samples from many different studies and meta-analyze them together.

## Current Results From Genomewide SNP Association Studies

In a landmark paper, [Risch and Merikangas \(1996\)](#) suggested that the power of GWAS to detect disease genes for complex diseases will be greater than that of family-based studies. This bold suggestion was presented 5 years before the sequence of the human genome was available and SNPs had emerged as potential tools for this type of study. Now, 20 years later, GWAS with hundreds of thousands of SNPs in tens of thousands of affected individuals and control subjects are identifying novel, hypothesis-free candidate genes for complex disorders.

Because of the numerous statistical tests required, a threshold of  $P < 5 \times 10^{-8}$  has been proposed to control for all independent genetic loci in the genome. Associations surpassing this threshold would then be replicated in independent samples ([Ioannidis et al. 2009](#); [Kraft et al. 2009](#)). The standard presentation of data from GWAS is in a Manhattan plot ([Figure 3-3](#)). The chromosomes of the human genome (indicated by the *red* and *blue* portions of the x axis) and the positions on chromosomes are plotted (x axis) against the  $-\log_{10}$  of the statistically significant association identified (y axis). In case-control studies, the association is tested for a difference in genotype or allele distribution between the two groups. A significant threshold line is often drawn at  $P < 5 \times 10^{-8}$  (indicated by the *red horizontal line* in [Figure 3-3](#)). Significant signals are often located in LD with other SNPs that, in consequence, also show strong associations, so that towers of high  $-\log_{10} P$  values rise above the threshold, thus evoking the city skyline that gives the chart its name.



**FIGURE 3-3.** Manhattan plot showing schizophrenia associations.

*See Plate 13 to view this figure in color.*

Manhattan plot of the discovery genomewide association meta-analysis of 49 case-control samples (34,241 case participants and 45,604 control participants) and 3 family-based association studies (1,235 parent-affected offspring trios). The x axis is the chromosomal position (the *red* and *blue* blocks along the axis are provided to enhance visualization of the chromosome number), and the y axis is the significance ( $-\log_{10} P$ ) of association derived by logistic regression. The *red horizontal line* shows the threshold for genomewide significance ( $5 \times 10^{-8}$ ). Single nucleotide polymorphisms (SNPs) in *green* are in linkage disequilibrium with the index SNPs (*diamonds*) which represent independent genomewide significant associations. Schizophrenia was associated with 108 independent loci.

*Source.* Reprinted from Schizophrenia Working Group of the Psychiatric Genomics Consortium: "Biological Insights From 108 Schizophrenia-Associated Genetic Loci." *Nature* 511(7510):421-

Although the initial years for GWAS in psychiatry were fraught with disappointment, they brought the realization that only very large numbers can yield reliable associations. This realization led to establishment of the international Psychiatric Genomics Consortium (PGC; [www.med.unc.edu/pgc](http://www.med.unc.edu/pgc)) in 2007 that leads the way on GWAS in psychiatry as a result of its very large clinical cohorts (Sullivan 2010). The PGC involves more than 800 scientists worldwide and currently has samples from more than 900,000 individuals.

The largest molecular study ever to focus on schizophrenia, carried out by the PGC, was published in 2014 (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). This groundbreaking study analyzed 36,989 case participants and 113,075 control participants and found 108 independent loci that met genomewide significance (see Figure 3-3). Through this effort, the explained variance of schizophrenia by genetic variation has increased from 3% (in GWAS from 2009) to close to 20% (as of 2014). This study has truly changed the view of genetics in psychiatry, cementing its role unquestionably in the etiology of schizophrenia at least (Flint and Munafò 2014a, 2014b; Need and Goldstein 2014). From the 108 loci identified, the authors estimated more than 600 genes to be involved. Notably, they highlighted the region encoding the extended major histocompatibility complex (MHC). The MHC had already been identified in several previous studies (Purcell et al. 2009) as playing an important role in schizophrenia. Perhaps unsurprisingly, the locus corresponding to the

*DRD2* gene also has been implicated. This gene encodes the D<sub>2</sub> dopamine receptor, a target of many antipsychotic medications. Other interesting genes implicated in the 108 loci include calcium channel subunits and proteins involved in synaptic plasticity. These findings tie in well ([Hall et al. 2015](#)) with the findings of another recent GWAS that implicated calcium signaling ([Ripke et al. 2013a](#)) as well as with the findings of studies on de novo mutations in schizophrenia, which also identified synaptic networks ([Fromer et al. 2014](#)), voltage-gated calcium ion channels, and the signaling complex formed by the activity-regulated cytoskeleton-associated scaffold protein of the postsynaptic density ([Purcell et al. 2014](#)).

Although it has been established that genetics plays an important role in the development of depression (twin studies estimate a heritability of 0.4-0.5), no GWAS to date have been able to conclusively find a consistent genetic association ([Dunn et al. 2015](#)). It has been suggested that the reasons for this limited success are either the highly heterogeneous nature of depression or the failure to take the environmental contributions into account. The PGC has a working group for depression, and in 2013 they published a “mega-analysis” of GWAS for depression ([Ripke et al. 2013b](#)). The authors stated that although this study was the largest case-control GWAS of depression ever to be carried out (with 9,240 case participants and 9,519 control participants), it nonetheless had insufficient power to detect effects seen in complex disorders, so no SNP reached genomewide significance. The PGC now has GWAS data on more than 60,000 individuals.

The CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium carried out a GWAS meta-analysis with a discovery sample of 34,549 ([Hek et al.](#)

2013). In this study, the investigators examined current depressive symptoms as opposed to lifetime diagnosis of depression. Again, no SNP reached genomewide significance. The authors estimated that a sample of more than 50,000 subjects would be necessary to gain sufficient power. Indeed, when the discovery sample was combined with the replication sample ( $N=51,258$ ), one SNP reached genomewide significance. This association was band 5q21.

The CONVERGE (China, Oxford, and Virginia Commonwealth University Experimental Research on Genetic Epidemiology) Consortium aimed to address the issue of heterogeneity by using a large, homogeneous cohort of patients (CONVERGE Consortium 2015). In 2015, the consortium reported two loci that reached genomewide significance: *SIRT1* and *LHPP*. The cohort consisted of 5,303 Han Chinese women with recurrent depression. When the investigators restricted cases to those with the more severe subtype, melancholia, the *SIRT1* association became even stronger (CONVERGE Consortium 2015).

Whole-genome SNP association studies have been more successful in bipolar disorder, and polymorphisms in the genes encoding ankyrin G (*ANK3*) and the alpha 1C subunit of the L-type voltage-gated calcium channel (*CACNA1C*) have emerged as new candidates for this disorder from data combining several large samples (Ferreira et al. 2008; Kloiber et al. 2012; Schulze et al. 2008). The *CACNA1* gene family also may be of relevance in schizophrenia (Moskvina et al. 2009). Interestingly, the independent samples (Baum et al. 2008a, 2008b; Craddock et al. 2010; Sklar et al. 2008; Wellcome Trust Case Control Consortium 2007) mostly yielded no genomewide significant associations or could not be replicated in single association studies, showing the importance of large sample sizes for these studies.



The ever-growing sets of GWAS data in psychiatric genetics are providing new insights into the genetics of psychiatric disorders. Although promising, these data raise several important issues:

- *Multiple genes of small effects contribute to psychiatric disease.* To identify these effects with sufficient power, large sample sizes of around 25,000 cases will be required, and international collaborations are essential.
- *Genetic susceptibility in psychiatry represents a mixture of contributions from common and rare variants, with rare variants likely predominating in autism spectrum disorder and schizophrenia* ([Lencz et al. 2007](#); [Sutcliffe et al. 2005](#)). Linkage and association studies will need to be combined with resequencing studies to identify these rare variants.
- *Structural variations (CNVs, insertion/deletions, and balanced translocations) in psychiatric genetics are important.* In schizophrenia and autism spectrum disorder, investigation of structural variation has been demonstrated to be a very powerful tool for dissecting the genetics of these disorders ([Cook and Scherer 2008](#); [Marshall et al. 2008](#); [Sebat et al. 2007](#); [St Clair 2009](#); [Szatmari et al. 2007](#); [Weiss et al. 2008](#)). Studies of structural variation have yet to be done for PTSD; for depression and anxiety, the results have been inconclusive or unreplicable (for a recent, thorough review, see [Smoller 2016](#)).

## Use of GWAS Data

Very large sample sizes (of more than 25,000 case participants) are required to adequately power GWAS for complex traits, and the genetic associations point to



multiple variants with small effect sizes. Several tools have been developed to help elucidate the polygenic aspects of disease risk. Two important tools are *pathway/gene set analysis* and *polygenic risk scores*.

**Pathway analysis of GWAS data.** Data generated by a GWAS can be mapped to known biological pathways using *pathway analysis* (also called *gene set enrichment analysis*), thereby providing an enriched set of genes. This analysis can increase the power of the data because association signals are grouped by functionally related genes. Pathway analysis can provide insight into the cell or molecular level pathways underlying the disorder. Pathway analysis has implicated voltage-gated ion channels ([Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011](#)) and hormone action ([Holmans et al. 2009](#)) in bipolar GWAS data sets and neuronal cell adhesion in schizophrenia and bipolar GWAS data sets ([O'Dushlaine et al. 2011](#)). A recent study looked for common biological pathways across schizophrenia, depression, and bipolar disorder from PGC GWAS data ([Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015](#)). Histone methylation showed the strongest association, but evidence for associations with immune and neuronal signaling pathways and postsynaptic density was also found.

**Polygenic analysis of GWAS data.** Over the past decade, there have been many attempts to identify genes associated with psychiatric disorders using SNP markers. Although GWAS have successfully identified some variants, it is becoming clear that in complex disorders, genetic risk is determined both by many common variants of small effect

and by rare and de novo variants of large effect. This dilemma again illustrates the inadequacy of the “common disease, common variant” model and the limitations of GWAS. As a result, it has been proposed that between these two extremes, there is a middle ground in which moderately penetrant but somewhat rarer variants are being missed (Maher 2008). These missing variants might be unearthed if a single *polygenic risk score (PGRS)* could be calculated. *Polygenic analysis* examines the extent to which heritability is due to the additive effects of many common loci variants that individually are of little effect (Dudbridge 2013). By using all SNPs to examine the net effect on disease risk, a composite score can be calculated, thus providing significant predictive ability. The PGRS is composed of many true but subthreshold variants that GWAS initially might have missed as a result of being underpowered to detect them at the conventional alpha level of  $P=5\times 10^{-8}$  (Gratten et al. 2014). PGRSs can be calculated with bioinformatics software such as PRSice (<http://prsice.info>). Polygenic risk profiling from GWAS can predict case-control status in independent samples. Recent research has suggested that adjustment for LD can improve the predictive performance of PGRSs (Vilhjálmsson et al. 2015).

This new polygenic analysis approach addresses the genetic complexity of psychiatric disorders because their underlying *genetic architecture* is highly polygenic. In the context of a particular disease, the term *genetic architecture* refers to “the number, frequency, and effect sizes of genetic risk alleles and the way in which they combine together” (Wray and Visscher 2010, p. 14). The PGRS also can be analyzed in relation to the clinical

phenotype and against quantitative traits related to the disorder.

The recent polygenic analysis study in schizophrenia ([Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014](#)) validated the polygenic analysis approach. PGRSs can predict schizophrenia case-control status, albeit with varying sensitivity and specificity, possibly because of differing sampling strategies ([Meier et al. 2016](#)). In contrast to twin and family studies, the polygenic heritability approach provides information on the frequency of the alleles underlying the phenotype.

By supplementing PGRSs with family history, risk prediction can be significantly improved. This strategy has yet to be used in the field of psychiatry but has been successful in improving the predictive performance of PGRSs in other disorders ([Chatterjee et al. 2013](#)).

In schizophrenia at least, PGRSs may improve future clinical decision making and may even inform prevention strategies. Evaluation of the clinical efficacy of a PGRS can be carried out via the receiver operating characteristic curve. The area under this curve expresses the accuracy with which high- and low-risk groups can be distinguished ([Janssens et al. 2007](#)). PGRSs may be able to personalize genomics in psychiatry in the future ([Smoller 2014](#)).

## Cross-Disorder Studies

The traditional view that psychiatric disorders are distinct in nature is being challenged by evidence emerging from studies looking at the genetic landscape ([Cross-Disorder Group of the Psychiatric Genomics Consortium 2013](#)). Some disorders clearly share genetic risks. The genetic

architecture correlation calculated with common SNPs was  $r=0.68$  for bipolar disorder and schizophrenia,  $r=0.47$  for bipolar disorder and depression, and  $r=0.43$  for schizophrenia and depression ([Cross-Disorder Group of the Psychiatric Genomics Consortium 2013](#)).

An attempt has been made to identify the underlying molecular source of the cross-disorder overlap. The [Cross-Disorder Group of the Psychiatric Genomics Consortium \(2013\)](#) examined the five PGC disorders: schizophrenia, depression, bipolar disorder, autism spectrum disorder, and ADHD (S.H. [Lee et al. 2013](#)). They looked for SNPs in a GWAS of samples from 33,332 case participants and 27,888 control participants. Findings from these cross-disorder studies seem to confirm the biological overlap of psychiatric traits. Four SNPs with genomewide significance on cross-disorder risk were found: *AS3MT*, *ITIH3*, and the L-type voltage-gated calcium channel subunits *CACNB2* and *CACNA1C*. These findings again implicate calcium channels in psychopathology.

## Gene × Environment Interaction Studies

To date, most genetic association studies have searched for main associations between sequence variants and psychiatric disorders. This approach ignores the clear reality that environmental factors contribute importantly to psychiatric illness. For example, it is clear that childhood traumatic experiences substantially increase the risk of stress-related disorders ([Heim et al. 2010](#)). Since the landmark paper of [Caspi and Moffitt \(2006\)](#), there has been increasing interest in G×E interactions in the field of

psychiatry. [Caspi et al. \(2003\)](#) showed that the 5HTTLPR genotype interacts with exposure to early trauma to increase the risk of depression differentially in carriers of the S allele.

Although most G×E interaction studies focus on detrimental effects of the environment, the genetic moderation of positive and protective environmental factors should not be ignored ([Kim-Cohen and Turkewitz 2012](#)). Examining the effect of negative versus positive as well as shared versus individual environmental factors against genetic variation will help to explain individual differences in risk or resilience ([Klengel and Binder 2013, 2015](#)). However, careful interpretation of G×E studies is required, because they can be fraught with methodological problems ([Duncan and Keller 2011](#); [Munafò et al. 2009](#)).

From a theoretical perspective, searching for such G×E interactions makes sense. Thus, any statistical interaction is bound at the upper end of its effect size by the magnitude of the main effects being considered. When environmental factors such as early trauma, which have large effect sizes, are examined together with genetic factors, which are expected generally to have small effect sizes, the result can be greater power to detect G×E interactions than to detect the main effects of the gene. Thus, an argument can be made (which by no means is accepted by all) that future genetic studies of psychiatric disorders and other complex disorders should be based on models that incorporate both genetic and environmental factors. Indeed, the modification of PGRSs by environmental effects is one way forward in translational research in psychiatry ([Duncan and Keller 2011](#); [Sharma et al. 2016](#)).

Unfortunately, most G×E studies conducted to date have been inadequately powered to detect a strong effect

([Duncan et al. 2014](#)); however, with the availability of established risk loci from GWAS, the field should open up to study a new range of G×E effects.

One notable, confirmed G×E interaction is that of genetic variants in *FKBP5* with childhood abuse, contributing to the risk of several psychiatric disorders in the presence of childhood trauma ([Zannas et al. 2016](#)). This interaction influences the epigenetic response to childhood trauma as well as neural circuit activation in response to stress and threat ([Klengel and Binder 2015](#); [Klengel et al. 2013](#)). Other confirmed G×E interactions include that between an SNP in the *AKT1* gene and cannabis use in the development of psychosis ([Di Forti et al. 2012](#)), that between an SNP in the serotonin transporter gene and childhood maltreatment in the development of depression ([Karg et al. 2011](#)), and that between the *BDNF* gene and stressful life events in the development of bipolar disorder.

The ENCODE project has laid to rest the postgenomic idea that non-protein-coding DNA is “junk DNA” by successfully assigning biological functions to 80% of the genome and discovering that 95% of the genome is within 8 kilobases of a protein–gene interaction. It is hoped that the ENCODE project ([Kavanagh et al. 2013](#)) will continue to provide new insights into G×E interactions as it annotates regulatory regions that are inherently relevant to the genomic response to environmental cues.

---

## Conclusion

---

Taken together, epidemiological, cytogenetic, linkage, and association studies in psychiatric genetics to date paint a

picture of highly complex genetic influences on psychiatric disorders. As [Kendler \(2005\)](#) pointed out more than a decade ago, the phrase “a gene for...” will *not* apply to psychiatric genetics. As [Kendler \(2005, p. 1243\)](#) went on to note: “the impact of individual genes on risk for psychiatric illness is small, often nonspecific, and embedded in a complex causal pathway.” We suggest that the field adopt strategies that are tailored to the most likely disease models. Three main strategies for addressing this issue are proposed.

First, we may need to reconsider how we define cases or the phenotype of interest. Our current classification schemes are not likely directly reflective of the underlying biology—and thus the genetic determinants—of psychiatric disease. The currently used diagnostic algorithms (DSM-5 [[American Psychiatric Association 2013](#)] and ICD-10 [[World Health Organization 1992](#)]) group diagnoses by symptoms and clinical course, which may not reflect a common biology but rather a final common pathway of several different pathophysiological disturbances. That recognition has led some to propose the use of intermediate phenotypes, including neurophysiological, biochemical, cognitive, and endocrine measures ([Gottesman and Gould 2003](#); [Hasler et al. 2004](#); [Insel 2014](#)), in psychiatric genetic studies in order to create biologically more homogeneous subgroups of patients and thus to increase the power to detect case-control associations. Another important consideration is that some symptoms are common to several different diagnoses, and the genetic susceptibility to develop these symptoms may be common across disorders ([Doherty and Owen 2014](#)). In fact, evidence indicates that the major psychiatric disorders may share susceptibility genes ([Cross-](#)

Disorder Group of the Psychiatric Genomics Consortium 2013).

Second, environmental measures should be included more consistently in genetic studies, including whole-genome association studies. Epidemiological (Kendler 1995) as well as molecular genetic studies have now repeatedly shown the importance of G×E interactions in psychiatric disease (Klengel and Binder 2015). Genetic effects may be obscured by unmeasured environmental effects, so that different environmental exposures in replication samples may be one source of nonreplication of genetic association.

Third, one should not forget that SNPs are simply the most common and convenient type of genetic variant, not the only type. Other types of variation, such as CNVs, are equally important (Zarrei et al. 2015; Sebat et al. 2004).

Thanks to ever-advancing technologies, genetics and genomics are entering a new and exciting era. Progress will no doubt advance rapidly, bringing with it the potential to redefine psychiatry.

---

## References

---

- 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, et al: A map of human genome variation from population-scale sequencing. *Nature* 467(7319):1061–1073, 2010 20981092
- 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, et al: An integrated map of genetic variation from 1,092 human genomes. *Nature* 491(7422):56–65, 2012 23128226



- Alda M: Lithium in the treatment of bipolar disorder: pharmacology and pharmacogenetics. *Mol Psychiatry* 20(6):661–670, 2015 25687772
- Altshuler D, Pollara VJ, Cowles CR, et al: An SNP map of the human genome generated by reduced representation shotgun sequencing. *Nature* 407(6803):513–516, 2000 11029002
- Altshuler DM, Gibbs RA, Peltonen L, et al; International HapMap 3 Consortium: Integrating common and rare genetic variation in diverse human populations. *Nature* 467(7311):52–58, 2010 20811451
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Angst J: A clinical analysis of the effects of tofranil in depression. Longitudinal and follow-up studies. Treatment of blood-relations. *Psychopharmacology (Berl)* 2:381–407, 1961 13861628
- Auton A, Brooks LD, Durbin RM, et al; 1000 Genomes Project Consortium: A global reference for human genetic variation. *Nature* 526(7571):68–74, 2015 26432245
- Bailey A, Le Couteur A, Gottesman I, et al: Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med* 25(1):63–77, 1995 7792363
- Baum AE, Akula N, Cabanero M, et al: A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol Psychiatry* 13(2):197–207, 2008a 17486107
- Baum AE, Hamshire M, Green E, et al: Meta-analysis of two genome-wide association studies of bipolar disorder reveals important points of agreement. *Mol Psychiatry* 13(5):466–467, 2008b 18421293
- Berm EJ, Hak E, Postma M, et al: Effects and cost-effectiveness of pharmacogenetic screening for CYP2D6

among older adults starting therapy with nortriptyline or venlafaxine: study protocol for a pragmatic randomized controlled trial (CYSCETrial). *Trials* 16:37, 2015 25636328

Bertilsson L, Dahl ML, Dalén P, et al: Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Br J Clin Pharmacol* 53(2):111–122, 2002 11851634

Biesecker BB, Peay HL: Genomic sequencing for psychiatric disorders: promise and challenge. *Int J Neuropsychopharmacol* 16(7):1667–1672, 2013 23575420

Blackwood D, Muir W: Molecular genetics and the epidemiology of bipolar disorder. *Ann Med* 33(4):242–247, 2001 11405545

Blackwood DH, Fordyce A, Walker MT, et al: Schizophrenia and affective disorders—cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. *Am J Hum Genet* 69(2):428–433, 2001 11443544

Bleuler M: Psychiatry of cerebral diseases. *BMJ* 2(4742):1233–1238, 1951 14879055

Boks MPM: Epigenetic effects of currently used psychotropic drugs, in *Epigenetics in Psychiatry*. Edited by Peedicayil J, Grayson DR, Avramopoulos D. Amsterdam, Elsevier, 2014, pp 481–496

Boyadjieva N, Varadinova M: Epigenetics of psychoactive drugs. *J Pharm Pharmacol* 64(10):1349–1358, 2012 22943166

Brunner HG, Nelen M, Breakefield XO, et al: Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* 262(5133): 578–580, 1993 8211186

Bulik CM, Sullivan PF, Wade TD, et al: Twin studies of eating disorders: a review. *Int J Eat Disord* 27(1):1–20, 2000 10590444

- Bulik CM, Sullivan PF, Tozzi F, et al: Prevalence, heritability, and prospective risk factors for anorexia nervosa. *Arch Gen Psychiatry* 63(3):305–312, 2006 16520436
- Busjahn A: Twin registers across the globe: what's out there in 2002? *Twin Res* 5(5):v–vi, 2002 12613497
- Cadoret RJ: Adoption studies: historical and methodological critique. *Psychiatr Dev* 4(1):45–64, 1986 3517848
- Cadoret RJ, Yates WR, Troughton E, et al: Adoption study demonstrating two genetic pathways to drug abuse. *Arch Gen Psychiatry* 52(1):42–52, 1995a 7811161
- Cadoret RJ, Yates WR, Troughton E, et al: Genetic-environmental interaction in the genesis of aggressivity and conduct disorders. *Arch Gen Psychiatry* 52(11):916–924, 1995b 7487340
- Carayol J, Schellenberg GD, Dombroski B, et al: A scoring strategy combining statistics and functional genomics supports a possible role for common polygenic variation in autism. *Front Genet* 5:33, 2014 24600472
- Caspi A, Moffitt TE: Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci* 7(7):583–590, 2006 16791147
- Caspi A, Sugden K, Moffitt TE, et al: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301(5631):386–389, 2003 12869766
- Chapman NH, Nato AQ Jr, Bernier R, et al: Whole exome sequencing in extended families with autism spectrum disorder implicates four candidate genes. *Hum Genet* 134(10):1055–1068, 2015 26204995
- Chatterjee N, Wheeler B, Sampson J, et al: Projecting the performance of risk prediction based on polygenic analyses of genome-wide association studies. *Nat Genet* 45(4):400–405, 405e1–405e3, 2013 23455638
- Chen CH, Lee CS, Lee MT, et al; Taiwan Bipolar Consortium: Variant GADL1 and response to lithium therapy in bipolar I disorder. *N Engl J Med* 370(2):119–128, 2014 24369049

CONVERGE Consortium: Sparse whole-genome sequencing identifies two loci for major depressive disorder. *Nature* 523(7562):588–591, 2015 26176920

Cook EH Jr: Genetics of autism. *Child Adolesc Psychiatr Clin N Am* 10(2):333–350, 2001 11351802

Cook EH Jr, Scherer SW: Copy-number variations associated with neuropsychiatric conditions. *Nature* 455(7215):919–923, 2008 18923514

Craddock N, Jones L, Jones IR, et al: Strong genetic evidence for a selective influence of GABAA receptors on a component of the bipolar disorder phenotype. *Mol Psychiatry* 15(2):146–153, 2010 19078961

Cross-Disorder Group of the Psychiatric Genomics Consortium: Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 381(9875):1371–1379, 2013 23453885

Daly MJ, Rioux JD, Schaffner SF, et al: High-resolution haplotype structure in the human genome. *Nat Genet* 29(2):229–232, 2001 11586305

Devlin B, Roeder K: Genomic control for association studies. *Biometrics* 55(4):997–1004, 1999 11315092

Di Forti M, Iyegbe C, Sallis H, et al: Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. *Biol Psychiatry* 72(10):811–816, 2012 22831980

Doherty JL, Owen MJ: Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. *Genome Med* 6(4):29, 2014 24944580

Dudbridge F: Power and predictive accuracy of polygenic risk scores. *PLoS Genet* 9(3):e1003348, 2013 23555274

Duncan LE, Keller MC: A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry* 168(10):1041–1049, 2011 21890791

- Duncan LE, Pollastri AR, Smoller JW: Mind the gap: why many geneticists and psychological scientists have discrepant views about gene-environment interaction (G×E) research. *Am Psychol* 69(3):249–268, 2014 24750075
- Dunn EC, Brown RC, Dai Y, et al: Genetic determinants of depression: recent findings and future directions. *Harv Rev Psychiatry* 23(1):1–18, 2015 25563565
- Egan MF, Goldberg TE, Kolachana BS, et al: Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A* 98(12):6917–6922, 2001 11381111
- Fan JB, Zhang CS, Gu NF, et al: Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. *Biol Psychiatry* 57(2):139–144, 2005 15652872
- Faraone SV, Spencer TJ, Madras BK, et al: Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: a meta-analysis. *Mol Psychiatry* 19(8):880–889, 2014 24061496
- Farrell MS, Werge T, Sklar P, et al: Evaluating historical candidate genes for schizophrenia. *Mol Psychiatry* 20(5):555–562, 2015 25754081
- Ferreira MA, O'Donovan MC, Meng YA, et al; Wellcome Trust Case Control Consortium: Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet* 40(9):1056–1058, 2008 18711365
- Flint J, Munafò MR: Genetics: finding genes for schizophrenia. *Curr Biol* 24(16):R755–R757, 2014a 25137590
- Flint J, Munafò M: Schizophrenia: genesis of a complex disease. *Nature* 511(7510):412–413, 2014b 25056056
- Folstein SE, Rosen-Sheidley B: Genetics of autism: complex aetiology for a heterogeneous disorder. *Nat Rev Genet*

2(12):943-955, 2001 11733747

Franchini L, Serretti A, Gasperini M, et al: Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. *J Psychiatr Res* 32(5): 255-259, 1998 9789202

Fromer M, Pocklington AJ, Kavanagh DH, et al: De novo mutations in schizophrenia implicate synaptic networks. *Nature* 506(7487):179-184, 2014 24463507

Gabriel SB, Schaffner SF, Nguyen H, et al: The structure of haplotype blocks in the human genome. *Science* 296(5576):2225-2229, 2002 12029063

Gatt JM, Burton KL, Williams LM, et al: Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. *J Psychiatr Res* 60:1-13, 2015 25287955

Gelernter J, Cubells JF, Kidd JR, et al: Population studies of polymorphisms of the serotonin transporter protein gene. *Am J Med Genet* 88(1):61-66, 1999 10050969

Geschwind DH, Flint J: Genetics and genomics of psychiatric disease. *Science* 349(6255):1489-1494, 2015 26404826

Gillis RF, Rouleau GA: The ongoing dissection of the genetic architecture of autistic spectrum disorder. *Mol Autism* 2(1):12, 2011 21740537

Goldberg TE, Egan MF, Gscheidle T, et al: Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry* 60(9):889-896, 2003 12963670

Gottesman II, Gould TD: The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 160(4):636-645, 2003 12668349

Gratten J, Wray NR, Keller MC, et al: Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nat Neurosci* 17(6):782-790, 2014 24866044

- Greenwood TA, Kelsoe JR: Promoter and intronic variants affect the transcriptional regulation of the human dopamine transporter gene. *Genomics* 82(5):511-520, 2003 14559208
- Grof P, Alda M: Discrepancies in the efficacy of lithium. *Arch Gen Psychiatry* 57(2):191, 2000 10665623
- Hall J, Trent S, Thomas KL, et al: Genetic risk for schizophrenia: convergence on synaptic pathways involved in plasticity. *Biol Psychiatry* 77(1):52-58, 2015 25152434
- Hamer D, Sirota L: Beware the chopsticks gene. *Mol Psychiatry* 5(1):11-13, 2000 10673763
- Hasler G, Drevets WC, Manji HK, et al: Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29(10):1765-1781, 2004 15213704
- Hawley ME, Kidd KK: HAPLO: a program using the EM algorithm to estimate the frequencies of multi-site haplotypes. *J Hered* 86(5):409-411, 1995 7560877
- Heils A, Teufel A, Petri S, et al: Allelic variation of human serotonin transporter gene expression. *J Neurochem* 66(6):2621-2624, 1996 8632190
- Heim C, Shugart M, Craighead WE, et al: Neurobiological and psychiatric consequences of child abuse and neglect. *Dev Psychobiol* 52(7):671-690, 2010 20882586
- Hek K, Demirkan A, Lahti J, et al: A genome-wide association study of depressive symptoms. *Biol Psychiatry* 73(7):667-678, 2013 23290196
- Helgason A, Nicholson G, Stefánsson K, et al: A reassessment of genetic diversity in Icelanders: strong evidence from multiple loci for relative homogeneity caused by genetic drift. *Ann Hum Genet* 67(Pt 4):281-297, 2003 12914564
- Hettema JM, Neale MC, Kendler KS: A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry* 158(10):1568-1578, 2001 11578982

- Hirschhorn JN, Daly MJ: Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 6(2):95–108, 2005 15716906
- Holmans P, Green EK, Pahwa JS, et al; Wellcome Trust Case-Control Consortium: Gene ontology analysis of GWA study data sets provides insights into the biology of bipolar disorder. *Am J Hum Genet* 85(1):13–24, 2009 19539887
- Horvath S, Xu X, Laird NM: The family based association test method: strategies for studying general genotype—phenotype associations. *Eur J Hum Genet* 9(4):301–306, 2001 11313775
- Hou L, Heilbronner U, Degenhardt F, et al: Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. *Lancet* 387(10023):1085–1093, 2016 26806518
- Hu XZ, Lipsky RH, Zhu G, et al: Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet* 78(5):815–826, 2006 16642437
- Inoue-Murayama M, Adachi S, Mishima N, et al: Variation of variable number of tandem repeat sequences in the 3′-untranslated region of primate dopamine transporter genes that affects reporter gene expression. *Neurosci Lett* 334(3):206–210, 2002 12453630
- Insel TR: The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry* 171(4):395–397, 2014 24687194
- International Schizophrenia Consortium: Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* 455(7210):237–241, 2008 18668038
- Ioannidis JP, Thomas G, Daly MJ: Validating, augmenting and refining genome-wide association signals. *Nat Rev Genet* 10(5):318–329, 2009 19373277



- Janssens ACJW, Moonesinghe R, Yang Q, et al: The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. *Genet Med* 9(8):528-535, 2007 17700391
- Johansson C, Jansson M, Linnér L, et al: Genetics of affective disorders. *Eur Neuropsychopharmacol* 11(6):385-394, 2001 11704415
- Joober R, Gauthier J, Lal S, et al: Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Arch Gen Psychiatry* 59(7):662-663, 2002 12090821
- Karayiorgou M, Gogos JA: The molecular genetics of the 22q11-associated schizophrenia. *Brain Res Mol Brain Res* 132(2):95-104, 2004 15582150
- Karayiorgou M, Morris MA, Morrow B, et al: Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Natl Acad Sci U S A* 92(17):7612-7616, 1995 7644464
- Karg K, Burmeister M, Shedden K, Sen S: The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Arch Gen Psychiatry* 68(5):444-454, 2011 21199959
- Kato T: Whole genome/exome sequencing in mood and psychotic disorders. *Psychiatry Clin Neurosci* 69(2):65-76, 2015 25319632
- Kaufman J, Yang BZ, Douglas-Palumberi H, et al: Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci U S A* 101(49):17316-17321, 2004 15563601
- Kavanagh DH, Dwyer S, O'Donovan MC, et al: The ENCODE project: implications for psychiatric genetics. *Mol Psychiatry* 18(5):540-542, 2013 23478746
- Kawashima M, Tamiya G, Oka A, et al: Genomewide association analysis of human narcolepsy and a new

resistance gene. *Am J Hum Genet* 79(2):252-263, 2006  
16826516

Kendler KS: Twin studies of psychiatric illness: current status and future directions. *Arch Gen Psychiatry* 50(11):905-915, 1993 8215816

Kendler KS: Genetic epidemiology in psychiatry: taking both genes and environment seriously. *Arch Gen Psychiatry* 52(11): 895-899, 1995 7487337

Kendler KS: Twin studies of psychiatric illness: an update. *Arch Gen Psychiatry* 58(11):1005-1014, 2001 11695946

Kendler KS: "A gene for...": the nature of gene action in psychiatric disorders. *Am J Psychiatry* 162(7):1243-1252, 2005 15994704

Kendler KS, Gardner CO Jr: Twin studies of adult psychiatric and substance dependence disorders: are they biased by differences in the environmental experiences of monozygotic and dizygotic twins in childhood and adolescence? *Psychol Med* 28(3):625-633, 1998 9626718

Kendler KS, Greenspan RJ: The nature of genetic influences on behavior: lessons from "simpler" organisms. *Am J Psychiatry* 163(10):1683-1694, 2006 17012675

Kendler KS, Prescott CA: A population-based twin study of lifetime major depression in men and women. *Arch Gen Psychiatry* 56(1):39-44, 1999 9892254

Kendler KS, Walsh D: Gender and schizophrenia: results of an epidemiologically based family study. *Br J Psychiatry* 167(2):184-192, 1995 7582667

Kendler KS, Neale MC, Kessler RC, et al: The genetic epidemiology of phobias in women: the interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Arch Gen Psychiatry* 49(4):273-281, 1992 1558461

Kendler KS, Kessler RC, Walters EE, et al: Stressful life events, genetic liability, and onset of an episode of major

depression in women. *Am J Psychiatry* 152(6):833-842, 1995a 7755111

Kendler KS, Pedersen NL, Neale MC, et al: A pilot Swedish twin study of affective illness including hospital- and population-ascertained subsamples: results of model fitting. *Behav Genet* 25(3):217-232, 1995b 7598665

Kendler KS, Gardner CO, Neale MC, et al: Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? *Psychol Med* 31(4):605-616, 2001a 11352363

Kendler KS, Myers J, Prescott CA, et al: The genetic epidemiology of irrational fears and phobias in men. *Arch Gen Psychiatry* 58(3):257-265, 2001b 11231833

Kendler KS, Jacobson KC, Myers J, et al: Sex differences in genetic and environmental risk factors for irrational fears and phobias. *Psychol Med* 32(2):209-217, 2002 11866316

Kendler KS, Kuhn JW, Vittum J, et al: The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Arch Gen Psychiatry* 62(5):529-535, 2005 15867106

Kendler KS, Gatz M, Gardner CO, et al: A Swedish national twin study of lifetime major depression. *Am J Psychiatry* 163(1): 109-114, 2006 16390897

Kim S, Misra A: SNP genotyping: technologies and biomedical applications. *Annu Rev Biomed Eng* 9:289-320, 2007 17391067

Kim-Cohen J, Turkewitz R: Resilience and measured gene-environment interactions. *Dev Psychopathol* 24(4):1297-1306, 2012 23062298

Kirchheiner J, Nickchen K, Bauer M, et al: Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry* 9(5):442-473, 2004 15037866

- Kirov G, Pocklington AJ, Holmans P, et al: De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol Psychiatry* 17(2):142–153, 2012 22083728
- Klengel T, Binder EB: Gene-environment interactions in major depressive disorder. *Can J Psychiatry* 58(2):76–83, 2013 23442893
- Klengel T, Binder EB: Epigenetics of stress-related psychiatric disorders and gene  $\times$  environment interactions. *Neuron* 86(6):1343–1357, 2015 26087162
- Klengel T, Mehta D, Anacker C, et al: Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci* 16(1):33–41, 2013 23201972
- Kloiber S, Czamara D, Karbalai N, et al: ANK3 and CACNA1C—missing genetic link for bipolar disorder and major depressive disorder in two German case-control samples. *J Psychiatr Res* 46(8):973–979, 2012 22647524
- Knapp M, Seuchter SA, Baur MP: The haplotype-relative-risk (HRR) method for analysis of association in nuclear families. *Am J Hum Genet* 52(6):1085–1093, 1993 8503442
- Kraft P, Zeggini E, Ioannidis JP: Replication in genome-wide association studies. *Stat Sci* 24(4):561–573, 2009 20454541
- Kwok PY: High-throughput genotyping assay approaches. *Pharmacogenomics* 1(1):95–100, 2000 11258600
- Lachman HM, Papolos DF, Saito T, et al: Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 6(3):243–250, 1996 8807664
- Lander ES, Schork NJ: Genetic dissection of complex traits. *Science* 265(5181):2037–2048, 1994 8091226
- Lander ES, Linton LM, Birren B, et al; International Human Genome Sequencing Consortium: Initial sequencing and

analysis of the human genome. *Nature* 409(6822):860–921, 2001 11237011

Lee RS, Pirooznia M, Guintivano J, et al: Search for common targets of lithium and valproic acid identifies novel epigenetic effects of lithium on the rat leptin receptor gene. *Transl Psychiatry* 5:e600, 2015 26171981

Lee SH, DeCandia TR, Ripke S, et al; Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ); International Schizophrenia Consortium (ISC); Molecular Genetics of Schizophrenia Collaboration (MGS): Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nat Genet* 44(3):247–250, 2012 22344220

Lee SH, Ripke S, Neale BM, et al; Cross-Disorder Group of the Psychiatric Genomics Consortium; International Inflammatory Bowel Disease Genetics Consortium (IIBDGC): Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet* 45(9):984–994, 2013 23933821

Lencz T, Morgan TV, Athanasiou M, et al: Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. *Mol Psychiatry* 12(6):572–580, 2007 17522711

Lesch KP, Bengel D, Heils A, et al: Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274(5292): 1527–1531, 1996 8929413

Levy D, Ronemus M, Yamrom B, et al: Rare de novo and transmitted copy-number variation in autistic spectrum disorders. *Neuron* 70(5):886–897, 2011 21658582

Li MD: The genetics of smoking related behavior: a brief review. *Am J Med Sci* 326(4):168–173, 2003 14557728

Lichtenstein P, Yip BH, Björk C, et al: Common genetic determinants of schizophrenia and bipolar disorder in

- Swedish families: a population-based study. *Lancet* 373(9659):234-239, 2009 19150704
- Long JC, Williams RC, Urbanek M: An E-M algorithm and testing strategy for multiple-locus haplotypes. *Am J Hum Genet* 56(3):799-810, 1995 7887436
- Lotta T, Vidgren J, Tilgmann C, et al: Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry* 34(13):4202-4210, 1995 7703232
- Maher B: Personal genomes: The case of the missing heritability. *Nature* 456(7218): 18-21, 2008 18987709
- Marshall CR, Noor A, Vincent JB, et al: Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet* 82(2):477-488, 2008 18252227
- Martin CL, Ledbetter DH: Autism and cytogenetic abnormalities: solving autism one chromosome at a time. *Curr Psychiatry Rep* 9(2):141-147, 2007 17389126
- Martin J, O'Donovan MC, Thapar A, et al: The relative contribution of common and rare genetic variants to ADHD. *Transl Psychiatry* 5:e506, 2015 25668434
- Martinez D, Gelernter J, Abi-Dargham A, et al: The variable number of tandem repeats polymorphism of the dopamine transporter gene is not associated with significant change in dopamine transporter phenotype in humans. *Neuropsychopharmacology* 24(5):553-560, 2001 11282255
- Mattay VS, Goldberg TE, Fera F, et al: Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A* 100(10):6186-6191, 2003 12716966
- McGuffin P, Rijsdijk F, Andrew M, et al: The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 60(5): 497-502, 2003 12742871

- Meier SM, Agerbo E, Maier R, et al: High loading of polygenic risk in cases with chronic schizophrenia. *Mol Psychiatry* 21(7):969-974, 2016 26324100
- Menke A, Binder EB: Epigenetic alterations in depression and antidepressant treatment. *Dialogues Clin Neurosci* 16(3):395-404, 2014 25364288
- Merikangas AK, Segurado R, Heron EA, et al: The phenotypic manifestations of rare genic CNVs in autism spectrum disorder. *Mol Psychiatry* 20(11):1366-1372, 2015 25421404
- Mill J, Asherson P, Browes C, et al: Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *Am J Med Genet* 114(8):975-979, 2002 12457396
- Mill J, Asherson P, Craig I, et al: Transient expression analysis of allelic variants of a VNTR in the dopamine transporter gene (DAT1). *BMC Genet* 6(1):3, 2005 15683546
- Millar JK, Wilson-Annan JC, Anderson S, et al: Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Hum Mol Genet* 9(9):1415-1423, 2000 10814723
- Millar JK, Christie S, Anderson S, et al: Genomic structure and localisation within a linkage hotspot of Disrupted In Schizophrenia 1, a gene disrupted by a translocation segregating with schizophrenia. *Mol Psychiatry* 6(2):173-178, 2001 11317219
- Moskvina V, Craddock N, Holmans P, et al: Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. *Mol Psychiatry* 14(3):252-260, 2009 19065143
- Munafò MR, Durrant C, Lewis G, et al: Gene X environment interactions at the serotonin transporter locus. *Biol Psychiatry* 65(3):211-219, 2009 18691701

- Nadeau JH, Lee C: Genetics: copies count. *Nature* 439(7078):798-799, 2006 16482142
- Nakamura M, Ueno S, Sano A, et al: The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. *Mol Psychiatry* 5(1):32-38, 2000 10673766
- Need AC, Goldstein DB: Schizophrenia genetics comes of age. *Neuron* 83(4):760-763, 2014 25144873
- Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium: Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci* 18(2):199-209, 2015 25599223
- Nicholls RD, Knepper JL: Genome organization, function, and imprinting in Prader-Willi and Angelman syndromes. *Annu Rev Genomics Hum Genet* 2:153-175, 2001 11701647
- O'Dushlaine C, Kenny E, Heron E, et al; International Schizophrenia Consortium: Molecular pathways involved in neuronal cell adhesion and membrane scaffolding contribute to schizophrenia and bipolar disorder susceptibility. *Mol Psychiatry* 16(3):286-292, 2011 20157312
- O'Reilly RL, Bogue L, Singh SM: Pharmacogenetic response to antidepressants in a multicase family with affective disorder. *Biol Psychiatry* 36(7):467-471, 1994 7811843
- Okochi T, Ikeda M, Kishi T, et al: Meta-analysis of association between genetic variants in COMT and schizophrenia: an update. *Schizophr Res* 110(1-3):140-148, 2009 19329282
- Opmeer EM, Korteekaas R, Aleman A: Depression and the role of genes involved in dopamine metabolism and signalling. *Prog Neurobiol* 92(2):112-133, 2010 20558238
- Pare CM, Rees L, Sainsbury MJ: Differentiation of two genetically specific types of depression by the response



to antidepressants. *Lancet* 2(7270):1340–1343, 1962 13941389

Parsey RV, Hastings RS, Oquendo MA, et al: Effect of a triallelic functional polymorphism of the serotonin-transporter-linked promoter region on expression of serotonin transporter in the human brain. *Am J Psychiatry* 163(1):48–51, 2006 16390888

Patil N, Berno AJ, Hinds DA, et al: Blocks of limited haplotype diversity revealed by high-resolution scanning of human chromosome 21. *Science* 294(5547):1719–1723, 2001 11721056

Phillips MS, Lawrence R, Sachidanandam R, et al: Chromosome-wide distribution of haplotype blocks and the role of recombination hot spots. *Nat Genet* 33(3):382–387, 2003 12590262

Pickard BS, Millar JK, Porteous DJ, et al: Cytogenetics and gene discovery in psychiatric disorders. *Pharmacogenomics J* 5(2):81–88, 2005 15668732

Plomin R, Kosslyn SM: Genes, brain and cognition. *Nat Neurosci* 4(12):1153–1154, 2001 11723454

Porcelli S, Fabbri C, Serretti A: Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *Eur Neuropsychopharmacol* 22(4):239–258, 2012 22137564

Porteous DJ, Thomson P, Brandon NJ, et al: The genetics and biology of DISC1—an emerging role in psychosis and cognition. *Biol Psychiatry* 60(2):123–131, 2006 16843095

Porteous DJ, Thomson PA, Millar JK, et al: DISC1 as a genetic risk factor for schizophrenia and related major mental illness: response to Sullivan. *Mol Psychiatry* 19(2):141–143, 2014 24457522

Precone V, Del Monaco V, Esposito MV, et al: Cracking the code of human diseases using next-generation sequencing: applications, challenges, and perspectives. *Biomed Res Int* 2015:161648, 2015 26665001

- Prescott CA, Kendler KS: Influence of ascertainment strategy on finding sex differences in genetic estimates from twin studies of alcoholism. *Am J Med Genet* 96(6):754-761, 2000 11121175
- Prescott CA, Aggen SH, Kendler KS: Sex-specific genetic influences on the comorbidity of alcoholism and major depression in a population-based sample of US twins. *Arch Gen Psychiatry* 57(8):803-811, 2000 10920470
- Price AL, Patterson NJ, Plenge RM, et al: Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 38(8):904-909, 2006 16862161
- Pritchard JK, Stephens M, Donnelly P: Inference of population structure using multilocus genotype data. *Genetics* 155(2):945-959, 2000 10835412
- Psychiatric GWAS Consortium Bipolar Disorder Working Group: Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* 43(10):977-983, 2011 21926972
- Pulver AE, Nestadt G, Goldberg R, et al: Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. *J Nerv Ment Dis* 182(8):476-478, 1994 8040660
- Purcell SM, Wray NR, Stone JL, et al; International Schizophrenia Consortium: Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460(7256):748-752, 2009 19571811
- Purcell SM, Moran JL, Fromer M, et al: A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* 506(7487):185-190, 2014 24463508
- Quast C, Reif A, Brückl T, et al: Gender-specific association of variants in the AKR1C1 gene with dimensional anxiety in patients with panic disorder: additional evidence for the importance of neurosteroids in anxiety? *Depress Anxiety* 31(10):843-850, 2014 24390875

- Rees E, Kirov G, Sanders A, et al; Wellcome Trust Case Control Consortium: Evidence that duplications of 22q11.2 protect against schizophrenia. *Mol Psychiatry* 19(1):37-40, 2014a 24217254
- Rees E, Walters JT, Georgieva L, et al: Analysis of copy number variations at 15 schizophrenia-associated loci. *Br J Psychiatry* 204(2):108-114, 2014b 24311552
- Reich DE, Cargill M, Bolk S, et al: Linkage disequilibrium in the human genome. *Nature* 411(6834):199-204, 2001 11346797
- Reich DE, Schaffner SF, Daly MJ, et al: Human genome sequence variation and the influence of gene history, mutation and recombination. *Nat Genet* 32(1):135-142, 2002 12161752
- Rhee SH, Waldman ID: Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. *Psychol Bull* 128(3):490-529, 2002 12002699
- Ripke S, O'Dushlaine C, Chambert K, et al; Multicenter Genetic Studies of Schizophrenia Consortium; Psychosis Endophenotypes International Consortium; Wellcome Trust Case Control Consortium 2: Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet* 45(10):1150-1159, 2013a 23974872
- Ripke S, Wray NR, Lewis CM, et al; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium: A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry* 18(4):497-511, 2013b 22472876
- Risch N: Linkage strategies for genetically complex traits, I: multilocus models. *Am J Hum Genet* 46(2):222-228, 1990 2301392
- Risch N, Merikangas K: The future of genetic studies of complex human diseases. *Science* 273(5281):1516-1517, 1996 8801636

- Risch N, Herrell R, Lehner T, et al: Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA* 301(23):2462-2471, 2009 19531786
- Rosenberg NA, Pritchard JK, Weber JL, et al: Genetic structure of human populations. *Science* 298(5602):2381-2385, 2002 12493913
- Rosenfeld JA, Ballif BC, Torchia BS, et al: Copy number variations associated with autism spectrum disorders contribute to a spectrum of neurodevelopmental disorders. *Genet Med* 12(11):694-702, 2010 20808228
- Ruderfer DM, Fanous AH, Ripke S, et al; Schizophrenia Working Group of Psychiatric Genomics Consortium; Bipolar Disorder Working Group of Psychiatric Genomics Consortium; Cross-Disorder Working Group of Psychiatric Genomics Consortium: Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Mol Psychiatry* 19(9):1017-1024, 2014 24280982
- Rutter M: Genetic studies of autism: from the 1970s into the millennium. *J Abnorm Child Psychol* 28(1):3-14, 2000 10772346
- Sachidanandam R, Weissman D, Schmidt SC, et al; International SNP Map Working Group: A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 409(6822):928-933, 2001 11237013
- Sanders SJ, Ercan-Sencicek AG, Hus V, et al: Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron* 70(5):863-885, 2011 21658581
- Schizophrenia Working Group of the Psychiatric Genomics Consortium: Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511(7510):421-427, 2014 25056061

- Schneider M, Debbané M, Bassett AS, et al; International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome: Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry* 171(6):627-639, 2014 24577245
- Schreiber M, Dorschner M, Tsuang D: Next-generation sequencing in schizophrenia and other neuropsychiatric disorders. *Am J Med Genet B Neuropsychiatr Genet* 162B(7):671-678, 2013 24132899
- Schulze TG, Detera-Wadleigh SD, Akula N, et al: Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder. *Mol Psychiatry* 14(5):487-491, 2008 19088739
- Sebat J, Lakshmi B, Troge J, et al: Large-scale copy number polymorphism in the human genome. *Science* 305(5683):525-528, 2004 15273396
- Sebat J, Lakshmi B, Malhotra D, et al: Strong association of de novo copy number mutations with autism. *Science* 316(5823):445-449, 2007 17363630
- Seifuddin F, Mahon PB, Judy J, et al: Meta-analysis of genetic association studies on bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 159B(5):508-518, 2012 22573399
- Serretti A, Franchini L, Gasperini M, et al: Mode of inheritance in mood disorder families according to fluvoxamine response. *Acta Psychiatr Scand* 98(6):443-450, 1998 9879785
- Serretti A, Kato M, De Ronchi D, Kinoshita T: Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry* 12(3):247-257, 2007 17146470
- Sharma S, Powers A, Bradley B, Ressler KJ: Gene  $\times$  environment determinants of stress- and anxiety-related

- disorders. *Annu Rev Psychol* 67:239–261, 2016 26442668
- Shifman S, Darvasi A: The value of isolated populations. *Nat Genet* 28(4):309–310, 2001 11479587
- Shprintzen RJ, Goldberg R, Golding-Kushner KJ, et al: Late-onset psychosis in the velo-cardio-facial syndrome. *Am J Med Genet* 42(1):141–142, 1992 1308357
- Sjöberg RL, Nilsson KW, Nordquist N, et al: Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene. *Int J Neuropsychopharmacol* 9(4):443–449, 2006 16212676
- Sklar P, Smoller JW, Fan J, et al: Whole-genome association study of bipolar disorder. *Mol Psychiatry* 13(6):558–569, 2008 18317468
- Smeraldi E, Petrocione A, Gasperini M, et al: Outcomes on lithium treatment as a tool for genetic studies in affective disorders. *J Affect Disord* 6(2):139–151, 1984 6233346
- Smoller JW: Psychiatric genetics and the future of personalized treatment. *Depress Anxiety* 31(11):893–898, 2014 25407575
- Smoller JW: The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. *Neuropsychopharmacology* 41(1):297–319, 2016 26321314
- Spielman RS, McGinnis RE, Ewens WJ: Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet* 52(3):506–516, 1993 8447318
- St Clair D: Copy number variation and schizophrenia. *Schizophr Bull* 35(1):9–12, 2009 18990708
- St Clair D, Blackwood D, Muir W, et al: Association within a family of a balanced autosomal translocation with major mental illness. *Lancet* 336(8706):13–16, 1990 1973210
- Stranger BE, Forrest MS, Dunning M, et al: Relative impact of nucleotide and copy number variation on gene

- expression phenotypes. *Science* 315(5813):848–853, 2007 17289997
- Sudmant PH, Rausch T, Gardner EJ, et al; 1000 Genomes Project Consortium: An integrated map of structural variation in 2,504 human genomes. *Nature* 526(7571): 75–81, 2015 26432246
- Sullivan PF: The psychiatric GWAS consortium: big science comes to psychiatry. *Neuron* 68(2):182–186, 2010 20955924
- Sullivan PF: Questions about DISC1 as a genetic risk factor for schizophrenia. *Mol Psychiatry* 18(10):1050–1052, 2013 24056909
- Sullivan PF, Neale MC, Kendler KS: Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* 157(10):1552–1562, 2000 11007705
- Sullivan PF, Kendler KS, Neale MC: Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 60(12):1187–1192, 2003 14662550
- Sullivan PF, Daly MJ, O'Donovan M: Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat Rev Genet* 13(8):537–551, 2012 22777127
- Surtees PG, Wainwright NW, Willis-Owen SA, et al: Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. *Biol Psychiatry* 59(3):224–229, 2006 16154545
- Sutcliffe JS, Delahanty RJ, Prasad HC, et al: Allelic heterogeneity at the serotonin transporter locus (SLC6A4) confers susceptibility to autism and rigid-compulsive behaviors. *Am J Hum Genet* 77(2):265–279, 2005 15995945
- Sybert VP, McCauley E: Turner's syndrome. *N Engl J Med* 351(12):1227–1238, 2004 15371580
- Szatmari P, Paterson AD, Zwaigenbaum L, et al; Autism Genome Project Consortium: Mapping autism risk loci

- using genetic linkage and chromosomal rearrangements. Nat Genet 39(3):319–328, 2007 17322880
- Tamiya G, Shinya M, Imanishi T, et al: Whole genome association study of rheumatoid arthritis using 27 039 microsatellites. Hum Mol Genet 14(16):2305–2321, 2005 16000323
- Tennessen JA, Bigham AW, O'Connor TD, et al; NHLBI Exome Sequencing Project: Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science 337(6090):64–69, 2012 22604720
- Tienari PJ, Wynne LC: Adoption studies of schizophrenia. Ann Med 26(4):233–237, 1994 7946240
- Tienari P, Wynne LC, Sorri A, et al: Genotype-environment interaction in schizophrenia-spectrum disorder: long-term follow-up study of Finnish adoptees. Br J Psychiatry 184:216–222, 2004 14990519
- Toma C, Torricco B, Hervás A, et al: Exome sequencing in multiplex autism families suggests a major role for heterozygous truncating mutations. Mol Psychiatry 19(7):784–790, 2014 23999528
- Turecki G, Grof P, Grof E, et al: Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry 6(5):570–578, 2001 11526471
- Tyndale RF: Genetics of alcohol and tobacco use in humans. Ann Med 35(2):94–121, 2003 12795339
- Unschuld PG, Ising M, Roeske D, et al: Gender-specific association of galanin polymorphisms with HPA-axis dysregulation, symptom severity, and antidepressant treatment response. Neuropsychopharmacology 35(7):1583–1592, 2010 20237460
- van Dyck CH, Malison RT, Jacobsen LK, et al: Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. J Nucl Med 46(5):745–751, 2005 15872345



- van Grootheest DS, Cath DC, Beekman AT, et al: Twin studies on obsessive-compulsive disorder: a review. *Twin Res Hum Genet* 8(5):450–458, 2005 16212834
- Van Tol HH, Wu CM, Guan HC, et al: Multiple dopamine D4 receptor variants in the human population. *Nature* 358(6382):149–152, 1992 1319557
- Vandenbergh DJ, Persico AM, Hawkins AL, et al: Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. *Genomics* 14(4):1104–1106, 1992 1478653
- VanNess SH, Owens MJ, Kilts CD: The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. *BMC Genet* 6:55, 2005 16309561
- Veenstra-VanderWeele J, Cook EH Jr: Molecular genetics of autism spectrum disorder. *Mol Psychiatry* 9(9):819–832, 2004 15197396
- Venter JC, Adams MD, Myers EW, et al: The sequence of the human genome. *Science* 291(5507):1304–1351, 2001 11181995
- Vilhjálmsdóttir BJ, Yang J, Finucane HK, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium, Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE) study: Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *Am J Hum Genet* 97(4):576–592, 2015 26430803
- Visootsak J, Sherman S: Neuropsychiatric and behavioral aspects of trisomy 21. *Curr Psychiatry Rep* 9(2):135–140, 2007 17389125
- Visscher PM: Sizing up human height variation. *Nat Genet* 40(5):489–490, 2008 18443579
- Visscher PM, Brown MA, McCarthy MI, et al: Five years of GWAS discovery. *Am J Hum Genet* 90(1):7–24, 2012 22243964  
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257326/>)

- Vogels A, Fryns JP: The Prader-Willi syndrome and the Angelman syndrome. *Genet Couns* 13(4):385–396, 2002 12558108
- Vorstman JA, Breetvelt EJ, Duijff SN, et al; International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome: Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA Psychiatry* 72(4):377–385, 2015 25715178
- Walsh T, McClellan JM, McCarthy SE, et al: Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 320(5875):539–543, 2008 18369103
- Wang WY, Barratt BJ, Clayton DG, Todd JA: Genome-wide association studies: theoretical and practical concerns. *Nat Rev Genet* 6(2):109–118, 2005 15716907
- Weinshilboum R: Inheritance and drug response. *N Engl J Med* 348(6):529–537, 2003 12571261
- Weiss LA, Shen Y, Korn JM, et al; Autism Consortium: Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med* 358(7):667–675, 2008 18184952
- Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447(7145):661–678, 2007 17554300
- Wen Z, Nguyen HN, Guo Z, et al: Synaptic dysregulation in a human iPS cell model of mental disorders. *Nature* 515(7527):414–418, 2014 25132547
- Wilhelm K, Mitchell PB, Niven H, et al: Life events, first depression onset and the serotonin transporter gene. *Br J Psychiatry* 188:210–215, 2006 16507960
- World Health Organization: International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Geneva, World Health Organization, 1992
- Wray NR, Visscher PM: Narrowing the boundaries of the genetic architecture of schizophrenia. *Schizophr Bull*

36(1):14-23, 2010 19996148

Wu J, Xiao H, Sun H, et al: Role of dopamine receptors in ADHD: a systematic meta-analysis. *Mol Neurobiol* 45(3):605-620, 2012 22610946

Yoon KJ, Nguyen HN, Ursini G, et al: Modeling a genetic risk for schizophrenia in iPSCs and mice reveals neural stem cell deficits associated with adherens junctions and polarity. *Cell Stem Cell* 15(1):79-91, 2014 24996170

Zalsman G, Huang YY, Oquendo MA, et al: Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. *Am J Psychiatry* 163(9):1588-1593, 2006 16946185

Zannas AS, Wiechmann T, Gassen NC, Binder EB: Gene-Stress-Epigenetic Regulation of FKBP5: Clinical and Translational Implications. *Neuropsychopharmacology* 41(1):261-274, 2016 26250598

Zarrei M, MacDonald JR, Merico D, Scherer SW: A copy number variation map of the human genome. *Nat Rev Genet* 16(3):172-183, 2015 25645873

Zwick ME, Cutler DJ, Chakravarti A: Patterns of genetic variation in Mendelian and complex traits. *Annu Rev Genomics Hum Genet* 1:387-407, 2000 11701635

## CHAPTER 4

# Psychoneuroendocrinology

Roxanne Keynejad, M.A., M.B.B.S., M.R.C.P.

Ania Korszun, Ph.D., M.D., F.R.C.Psych.

Carmine M. Pariante, Ph.D., M.D., F.R.C.Psych.

The associations between hormonal changes and psychiatric disorders have long been recognized, but only in recent decades have the underlying mechanisms begun to be understood. A renewed interest in the associations linking stressful early life events, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, inflammatory processes, and potential vulnerability to depression, psychosis, and posttraumatic stress disorder (PTSD) has prompted a resurgence of research in this field. Although the association between reproductive hormone changes and psychiatric disorders has been less well studied, there is likewise a growing clinical recognition of the burden of postpartum psychopathology and a new impetus for

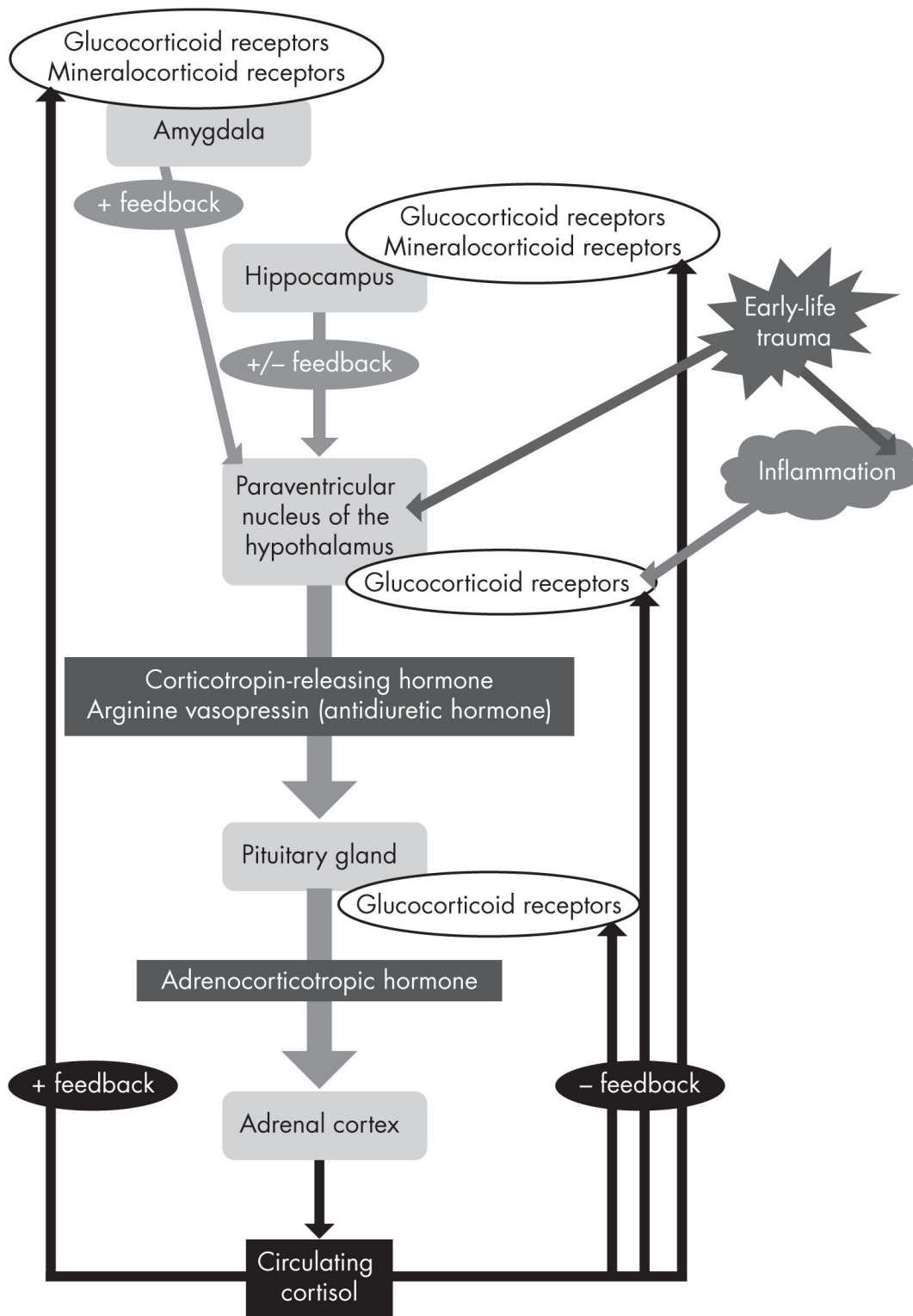
research progress in this area. A full account of how each endocrine system influences neurobehavioral function is beyond the scope of a single chapter; we focus here on summarizing the most firmly established findings from classic literature in the field, and on providing an overview of some recent promising research findings.

---

## Hypothalamic-Pituitary-Adrenal Axis

---

The HPA axis produces a primary response to stressors to ensure adaptation to environmental change and to maintain homeostasis ([Figure 4-1](#)). In response to a threat, which may be physical (such as starvation) or psychological (such as perceived danger or a stressful life event), an increase in synthesis of corticotropin-releasing hormone (CRH) occurs in the hypothalamus. CRH stimulates secretion of pituitary adrenocorticotrophic hormone (ACTH), which in turn triggers production of glucocorticoids by the adrenal cortex in a feedforward cascade. Cortisol is the main glucocorticoid, and its secretion is tightly controlled by the negative-feedback effects of glucocorticoids at both pituitary and brain sites, such as the hippocampus and hypothalamus ([Pariente and Lightman 2008](#)). These effects include rapid inhibition of the stress response, preventing oversecretion of glucocorticoids ([Keller-Wood and Dallman 1984](#)) via regulation of messenger ribonucleic acid (mRNA) and subsequent protein stores of the ACTH precursor pro-opiomelanocortin ([Roberts et al. 1979](#)) and CRH in the central nucleus of the amygdala ([Makino et al. 1994](#)).



**FIGURE 4-1.** Schematic diagram of the hypothalamic-pituitary-adrenal (HPA) axis.

***See [Plate 14](#) to view this figure in color.***

In response to a threat, the hypothalamus synthesizes corticotropin-releasing hormone (CRH), which stimulates pituitary secretion of adrenocorticotrophic hormone (ACTH), triggering adrenal glucocorticoid production in a feedforward cascade.

The HPA axis regulates peripheral body functions, including metabolism and immune response, as well as brain function. For example, glucocorticoids have well-established effects on carbohydrate metabolism, modulating pancreatic insulin release and hepatic and nonhepatic responses to insulin. Glucocorticoids have a wide range of enhancing and suppressive actions on both innate and adaptive immune responses, including upregulation of phagocytosis by neutrophils and macrophages; suppression of cytokine release by type 1 T helper (Th1) cells; and selective enhancement of type 2 T helper (Th2) cells ([Franchimont 2004](#)). Centrally, glucocorticoids regulate neuronal survival, neurogenesis, the acquisition of new memories, and the emotional appraisal of events, as well as the sizes of complex anatomical structures such as the hippocampus ([Herbert et al. 2006](#)).

Stressful stimuli activate all levels of the HPA axis, causing increases in CRH, ACTH, and cortisol secretion. However, these increases are superimposed on an intrinsic circadian pattern of HPA activity driven by the suprachiasmatic nucleus. HPA axis hormone secretion is pulsatile in nature, with the trough of integrated secretion occurring in the evening and early nighttime and the peak of secretion occurring just before awakening; active secretion continues throughout the morning and early afternoon. Under normal conditions, the pulsatile secretion of glucocorticoids causes

continuous mineralocorticoid receptor (MR) activation and phasic and short-acting glucocorticoid receptor (GR) activation after each endogenous pulse ([Conway-Campbell et al. 2007](#)). The synergy of MR and GR activation is key to mediating glucocorticoid feedback inhibition. The pulsatile or “ultradian” pattern of HPA axis hormone secretion is essential for optimal transcription as well as for maintenance of neuroendocrine and behavioral responsiveness to stress. Recent research suggests that chronic (e.g., obstructive sleep apnea) and acute disease states (e.g., cardiac surgery) are associated with disruptions of the dynamic changes in adrenocortical steroid-producing cells that are required to maintain the normal ultradian pattern ([Spiga and Lightman 2015](#)).

## The HPA Axis in Depression, Psychosis, and Posttraumatic Stress Disorder

### **Depression**

Major depressive disorder (MDD) is widely considered to represent a maladaptive, exaggerated response to stress, and although it is associated with abnormalities in multiple endocrine systems, the HPA axis seems to be the most significant of these systems, with overactivity being a well-established phenomenon in depression. Studies have demonstrated cortisol hypersecretion in a proportion of people with depression, as evidenced by elevated 24-hour urinary free cortisol (UFC) and plasma and cerebrospinal



fluid (CSF) cortisol concentrations ([Carroll et al. 1976](#); [Rubinow et al. 1984](#)).

The role of hypothalamic CRH secretion in triggering the HPA axis response led to the CRH hypothesis of depression ([Nemeroff 1996](#)), which proposed that HPA hyperactivity in depression is attributable to CRH overexpression. This hypothesis is supported by evidence of elevated CRH levels in the lumbar CSF of depressed patients compared with nondepressed controls ([Banki et al. 1992](#)) as well as postmortem evidence of elevated CRH levels in the cisternal CSF of people who died by suicide ([Arató et al. 1989](#)). The presence of elevated CSF CRH further suggests hypersecretion of CRH by sources outside the hypothalamus, such as the amygdala, which is noted to be overactive in depression ([Drevets 2003](#)). Studies in rodents have found that HPA axis hyperactivity can be stimulated by chronic overexpression of CRH by the central amygdala ([Flandreau et al. 2012](#)).

In addition, HPA axis hyperactivity is thought to result from impaired negative feedback, mediated by changes in the binding of endogenous glucocorticoids to MR and GR (see [Figure 4-1](#)). The MR has a high affinity for endogenous corticosteroids, whereas the GR has a high affinity for dexamethasone and a lower affinity for endogenous corticosteroids. This profile supports a potentially more important role for the GR in regulating responses to stress in disorders associated with high levels of endogenous glucocorticoids, such as depression. Indeed, impaired GR-mediated negative feedback by glucocorticoids in MDD is suggested by studies reporting nonsuppression of cortisol secretion on the dexamethasone suppression test and other studies demonstrating a lack of ACTH inhibition in response to CRH following dexamethasone pretreatment (i.e., the

combined dexamethasone/CRH test) ([Pariante and Lightman 2008](#)).

This hypothesis is supported by evidence that impaired HPA axis feedback inhibition by glucocorticoids resolves after successful antidepressant treatment. Furthermore, persistently impaired HPA axis negative feedback is associated with a high risk of early relapse and poor outcomes following discharge ([Zobel et al. 2001](#)). This inhibition of GR-mediated negative feedback could be due to reduced expression of the GR, as evidenced by both postmortem studies of human brains ([Webster and Carlstedt-Duke 2002](#)) and studies of the peripheral blood of depressed patients ([Cattaneo et al. 2013](#); [Nikkheslat et al. 2015](#)). Experimental models of GR resistance have shown that activation of the P38 mitogen-activated protein kinase pathway by proinflammatory cytokines can reduce GR function ([Miller and Raison 2006](#)), a result that yields a potential explanation for the association of depression with inflammation, HPA axis hyperactivity, and glucocorticoid resistance.

In addition to considerable evidence supporting the role played by the GR in HPA axis regulation, there has been increasing interest in the effects of the MR, which is found at high concentrations in limbic brain regions and has a high affinity for cortisol and corticosterone in rats. Dexamethasone binds only to GR, meaning that both the dexamethasone suppression test and the combined dexamethasone/CRH test assess only GR function. Spironolactone (the precursor of the MR antagonist canrenoate) activates the HPA axis through blockade of MR-mediated negative feedback by endogenous glucocorticoids. A 2003 study found elevated cortisol secretion in response to spironolactone challenge in

depressed patients compared with nondepressed controls ([Young et al. 2003](#)), suggesting increased MR activity in depression, whereas a more recent study found the opposite, perhaps because patients were treated with antidepressants and benzodiazepines ([Juruena et al. 2009](#)). Prednisolone is a synthetic glucocorticoid that, unlike dexamethasone, binds to the GR and the MR with similar affinity. [Juruena et al. \(2009\)](#) found normal cortisol secretion in response to administration of prednisolone (which affects both GR and MR) in depressed patients but impaired cortisol secretion in response to dexamethasone (which affects GR only). It is notable that nonsuppression in response to prednisolone (but not to dexamethasone) predicted lack of treatment response to antidepressants ([Juruena et al. 2009](#)).

Some studies suggest that HPA axis hyperactivity does not occur uniformly in all patients with depression at all times. For example, [Posener et al. \(2000\)](#) demonstrated different patterns of HPA axis abnormality in patients with psychotic and nonpsychotic depression. In this study, patients with nonpsychotic depression showed significantly lower 24-hour cortisol levels compared with controls but no difference in ACTH levels, whereas patients with psychotic depression showed significantly higher 24-hour mean ACTH levels compared with controls but no difference in cortisol levels ([Posener et al. 2000](#)).

The evidence described here highlights the role of the adrenal gland in HPA axis hyperactivity in depression. The process-oriented model proposed by [Parker et al. \(2003\)](#) postulated that in acute depression, excess cortisol results from hypersecretion of both hypothalamic CRH and pituitary ACTH, whereas in chronic depression, elevated cortisol levels are maintained by increased adrenal

sensitivity to ACTH and negative feedback by glucocorticoids despite lower ACTH levels ([Parker et al. 2003](#)). Quantification of hormone-level variability through use of the approximate entropy statistic (ApEN) yielded significantly increased cortisol ApEN and significantly reduced ACTH ApEN in men with MDD compared with control participants ([Posener et al. 2004](#)), a finding that suggests abnormal cortisol regulation and highlights the role of adrenal gland pathology in depression. This finding is in keeping with findings of previous studies demonstrating adrenocortical hypertrophy in people with depression compared with healthy controls ([Nemeroff et al. 1992](#)) as well as resolution of the hypertrophy following effective antidepressant treatment ([Rubin et al. 1995](#)). A recent study that used magnetic resonance imaging to investigate the association of depression with cardiovascular disease found elevations in adrenal gland volumes that correlated with increased intra-abdominal and pericardial volumes of adipose tissue ([Kahl et al. 2015](#)).

Of note, studies investigating early stressful life events suggest that HPA axis hyperactivity may be a premorbid risk factor for depression rather than a consequence or an epiphenomenon of depression. Neonatal rodents and nonhuman primates separated from their mothers for extended periods show HPA axis hyperactivity and CRH-containing circuit overactivation that persist into adulthood ([Sánchez et al. 2001](#)). In humans, marked HPA axis hyperactivity in adulthood has been demonstrated in women with a history of childhood physical and sexual abuse. In a study using laboratory tests of standardized psychosocial stress (e.g., the Trier Social Stress Test), participants with a history of childhood abuse exhibited elevated ACTH secretion and elevated heart rates

compared with participants without such a history, with the most elevated responses and markedly high cortisol levels observed in participants with a history of childhood abuse who were currently depressed ([Heim and Nemeroff 2002](#)). Another study, using the dexamethasone/CRH test, reported persistent HPA axis overactivation in men with a history of early life trauma ([Heim et al. 2008](#)). These findings suggest that the association between HPA axis hyperactivity and depression may indicate a persistent neurobiological predisposition to depression associated with early life stressors. Inconsistencies in the literature regarding HPA axis hyperactivity in depression may be explained by failure to control for exposure to childhood stressful life events. However, although these findings could explain the comorbidity between early life stressors and adult depression, they do not imply inevitability or irreversibility. Indeed, a key finding of mood disorder research has been that polymorphisms in stress-related genes can modify susceptibility to depression after stressful life events. Modification of susceptibility to depression has been shown for the genes encoding the 5-HT transporter ([Caspi et al. 2003](#)), CRH ([Bradley et al. 2008](#)), and the GR-bound protein FKBP5 ([Zannas et al. 2016](#)).

Complementary studies from immunology have demonstrated clinically significant inflammation in adulthood in healthy participants with a history of early life trauma, as evidenced by elevated levels of C-reactive protein (CRP; a peripheral inflammatory marker and an acute phase protein) and interleukin (IL) 6 during the Trier Social Stress Test ([Danese et al. 2007](#); [Pace et al. 2006](#)). Elevated levels of IL-6, IL-1 $\beta$ , tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and CRP have also been reported in patients with depression ([Raison et al. 2006](#)). Similarly to HPA axis

feedback impairment, CRP elevation normalizes following antidepressant treatment ([O'Brien et al. 2006](#)). One unifying hypothesis to explain these findings is that in patients with depression or a history of childhood trauma, glucocorticoid resistance (ineffective action of glucocorticoid hormones on target tissues, as seen in HPA axis hyperactivity) triggers immune activation ([Danese et al. 2008](#)).

## Psychosis

HPA axis abnormalities likewise have been demonstrated in patients with psychosis. Studying patients who are experiencing their first psychotic episode has been considered the preferred approach to avoid confounding by illness and treatment duration. A recent systematic review ([Borges et al. 2013](#)) reported evidence of HPA axis hyperactivity in first-episode psychosis, with higher baseline cortisol levels and blunted cortisol awakening responses in patients compared with control participants. Studies of patients at ultrahigh risk of developing psychosis have reported associations between higher cortisol levels and prodromal and psychotic symptoms ([Corcoran et al. 2012](#); [Mittal and Walker 2011](#)), and pituitary gland enlargement at baseline has been shown to predict future psychotic illness ([Garner et al. 2005](#)). The association of HPA axis abnormalities with psychosis-like symptoms has also been found in patients with schizotypal personality disorder ([Mittal et al. 2007](#)) and in healthy participants scoring high on measures of schizotypal traits ([Hori et al. 2011](#)). Elevated ACTH responses to stress ([Brunelin et al. 2008](#)) and raised cortisol at baseline and following stress ([Collip et al. 2011](#)) have been demonstrated in healthy relatives of patients with psychosis. Pituitary gland enlargement also

has been reported in first-degree relatives of people with schizophrenia compared with healthy controls ([Mondelli et al. 2008](#)). [Borges et al. \(2013\)](#) suggested that these studies point to the presence of a familial, potentially genetic, vulnerability to HPA axis hyperactivity in individuals who develop schizophrenia. It is noteworthy that studies in two independent samples have identified enlarged pituitary gland volumes—one study in the context of psychotic depression, psychotic mania, and schizophrenia ([Pariante et al. 2004](#)) and the other study in the context of the pre-psychosis prodromal phase ([Garner et al. 2005](#)). A possible mechanism for the pituitary gland enlargement seen in these studies may be ineffective negative feedback by circulating glucocorticoid hormones, leading to proliferation and expansion of the pituitary cells that produce ACTH.

## **Posttraumatic Stress Disorder**

Although there is evidence that HPA axis abnormalities are present in PTSD, methodological difficulties initially made some of the literature challenging to interpret, with evidence of both increased and decreased HPA axis activity based on comorbidity with depression, type of trauma, and other sociodemographic features of the sample. For example, in a study of combat veterans with a diagnosis of PTSD, both low cortisol and enhanced cortisol suppression in response to dexamethasone were reported, irrespective of comorbid MDD ([Yehuda 2002](#)). However, that sample included only male combat veterans, whereas in community samples, women are more likely to experience PTSD ([Frans et al. 2005](#); [Kessler et al. 1995](#)). Furthermore, studies of PTSD in veteran populations are subject to significant confounding with current and past alcohol and substance



use disorders. Additional evidence of elevated CSF CRH levels and blunted ACTH responses to CRH suggests that pituitary CRH receptors are downregulated in PTSD ([Bremner et al. 1997](#)). A study using serial CSF sampling over a period of 6 hours demonstrated elevated CRH despite normal free urinary cortisol in war veterans diagnosed with PTSD compared with veterans without PTSD and healthy controls ([Baker et al. 1999](#)). PTSD studies generally report comorbid depression in participants, and depression studies often fail to measure and report trauma histories. As a result, documented depression confounds much of literature on the HPA axis in PTSD, and undocumented trauma and abuse may confound some of the literature on the HPA axis in depression.

These problems were avoided by [Heim et al. \(2001\)](#) in their studies on childhood abuse and MDD, which examined multiple HPA axis challenges in the same participants. The authors found an effect of early abuse (with comorbid PTSD in 11 of 13 participants) and MDD on stress reactivity, documenting both increased ACTH and increased cortisol response to the stressor in depressed patients with a history of childhood abuse compared with either healthy controls or depressed patients without a history of childhood abuse. In this same cohort, patients with MDD showed a blunted response to CRH challenge irrespective of the presence or absence of an abuse history, whereas patients with a history of childhood abuse who were not depressed showed a heightened response to CRH challenge. Thus, childhood abuse produced an increased pituitary response with adaptive adrenal compensation, a change compatible with low or normal basal cortisol levels. Furthermore, lower cortisol levels and greater CRH suppression in the low-dose dexamethasone suppression



test were found in women with a history of abuse who developed depression but not in those without depression ([Newport et al. 2004](#)), irrespective of PTSD features.

A meta-analysis of 37 studies of basal cortisol levels in adults with current PTSD compared with adults without psychiatric disorders ([Meewisse et al. 2007](#)) examined data from 828 patients and 800 control participants. Although the authors found no significant differences in basal cortisol between the two groups, significantly lower serum cortisol was observed in studies that included only female participants, in studies that investigated physical or sexual abuse, and in studies that used afternoon cortisol sampling. A second meta-analysis of 47 studies comparing patients with PTSD, patients with PTSD and comorbid MDD, and control subjects with and without trauma exposure ([Morris et al. 2012](#)) found that cortisol levels were lower for the PTSD and the PTSD + MDD groups than for the no-trauma control group (which did not differ significantly from the trauma-exposed control group). Cortisol levels in response to dexamethasone suppression testing were lower in the PTSD group, the PTSD + MDD group, and the trauma-exposed control group relative to the no-trauma control group, with effect sizes moderated by age, time since traumatic event, and age at traumatic experience. The authors proposed that whereas lower daily cortisol may represent a marker of PTSD, increased HPA axis response to dexamethasone suppression testing may represent a marker of trauma exposure more generally.

Studies demonstrating increased GR binding and function in patients with PTSD have given rise to the suggestion that hypocortisolism may result from hypersensitivity of negative feedback inhibition ([Yehuda 2006](#)). Indeed, prospective studies have found evidence that the presence of

hypocortisolism prior to traumatic experiences may predict vulnerability to PTSD ([Yehuda et al. 1998](#)), prompting the hypothesis that low baseline cortisol could represent a risk factor for abnormal stress response ([Sherin and Nemeroff 2011](#)). Furthermore, some studies report that PTSD can be averted by hydrocortisone treatment following trauma ([de Quervain 2008](#)), while others suggest that treatment aimed at replicating the normal cortisol secretion pattern is effective ([Aerni et al. 2004](#)). A possible explanation for hypocortisolism in PTSD is that cortisol may interfere with traumatic memory retrieval ([de Quervain and Margraf 2008](#)). A recent intriguing study of intergenerational transmission of susceptibility to PTSD reported differential effects of paternal and maternal PTSD on the offspring of Holocaust survivors ([Yehuda et al. 2014](#)). Offspring with paternal PTSD but no maternal PTSD showed higher methylation of the exon 1<sub>F</sub> promoter of the glucocorticoid receptor (GR-1<sub>F</sub>) gene (*NR3C1*), whereas offspring with both maternal and paternal PTSD showed lower methylation.

---

## Hypothalamic-Pituitary-Thyroid Axis

---

Despite the well-recognized importance of the hypothalamic-pituitary-thyroid (HPT) axis in clinical psychiatry, it has been far less researched in recent times than the HPA axis. In this important hormonal system, hypothalamic secretion of thyrotropin-releasing hormone (TRH) stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH). TSH in turn stimulates

thyroid secretion of triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ), which exert negative feedback on the pituitary gland and hypothalamus. There is a well-known association between hypothyroidism and mood disorders, including depression and rapid-cycling bipolar disorder, and between hyperthyroidism and symptoms of anxiety and dysphoria ([Hendrick et al. 1998](#)). Studies of depressed patients have found evidence of changes in the TSH response to TRH, higher levels of antithyroid antibodies, and elevated concentrations of TRH in the CSF ([Musselman and Nemeroff 1996](#)). However, despite these promising findings, a double-blind randomized, placebo-controlled trial of  $T_3$  augmentation of sertraline treatment in patients with MDD found no added benefit from combining  $T_3$  with sertraline ([Garlow et al. 2012](#)).

Studies examining the relationship between HPT axis abnormalities and PTSD have been limited, but there is some evidence of thyroid abnormalities in combat veterans. Elevated  $T_3$  and  $T_4$  were reported in Vietnam veterans diagnosed with PTSD ([Prange 1999](#)), whereas in World War II veterans with more chronic PTSD diagnoses,  $T_3$  was elevated but  $T_4$  levels were normal ([Wang and Mason 1999](#)).

---

## **Growth Hormone and the Hypothalamic-Pituitary-Somatotrophic Axis**

---

Like the role of the HPT, the role of the hormonal system regulating growth hormone (GH, or somatotropin)—the hypothalamic-pituitary-somatotrophic axis—in mental health has been understudied. GH is synthesized by the anterior pituitary gland and is used in research predominantly as a marker of the integrity of the noradrenergic system following challenge. GH-releasing hormone (GHRH) and somatostatin regulate GH secretion through stimulation and inhibition, respectively, and are themselves regulated by a number of neurotransmitters, including acetylcholine, dopamine,  $\gamma$ -aminobutyric acid (GABA), norepinephrine, and serotonin. GH and insulin-like growth factors exert negative feedback to inhibit GH secretion. Studies of clonidine-induced GH release have documented a blunted GH response in depression that is thought to result from HPA axis changes ([Dinan 1998](#)). Reduced serum levels of GH have been observed in patients with schizophrenia, and reduced pituitary levels of GH have been found postmortem in people with chronic schizophrenia ([Guest et al. 2011](#)). A recent study reported a higher insulin:GH ratio in patients with schizophrenia, their siblings with a mood disorder diagnosis, and their unaffected siblings compared with healthy control participants ([van Beveren et al. 2014](#)).

---

## Prolactin

---

Prolactin is secreted by the anterior pituitary gland in 14 pulses over 24 hours in a circadian pattern consisting of increased pulsation at the time of sleep onset, with the peak level occurring halfway through the sleep period and the

trough level occurring on awakening. Prolactin trough levels are higher during the luteal phase of the menstrual cycle. Dopamine acts at anterior pituitary D<sub>2</sub> receptors to inhibit prolactin secretion, whereas serotonin exerts a stimulatory effect. Studies using serotonin-challenge agents to examine basal prolactin in patients with depression have yielded mixed findings, likely attributable to issues such as methodological difficulties, the complexity of the serotonin system, and the multifactorial nature of depression itself ([Nicholas et al. 1998](#)). A study in antipsychotic-naïve adults identified hyperprolactinemia (which is frequently attributed to iatrogenic causes) in more than 30% of individuals diagnosed as being at risk for psychosis ( $n=43$ ) and more than 20% of those experiencing a first psychotic episode ( $n=26$ ) ([Aston et al. 2010](#)).

---

## Hypothalamic-Pituitary-Gonadal Axis

---

In contrast to the HPT and HPS axes, the hypothalamic-pituitary-gonadal (HPG) axis has been far more widely investigated in relation to mental health. Secretion of the principal gonadal steroids, estrogen and progesterone, is governed by cyclic changes in ovarian follicular and corpus luteum development over the course of the menstrual cycle. Critical to the proper functioning and timing of the monthly hormonal cycle is the pulsatile secretion of gonadotropin-releasing hormone (GnRH). GnRH secretion from the hypothalamus drives the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from pituitary gonadotropes.

The pulsatile secretion of GnRH is driven by a pulse generator in the arcuate nucleus of the hypothalamus. This pulsatile pattern is critical for the control of serum LH, FSH, and ovulation. LH secretory pulses in the peripheral circulation are used as the marker of GnRH secretory pulses. In humans, the follicular phase of the menstrual cycle is characterized by LH pulses of relatively constant amplitude every 1–2 hours ([Reame et al. 1984](#)).

It has been established that an increased incidence of depression in women ([Weissman and Klerman 1977](#)) extends from adolescence until menopause ([Kessler et al. 1993](#)), suggesting a potential role for ovarian steroids in the etiology of depressive disorders. This hypothesis is supported by evidence that in women with a history of depression, times of rapidly changing gonadal steroid concentrations, such as those occurring premenstrually or postpartum, constitute periods of particular vulnerability to depressive symptoms. Several studies have shown that a history of depression increases the risk of both postpartum “blues” and postpartum MDD ([O’Hara 1986](#); [O’Hara et al. 1991](#)) and that premenstrual hormonal changes may affect mood ([Halbreich et al. 1984](#)). Other studies found a relationship between elevated estrogen and testosterone levels and the rising incidence of depression in girls during adolescence ([Angold et al. 1999](#)).

Premenstrual syndrome (PMS) is one of the best-studied depressive disorders in terms of the effects of ovarian steroids on mood. Studies of follicular, mid-luteal, and late-luteal phases of the menstrual cycle found no significant differences between healthy controls and women diagnosed with PMS ([Reame et al. 1984](#)). The hypothesis that PMS symptoms are related to delayed effects of progesterone on mood prompted several studies of RU486, a progesterone

antagonist. [Schmidt et al. \(1991\)](#) found no reduction in mood symptoms following RU486 creation of an artificial follicular phase during the second half of the menstrual cycle. Furthermore, human chorionic gonadotropin did not reduce mood symptoms; progesterone blockade caused early menses without preventing depression. A subsequent 6-month randomized double-blind, placebo-controlled crossover study also showed no benefit of RU486 on depressive symptoms ([Chan et al. 1994](#)). [Rubinow and Schmidt \(1989\)](#) proposed that PMS is a cyclical mood disorder “entrained” to the menstrual cycle, rather than a disorder caused by changes in ovarian steroids.

Because of the documented increased incidence of depression at critical hormonal transition phases (e.g., postpartum, perimenopause), much speculation has focused on estrogen’s role as a precipitant. Two epidemiological cohort studies ([Cohen et al. 2006](#); [Freeman et al. 2006](#)) also identified an increased incidence of depressive symptoms and MDD during the menopausal transition. Both high and low estrogen levels were associated with depression ([Freeman et al. 2004, 2006](#)), suggesting that estrogen levels may drive depression, and women who showed rapid changes in estrogen (from high to low levels and vice versa) tended to develop depressive symptoms during the perimenopause transition. [Schmidt and Rubinow \(2009\)](#) proposed that in some women, menopausal changes in estrogen secretion may trigger CNS effects that predispose to depression. These authors pointed to evidence that perimenopausal depressive episodes tend to occur during the late menopausal transition ([Steinberg et al. 2008](#)), a phase of estradiol withdrawal ([Santoro et al. 1996](#)). Furthermore, double-blind, placebo-controlled trials of estradiol therapy in perimenopausal women diagnosed with

depression have shown significant improvement in symptoms after 3 weeks of treatment ([Schmidt et al. 2000](#); [Soares et al. 2001](#)). Finally, a randomized double-blind, placebo-controlled trial of the effect of estradiol withdrawal on mood in women with a history of perimenopausal depression documented a recurrence of depressive symptoms during blinded hormone withdrawal ([Schmidt et al. 2015](#)).

Another time of increased vulnerability to depression in women is pregnancy and the postpartum period. Although it is known that this period coincides with a sudden drop in progesterone and estradiol levels, there is limited evidence on how this drop relates to depression onset. A recent systematic review of risk factors for antenatal and postnatal depression identified a wide range of biological, psychological, and social factors in both high- and low-income countries ([Howard et al. 2014](#)). Studies of both animals and humans provide evidence of a subtype of depression associated with 1) sensitivity to reproductive hormone changes; 2) higher rates of depression premenstrually, postnatally, and perimenopausally ([Craig 2013](#); [Schiller et al. 2015](#)); and 3) a personal or family history of postnatal depression ([Cooper and Murray 1995](#); [Forty et al. 2006](#)). Although some studies have reported elevated CRH ([Yim et al. 2009](#)), glucocorticoid, and CRH receptor polymorphisms ([Engineer et al. 2013](#)) and raised leptin levels ([Skalkidou et al. 2009](#)) as risk factors during pregnancy, the relative paucity of literature addressing this clinically significant area underscores the need for replication studies and further research.

In their review of perinatal bipolar disorder, affective psychosis, and schizophrenia, [Jones et al. \(2014\)](#) concluded that most of the evidence supporting a role for hormones in



these disorders has been circumstantial ([Bloch et al. 2003](#)). The reviewers suggested that rather than indicating abnormal hormone levels, postpartum psychotic disorders may indicate abnormal responses to normal perinatal hormone changes ([Bloch et al. 2000](#)). Furthermore, [Jones et al. \(2014\)](#) pointed to evidence of a dysregulated immune-neuroendocrine set point in postpartum psychosis, including monocyte and macrophage overactivity ([Bergink et al. 2013](#); [Weigelt et al. 2013](#)), a finding that requires further investigation.

## Effects of the Hypothalamic-Pituitary-Adrenal Axis on the Hypothalamic-Pituitary-Gonadal Axis

Stress has long been known to inhibit the HPG axis, and there is a well-established association between infertility and high population density. Shortly after the isolation and sequencing of the CRH gene, it was demonstrated in rats that CRH inhibited LH secretion ([Rivier and Vale 1984](#)) and GnRH secretion ([Petraglia et al. 1987](#)), and further primate studies showed inhibition of LH secretion by injection of CRH ([Olster and Ferin 1987](#)).

Studies in ewes found that LH secretory amplitude was inhibited by stress, that the effects of stress were reversed by metyrapone inhibition of cortisol synthesis, and that infusion of stress levels of cortisol could produce inhibition of LH pulse amplitude but not frequency ([Breen et al. 2004](#); [Debus et al. 2002](#)). These data suggest that cortisol, in addition to central CRH, may play a role in LH disruption.

Human studies have linked HPG axis abnormalities to HPA axis activation in anorexia nervosa, exercise-induced amenorrhea, and hypothalamic amenorrhea. In all three syndromes, hypercortisolemia has been observed, indicating overactivity of the HPA axis ([Berga et al. 1989](#); [Casanueva et al. 1987](#); [Hohtari et al. 1988](#); [Loucks et al. 1989](#); [Suh et al. 1988](#); [Villanueva et al. 1986](#)). In all three conditions, exogenous CRH challenge elicits diminished ACTH or cortisol responses, suggesting that high baseline cortisol exerts negative feedback on hormonal effects of CRH ([Berger et al. 1983](#); [Biller et al. 1990](#); [Gold et al. 1986](#); [Hohtari et al. 1991](#)). In anorexia nervosa, the hormonal abnormalities in the HPA and HPG axes are secondary to the weight loss. Weight restriction and low body weight are also observed in exercise-induced amenorrhea, and low body weight has been reported in hypothalamic amenorrhea. Even relatively mild degrees of weight loss in normal-weight or obese patients can lead to disturbances in both of these axes, as manifested by resistance to dexamethasone and by disturbances in menstrual cycle regularity or amenorrhea ([Berger et al. 1983](#); [Edelstein et al. 1983](#); [Pirke et al. 1985](#)). In anorexia nervosa, LH secretory patterns may revert to prepubertal levels of low nonpulsatile secretion or to a pubertal pattern of entrainment of LH secretion to the sleep cycle. Studies by [Reame et al. \(1985\)](#) in women with hypothalamic amenorrhea demonstrated that LH secretion during the follicular phase was slowed to the rate normally observed during the luteal phase.

---

## Conclusion

---

In this chapter, we have sought to provide an overview of the established findings and the most promising developments in the dynamic field of psychoneuroendocrinology. Following a resurgence of research in this area, the interrelationships among early stressful life events, HPA axis dysregulation, altered immune function, vulnerability to psychiatric disorders, and inadequate response to treatment have become increasingly well characterized, although many findings remain correlational in nature. The growing clinical recognition of the burden of postpartum psychopathology and the associations between reproductive hormone changes and psychiatric disorders has provided further impetus for academic progress in this area. Stressful life events are strongly associated with depression, psychosis, and PTSD, but the relative contributions of genetic, developmental, and environmental factors to an individual's vulnerability have yet to be fully understood.

---

## References

---

- Aerni A, Traber R, Hock C, et al: Low-dose cortisol for symptoms of posttraumatic stress disorder. *Am J Psychiatry* 161(8): 1488-1490, 2004 15285979
- Angold A, Costello EJ, Erkanli A, Worthman CM: Pubertal changes in hormone levels and depression in girls. *Psychol Med* 29(5):1043-1053, 1999 10576297
- Arató M, Bánki CM, Bissette G, Nemeroff CB: Elevated CSF CRF in suicide victims. *Biol Psychiatry* 25(3):355-359, 1989 2536563
- Aston J, Rechsteiner E, Bull N, et al: Hyperprolactinaemia in early psychosis—not only due to antipsychotics. *Prog*

- Neuropsychopharmacol Biol Psychiatry 34(7): 1342-1344, 2010 20188136
- Baker DG, West SA, Nicholson WE, et al: Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry 156(4): 585-588, 1999 10200738
- Banki CM, Karmacsi L, Bissette G, Nemeroff CB: Cerebrospinal fluid neuropeptides in mood disorder and dementia. J Affect Disord 25(1):39-45, 1992 1352520
- Berga SL, Mortola JF, Girton L, et al: Neuroendocrine aberrations in women with functional hypothalamic amenorrhea. J Clin Endocrinol Metab 68(2):301-308, 1989 2493024
- Berger M, Pirke KM, Doerr P, et al: Influence of weight loss on the dexamethasone suppression test. Arch Gen Psychiatry 40(5):585-586, 1983 6838337
- Bergink V, Burgerhout KM, Weigelt K, et al: Immune system dysregulation in first-onset postpartum psychosis. Biol Psychiatry 73(10):1000-1007, 2013 23270599
- Biller BM, Federoff HJ, Koenig JI, Klibanski A: Abnormal cortisol secretion and responses to corticotropin-releasing hormone in women with hypothalamic amenorrhea. J Clin Endocrinol Metab 70(2):311-317, 1990 2153693
- Bloch M, Schmidt PJ, Danaceau M, et al: Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 157(6):924-930, 2000 10831472
- Bloch M, Daly RC, Rubinow DR: Endocrine factors in the etiology of postpartum depression. Compr Psychiatry 44(3):234-246, 2003 12764712
- Borges S, Gayer-Anderson C, Mondelli V: A systematic review of the activity of the hypothalamic-pituitary-adrenal axis in first episode psychosis.

Psychoneuroendocrinology 38(5):603–611, 2013  
23369532

Bradley RG, Binder EB, Epstein MP, et al: Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. Arch Gen Psychiatry 65(2):190–200, 2008 18250257

Breen KM, Stackpole CA, Clarke IJ, et al: Does the type II glucocorticoid receptor mediate cortisol-induced suppression in pituitary responsiveness to gonadotropin-releasing hormone? Endocrinology 145(6):2739–2746, 2004 15033919

Bremner JD, Licinio J, Darnell A, et al: Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry 154(5):624–629, 1997 9137116

Brunelin J, d'Amato T, van Os J, et al: Effects of acute metabolic stress on the dopaminergic and pituitary-adrenal axis activity in patients with schizophrenia, their unaffected siblings and controls. Schizophr Res 100:206–211, 2008 18155448

Carroll BJ, Curtis GC, Mendels J: Cerebrospinal fluid and plasma free cortisol concentrations in depression. Psychol Med 6(2):235–244, 1976 1005564

Casanueva FF, Borras CG, Burguera B, et al: Steroids and neuroendocrine function in anorexia nervosa. J Steroid Biochem 27(1–3):635–640, 1987 3121928

Caspi A, Sugden K, Moffitt TE, et al: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301(5631):386–389, 2003 12869766

Cattaneo A, Gennarelli M, Uher R, et al: Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology 38(3):377–385, 2013 22990943

- Chan AF, Mortola JF, Wood SH, Yen SS: Persistence of premenstrual syndrome during low-dose administration of the progesterone antagonist RU 486. *Obstet Gynecol* 84(6):1001-1005, 1994 7970453
- Cohen LS, Soares CN, Vitonis AF, et al: Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry* 63(4):385-390, 2006 16585467
- Collip D, Nicolson NA, Lardinois M, et al; G.R.O.U.P: Daily cortisol, stress reactivity and psychotic experiences in individuals at above average genetic risk for psychosis. *Psychol Med* 41(11):2305-2315, 2011 21733219
- Conway-Campbell BL, McKenna MA, Wiles CC, et al: Proteasome-dependent down-regulation of activated nuclear hippocampal glucocorticoid receptors determines dynamic responses to corticosterone. *Endocrinology* 148(11):5470-5477, 2007 17690167
- Cooper PJ, Murray L: Course and recurrence of postnatal depression. Evidence for the specificity of the diagnostic concept. *Br J Psychiatry* 166(2):191-195, 1995 7728362
- Corcoran CM, Smith C, McLaughlin D, et al: HPA axis function and symptoms in adolescents at clinical high risk for schizophrenia. *Schizophr Res* 135(1-3):170-174, 2012 22226904
- Craig MC: Should psychiatrists be prescribing oestrogen therapy to their female patients? *Br J Psychiatry* 202(1):9-13, 2013 23284147
- Danese A, Pariante CM, Caspi A, et al: Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci U S A* 104(4):1319-1324, 2007 17229839
- Danese A, Moffitt TE, Pariante CM, et al: Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry* 65(4):409-415, 2008 18391129

- de Quervain DJ: Glucocorticoid-induced reduction of traumatic memories: implications for the treatment of PTSD. *Prog Brain Res* 167:239–247, 2008 18037019
- de Quervain DJ, Margraf J: Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: a novel therapeutic approach. *Eur J Pharmacol* 583(2–3):365–371, 2008 18275950
- Debus N, Breen KM, Barrell GK, et al: Does cortisol mediate endotoxin-induced inhibition of pulsatile luteinizing hormone and gonadotropin-releasing hormone secretion? *Endocrinology* 143(10): 3748–3758, 2002 12239084
- Dinan TG: Psychoneuroendocrinology of depression. Growth hormone. *Psychiatr Clin North Am* 21(2):325–339, 1998 9670229
- Drevets WC: Neuroimaging abnormalities in the amygdala in mood disorders. *Ann N Y Acad Sci* 985:420–444, 2003 12724175
- Edelstein CK, Roy-Byrne P, Fawzy FI, Dornfeld L: Effects of weight loss on the dexamethasone suppression test. *Am J Psychiatry* 140(3):338–341, 1983 6829806
- Engineer N, Darwin L, Nishigandh D, et al: Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum. *J Psychiatr Res* 47(9):1166–1173, 2013 23726670
- Flandreau EI, Ressler KJ, Owens MJ, Nemeroff CB: Chronic overexpression of corticotropin-releasing factor from the central amygdala produces HPA axis hyperactivity and behavioral anxiety associated with gene-expression changes in the hippocampus and paraventricular nucleus of the hypothalamus. *Psychoneuroendocrinology* 37(1):27–38, 2012 21616602
- Forty L, Jones L, Macgregor S, et al: Familiality of postpartum depression in unipolar disorder: results of a

family study. *Am J Psychiatry* 163(9):1549-1553, 2006 16946179

Franchimont D: Overview of the actions of glucocorticoids on the immune response: a good model to characterize new pathways of immunosuppression for new treatment strategies. *Ann N Y Acad Sci* 1024:124-137, 2004 15265777

Frans O, Rimmö PA, Aberg L, Fredrikson M: Trauma exposure and post-traumatic stress disorder in the general population. *Acta Psychiatr Scand* 111(4):291-299, 2005 15740465

Freeman EW, Sammel MD, Liu L, et al: Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry* 61(1):62-70, 2004 14706945

Freeman EW, Sammel MD, Lin H, Nelson DB: Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 63(4):375-382, 2006 16585466

Garlow SJ, Dunlop BW, Ninan PT, Nemeroff CB: The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in the treatment of major depressive disorder. *J Psychiatr Res* 46(11):1406-1413, 2012 22964160

Garner B, Pariante CM, Wood SJ, et al: Pituitary volume predicts future transition to psychosis in individuals at ultra-high risk of developing psychosis. *Biol Psychiatry* 58(5):417-423, 2005 16026767

Gold PW, Loriaux DL, Roy A, et al: Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. *N Engl J Med* 314(21):1329-1335, 1986 3010108

Guest PC, Schwarz E, Krishnamurthy D, et al: Altered levels of circulating insulin and other neuroendocrine hormones associated with the onset of schizophrenia.



- Psychoneuroendocrinology 36(7):1092-1096, 2011  
21251762
- Halbreich U, Vital-Herne J, Goldstein S, Zander K: Sex differences in biological factors putatively related to depression. J Affect Disord 7(3-4):223-233, 1984  
6151956
- Heim C, Nemeroff CB: Neurobiology of early life stress: clinical studies. Semin Clin Neuropsychiatry 7(2):147-159, 2002 11953939
- Heim C, Newport DJ, Bonsall R, et al: Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry 158(4):575-581, 2001 11282691
- Heim C, Mletzko T, Purselle D, et al: The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. Biol Psychiatry 63(4):398-405, 2008 17825799
- Hendrick V, Altshuler L, Whybrow P: Psychoneuroendocrinology of mood disorders. The hypothalamic-pituitary-thyroid axis. Psychiatr Clin North Am 21(2):277-292, 1998 9670226
- Herbert J, Goodyer IM, Grossman AB, et al: Do corticosteroids damage the brain? J Neuroendocrinol 18(6):393-411, 2006 16684130
- Hohtari H, Elovainio R, Salminen K, Laatikainen T: Plasma corticotropin-releasing hormone, corticotropin, and endorphins at rest and during exercise in eumenorrheic and amenorrheic athletes. Fertil Steril 50(2):233-238, 1988 2840309
- Hohtari H, Salminen-Lappalainen K, Laatikainen T: Response of plasma endorphins, corticotropin, cortisol, and luteinizing hormone in the corticotropin-releasing hormone stimulation test in eumenorrheic and amenorrheic athletes. Fertil Steril 55(2):276-280, 1991 1846825

- Hori H, Teraishi T, Ozeki Y, et al: Schizotypal personality in healthy adults is related to blunted cortisol responses to the combined dexamethasone/corticotropin-releasing hormone test. *Neuropsychobiology* 63(4):232-241, 2011 21494051
- Howard LM, Molyneaux E, Dennis C-L, et al: Non-psychotic mental disorders in the perinatal period. *Lancet* 384(9956):1775-1788, 2014 25455248
- Jones I, Chandra PS, Dazzan P, Howard LM: Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period. *Lancet* 384(9956):1789-1799, 2014 25455249
- Juruena MF, Pariante CM, Papadopoulos AS, et al: Prednisolone suppression test in depression: prospective study of the role of HPA axis dysfunction in treatment resistance. *Br J Psychiatry* 194(4):342-349, 2009 19336786
- Kahl KG, Schweiger U, Pars K, et al: Adrenal gland volume, intra-abdominal and pericardial adipose tissue in major depressive disorder. *Psychoneuroendocrinology* 58:1-8, 2015 25935636
- Keller-Wood ME, Dallman MF: Corticosteroid inhibition of ACTH secretion. *Endocr Rev* 5(1):1-24, 1984 6323158
- Kessler RC, McGonagle KA, Swartz M, et al: Sex and depression in the National Comorbidity Survey, I: lifetime prevalence, chronicity and recurrence. *J Affect Disord* 29(2-3):85-96, 1993 8300981
- Kessler RC, Sonnega A, Bromet E, et al: Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 52(12):1048-1060, 1995 7492257
- Loucks AB, Mortola JF, Girton L, Yen SS: Alterations in the hypothalamic-pituitary-ovarian and the hypothalamic-pituitary-adrenal axes in athletic women. *J Clin Endocrinol Metab* 68(2):402-411, 1989 2537332
- Makino S, Gold PW, Schulkin J: Effects of corticosterone on CRH mRNA and content in the bed nucleus of the stria

terminalis; comparison with the effects in the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus. *Brain Res* 657(1-2):141-149, 1994 7820612

Meewisse M-L, Reitsma JB, de Vries G-J, et al: Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *Br J Psychiatry* 191:387-392, 2007 17978317

Miller AH, Raison CL: Cytokines, p38 MAP kinase and the pathophysiology of depression. *Neuropsychopharmacology* 31(10):2089-2090, 2006 16980982

Mittal VA, Walker EF: Minor physical anomalies and vulnerability in prodromal youth. *Schizophr Res* 129(2-3):116-121, 2011 21429715

Mittal VA, Dhruv S, Tessner KD, et al: The relations among putative biorisk markers in schizotypal adolescents: minor physical anomalies, movement abnormalities, and salivary cortisol. *Biol Psychiatry* 61(10):1179-1186, 2007 17188254

Mondelli V, Dazzan P, Gabilondo A, et al: Pituitary volume in unaffected relatives of patients with schizophrenia and bipolar disorder. *Psychoneuroendocrinology* 33(7):1004-1012, 2008 18640787

Morris MC, Compas BE, Garber J: Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: a systematic review and meta-analysis. *Clin Psychol Rev* 32(4):301-315, 2012 22459791

Musselman DL, Nemeroff CB: Depression and endocrine disorders: focus on the thyroid and adrenal system. *Br J Psychiatry Suppl* 30(30):123-128, 1996 8864158

Nemeroff CB: The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol Psychiatry* 1(4):336-342, 1996 9118360

- Nemeroff CB, Krishnan KR, Reed D, et al: Adrenal gland enlargement in major depression. A computed tomographic study. *Arch Gen Psychiatry* 49(5):384-387, 1992 1586274
- Newport DJ, Heim C, Bonsall R, et al: Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse. *Biol Psychiatry* 55(1):10-20, 2004 14706420
- Nicholas L, Dawkins K, Golden RN: Psychoneuroendocrinology of depression. Prolactin. *Psychiatr Clin North Am* 21(2): 341-358, 1998 9670230
- Nikkheslat N, Zunszain PA, Horowitz MA, et al: Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behav Immun* 48:8-18, 2015 25683698
- O'Brien SM, Scott LV, Dinan TG: Antidepressant therapy and C-reactive protein levels. *Br J Psychiatry* 188:449-452, 2006 16648531
- O'Hara MW: Social support, life events, and depression during pregnancy and the puerperium. *Arch Gen Psychiatry* 43(6): 569-573, 1986 3707289
- O'Hara MW, Schlechte JA, Lewis DA, Wright EJ: Prospective study of postpartum blues. Biologic and psychosocial factors. *Arch Gen Psychiatry* 48(9):801-806, 1991 1929770
- Olster DH, Ferin M: Corticotropin-releasing hormone inhibits gonadotropin secretion in the ovariectomized rhesus monkey. *J Clin Endocrinol Metab* 65(2):262-267, 1987 3110201
- Pace TW, Mletzko TC, Alagbe O, et al: Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry* 163(9):1630-1633, 2006 16946190
- Pariante CM, Lightman SL: The HPA axis in major depression: classical theories and new developments.

- Trends Neurosci 31(9):464–468, 2008 18675469
- Pariente CM, Vassilopoulou K, Velakoulis D, et al: Pituitary volume in psychosis. Br J Psychiatry 185:5–10, 2004 15231549
- Parker KJ, Schatzberg AF, Lyons DM: Neuroendocrine aspects of hypercortisolism in major depression. Horm Behav 43(1):60–66, 2003 12614635
- Petraglia F, Sutton S, Vale W, Plotsky P: Corticotropin-releasing factor decreases plasma luteinizing hormone levels in female rats by inhibiting gonadotropin-releasing hormone release into hypophysial-portal circulation. Endocrinology 120(3):1083–1088, 1987 3542513
- Pirke KM, Schweiger U, Lemmel W, et al: The influence of dieting on the menstrual cycle of healthy young women. J Clin Endocrinol Metab 60(6):1174–1179, 1985 3923022
- Posener JA, DeBattista C, Williams GH, et al: 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. Arch Gen Psychiatry 57(8):755–760, 2000 10920463
- Posener JA, Charles DeBattista, Veldhuis JD, et al: Process irregularity of cortisol and adrenocorticotropin secretion in men with major depressive disorder. Psychoneuroendocrinology 29(9):1129–1137, 2004 15219636
- Prange AJ Jr: Thyroid axis sustaining hypothesis of posttraumatic stress disorder. Psychosom Med 61(2):139–140, 1999 10204963
- Raison CL, Capuron L, Miller AH: Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27(1):24–31, 2006 16316783
- Reame N, Sauder SE, Kelch RP, Marshall JC: Pulsatile gonadotropin secretion during the human menstrual cycle: evidence for altered frequency of gonadotropin-releasing hormone secretion. J Clin Endocrinol Metab 59(2):328–337, 1984 6429184

- Reame NE, Sauder SE, Case GD, et al: Pulsatile gonadotropin secretion in women with hypothalamic amenorrhea: evidence that reduced frequency of gonadotropin-releasing hormone secretion is the mechanism of persistent anovulation. *J Clin Endocrinol Metab* 61(5):851-858, 1985 3900122
- Rivier C, Vale W: Influence of corticotropin-releasing factor on reproductive functions in the rat. *Endocrinology* 114(3): 914-921, 1984 6321146
- Roberts JL, Budarf ML, Baxter JD, Herbert E: Selective reduction of proadrenocorticotropin/endorphin proteins and messenger ribonucleic acid activity in mouse pituitary tumor cells by glucocorticoids. *Biochemistry* 18(22):4907-4915, 1979 228704
- Rubin RT, Phillips JJ, Sadow TF, McCracken JT: Adrenal gland volume in major depression. Increase during the depressive episode and decrease with successful treatment. *Arch Gen Psychiatry* 52(3): 213-218, 1995 7872849
- Rubinow DR, Schmidt PJ: Models for the development and expression of symptoms in premenstrual syndrome. *Psychiatr Clin North Am* 12(1):53-68, 1989 2652113
- Rubinow DR, Post RM, Savard R, Gold PW: Cortisol hypersecretion and cognitive impairment in depression. *Arch Gen Psychiatry* 41(3):279-283, 1984 6703846
- Sánchez MM, Ladd CO, Plotsky PM: Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev Psychopathol* 13(3):419-449, 2001 11523842
- Santoro N, Brown JR, Adel T, Skurnick JH: Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab* 81(4):1495-1501, 1996 8636357
- Schiller CE, Meltzer-Brody S, Rubinow DR: The role of reproductive hormones in postpartum depression. *CNS*

- Spectr 20(1):48-59, 2015 25263255
- Schmidt PJ, Rubinow DR: Sex hormones and mood in the perimenopause. *Ann N Y Acad Sci* 1179:70-85, 2009 19906233
- Schmidt PJ, Nieman LK, Grover GN, et al: Lack of effect of induced menses on symptoms in women with premenstrual syndrome. *N Engl J Med* 324(17):1174-1179, 1991 2011161
- Schmidt PJ, Nieman L, Danaceau MA, et al: Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 183(2):414-420, 2000 10942479
- Schmidt PJ, Ben Dor R, Martinez PE, et al: Effects of estradiol withdrawal on mood in women with past perimenopausal depression: a randomized clinical trial. *JAMA Psychiatry* 72(7):714-726, 2015 26018333
- Sherin JE, Nemeroff CB: Post-traumatic stress disorder: the neurobiological impact of psychological trauma. *Dialogues Clin Neurosci* 13(3):263-278, 2011 22034143
- Skalkidou A, Sylvén SM, Papadopoulos FC, et al: Risk of postpartum depression in association with serum leptin and interleukin-6 levels at delivery: a nested case-control study within the UPPSAT cohort. *Psychoneuroendocrinology* 34(9):1329-1337, 2009 19427131
- Soares CN, Almeida OP, Joffe H, Cohen LS: Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 58(6):529-534, 2001 11386980
- Spiga F, Lightman SL: Dynamics of adrenal glucocorticoid steroidogenesis in health and disease. *Mol Cell Endocrinol* 408: 227-234, 2015 25662280
- Steinberg EM, Rubinow DR, Bartko JJ, et al: A cross-sectional evaluation of perimenopausal depression. *J Clin Psychiatry* 69(6):973-980, 2008 18505304

- Suh BY, Liu JH, Berga SL, et al: Hypercortisolism in patients with functional hypothalamic-amenorrhea. *J Clin Endocrinol Metab* 66(4):733-739, 1988 3346352
- van Beveren NJ, Schwarz E, Noll R, et al: Evidence for disturbed insulin and growth hormone signaling as potential risk factors in the development of schizophrenia. *Transl Psychiatry* 4:e430, 2014 25158005
- Villanueva AL, Schlosser C, Hopper B, et al: Increased cortisol production in women runners. *J Clin Endocrinol Metab* 63(1): 133-136, 1986 3011836
- Wang S, Mason J: Elevations of serum T3 levels and their association with symptoms in World War II veterans with combat-related posttraumatic stress disorder: replication of findings in Vietnam combat veterans. *Psychosom Med* 61(2):131-138, 1999 10204962
- Webster JI, Carlstedt-Duke J: Involvement of multidrug resistance proteins (MDR) in the modulation of glucocorticoid response. *J Steroid Biochem Mol Biol* 82(4-5):277-288, 2002 12589934
- Weigelt K, Bergink V, Burgerhout KM, et al: Down-regulation of inflammation-protective microRNAs 146a and 212 in monocytes of patients with postpartum psychosis. *Brain Behav Immun* 29:147-155, 2013 23295264
- Weissman MM, Klerman GL: Sex differences and the epidemiology of depression. *Arch Gen Psychiatry* 34(1):98-111, 1977 319772
- Yehuda R: Current status of cortisol findings in post-traumatic stress disorder. *Psychiatr Clin North Am* 25(2):341-368, vii, 2002 12136504
- Yehuda R: Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. *Ann N Y Acad Sci* 1071:137-166, 2006 16891568
- Yehuda R, McFarlane AC, Shalev AY: Predicting the development of posttraumatic stress disorder from the



- acute response to a traumatic event. *Biol Psychiatry* 44(12): 1305-1313, 1998 9861473
- Yehuda R, Daskalakis NP, Lehrner A, et al: Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. *Am J Psychiatry* 171(8):872-880, 2014 24832930
- Yim IS, Glynn LM, Dunkel-Schetter C, et al: Risk of postpartum depressive symptoms with elevated corticotropin-releasing hormone in human pregnancy. *Arch Gen Psychiatry* 66(2):162-169, 2009 19188538
- Young EA, Lopez JF, Murphy-Weinberg V, et al: Mineralocorticoid receptor function in major depression. *Arch Gen Psychiatry* 60(1):24-28, 2003 12511169
- Zannas AS, Wiechmann T, Gassen NC, Binder EB: Gene-stress-epigenetic regulation of FKBP5: clinical and translational implications. *Neuropsychopharmacology* 41(1):261-274, 2016 26250598
- Zobel AW, Nickel T, Sonntag A, et al: Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. a prospective study. *J Psychiatr Res* 35(2): 83-94, 2001 11377437

# CHAPTER 5

## **Brain-Immune System Interactions**

Relevance to the Pathophysiology and Treatment of Neuropsychiatric Disorders

Firdaus S. Dhabhar, Ph.D.

Charles L. Raison, M.D.

Andrew H. Miller, M.D.

**Multidirectional** interactions among psychological factors and the nervous, endocrine, and immune systems form the basis of important physiological pathways that are crucial for maintaining mental and physical health. These multisystem interactions can also mediate the pathological aspects of numerous diseases. Therefore, elucidating psychoneuroendocrine-immune pathways and mechanisms is likely to be critically useful for restoring health in the presence of disease or promoting health in the absence of

disease. In this chapter we begin with an overview of the immune system and introduce its three major functional dimensions. We then go on to describe the effects of behavior, brain, and hormones on immune function and the effects of the immune system on the nervous and endocrine systems and on mental and psychological states. Finally, we discuss the relevance of psychoneuroendocrine-immune interactions for mental health.

---

## **The Immune Triad: Immunoprotection, Immunopathology, and Immunoregulation**

---

The immune system is a highly distributed physiological system. It consists of primary (bone marrow and thymus), secondary (lymph nodes, spleen, tonsils, and parts of mucosal tissues), and tertiary (most other organs in the body) organs, immune cells or leukocytes (granulocytes, monocytes, T cells, B cells, natural killer cells), and humoral factors (e.g., antibodies, cytokines, complement peptides) that traverse the body through a network of vascular and lymphatic vessels. When discussing immune responses, it is useful to categorize them in terms of their principal cellular and molecular components. For example, innate, adaptive, and helper T cell (e.g., Th1, Th2, Th17) immune responses are all defined in terms of their cellular, cytokine, and humoral components. In addition to these categories, it is also useful to define immune responses in terms of their

integrated functional effects. [Dhabhar \(2009a, 2009b, 2014\)](#) proposed that immune responses be categorized as being immunoprotective, immunopathological, and immunoregulatory/inhibitory. It is important to bear in mind that although such categories provide useful constructs with which to organize ideas, concepts, and models, an overall in vivo immune response is likely to consist of several types of responses with varying amounts of dominance from each category. The composition and nature of an immune response is also affected by—and changes with—time. The three major types of immune responses are defined below in terms of their functional end effects ([Dhabhar 2009a, 2009b, 2014](#)).

*Immunoprotective responses* are defined as those that promote efficient wound healing, eliminate infections and cancer, and mediate vaccine-induced immunological memory ([Dhabhar 2009a, 2009b](#)). Key characteristics of immunoprotection include active immune surveillance, a rapid and robust response on immune activation, and efficient clearance of the activating agent or pathogen, followed by rapid resolution. Immunoprotective responses are critical for completion of the proliferative and remodeling phases of wound healing. Wound healing is important not only for frank wounds (where the initiating event is tissue damage itself) but also for tissue-intrinsic “wounds” (where the initiating event is an immune response precipitated by intracellular infection, during which there can be collateral tissue damage). Different types and combinations of immune response—innate, adaptive, Th1, Th2—can confer immunoprotection, depending on the type of pathogen involved (viral, bacterial, protozoan, fungal, helminthic), on whether the pathogen is intracellular or extracellular, and on the

accompanying wounding conditions (sterile, infected, external, or internal wounds).

*Immunopathological responses* are defined as those that are directed against the self (as in autoimmune diseases such as multiple sclerosis, arthritis, or systemic lupus erythematosus) or against innocuous antigens (asthma, allergies) and responses that are directed against chronic, nonresolving inflammation ([Dhabhar 2009a, 2009b](#)). Immunopathology is also involved in low-level, long-term elevations in local and/or systemic inflammatory mediators (e.g., C-reactive protein or interleukin 6 [IL-6]), which are thought to contribute to disorders such as cardiovascular disease, obesity, and depression ([Dantzer et al. 2008](#); [Maes 1993](#); [Van Gaal et al. 2006](#)).

*Immunoregulatory responses* are defined as those that involve immune cells and factors that regulate (mainly downregulate) the function of other immune cells ([Dhabhar 2009a, 2009b](#)). Although the earlier concept of suppressor T cells became mired in controversy, newer studies suggest that there is an arm of the immune system that functions to inhibit immune responses ([Piccirillo 2008](#); [Simpson 2008](#); [Wing and Sakaguchi 2010](#)). For example, regulatory CD4+ CD25+FOXP3+T cells, IL-10, and transforming growth factor  $\beta$  have been shown to have immunoregulatory/inhibitory functions. The physiological function of these factors is to keep proinflammatory, allergic, and autoimmune responses in check ([Bluestone and Tang 2005](#); [Wing and Sakaguchi 2010](#)). However, it has also been suggested that immunoregulatory/inhibitory factors may suppress anti-tumor immunity and that their presence may be indicative of a negative prognosis for cancer ([Finn 2008](#); [Olson and McNeel 2013](#); [Saul et al. 2005](#); [Whiteside 2014](#)).

---

# Effects of the Brain and Behavior on the Body

---

More than four decades ago, Ader and Cohen showed that an immune response could be modified through classical Pavlovian conditioning ([Ader and Cohen 1975](#)). Numerous studies have confirmed and extended this initial insight and have established beyond argument the ability of brain states to significantly modulate immune system functioning ([Bower and Irwin 2016](#); [Irwin and Rothmundt 2012](#); [Kelley and McCusker 2014](#); [Nemeroff 2013](#); [Padro and Sanders 2014](#); [Quan 2014](#); [Schedlowski et al. 2014](#); [Straub 2014](#)). The majority of these studies have focused on the effects of stress on the immune response ([Dhabhar 2014](#); [Straub et al. 2013](#)).

## Effects of Stress on Immune Function

Even though the word *stress* generally has negative connotations, stress is a familiar and ubiquitous aspect of life, representing a stimulant for some individuals but a burden for many others. Numerous definitions have been proposed for the concept of stress, each focusing on aspects of an internal or external challenge, disturbance, or stimulus; on stimulus perception; or on a physiological response ([Goldstein and McEwen 2002](#); [McEwen 2002](#); [Sapolsky 2005](#)). An integrated definition states that stress is a constellation of events consisting of a stimulus (*stressor*) that precipitates a reaction in the brain (*stress*

*perception and evaluation*) that activates physiological fight-or-flight systems in the body (*biological stress response*) ([Dhabhar and McEwen 1997](#)).

Short-term stress involves changes in stress-related factors that last for minutes to hours, whereas chronic stress involves changes that last for months or years. The only way that a stressor can affect the brain or body is through the biological stress response. Although many factors are involved, the major mediators of stress effects are norepinephrine and epinephrine, which are released by the sympathetic nervous system, and corticotropin-releasing hormone (CRH), adrenocorticotropin, and cortisol, which arise following activation of the hypothalamic-pituitary-adrenal (HPA) axis. Virtually every cell in the body expresses receptors for one or more of these factors. Therefore, stress hormones can induce changes in almost all cells and tissues and inform them about the presence of a stressor. Virtually every type of stressor, ranging from laboratory stressors (e.g., public speaking, mental arithmetic) to life-related stressors (e.g., exercise, process of undergoing surgery, sky diving, bereavement, loneliness, academic examinations), has demonstrated a measurable effect on the immune system ([Dhabhar 2014](#); [Raison et al. 2002](#)).

Although stress has a bad reputation, it is important to recognize that the adaptive purpose of a physiological stress response is to promote survival during fight or flight. Whereas long-term stress is generally harmful, short-term stress can be protective in that it prepares the organism to deal with threats or challenges. It has been proposed that a psychophysiological stress response is one of nature's fundamental survival mechanisms that could be therapeutically harnessed to augment immune function

during vaccination, wound healing, or infection ([Dhabhar 2009a, 2009b, 2014](#); [Dhabhar and McEwen 1999](#); [Dhabhar and Viswanathan 2005](#)). Mechanisms of acute stress-induced immunoenhancement include the following:

1. Subpopulation-specific changes in neutrophil, macrophage, and lymphocyte redistribution ([Dhabhar and McEwen 1997](#); [Dhabhar et al. 2012](#); [Rosenberger et al. 2009](#))
2. Increased leukocyte infiltration into sites of immune activation ([Viswanathan and Dhabhar 2005](#))
3. Increased dendritic cell and macrophage maturation and traffic to draining lymph nodes ([Viswanathan and Dhabhar 2005](#))
4. Enhanced local cytokine production with a key role for  $\gamma$ -interferon ([Dhabhar et al. 2000](#))
5. Enhanced systemic production of cytokines such as IL-1 and IL-6, which is also likely to contribute to enhancement of immune function induced by short-term stress ([Aschbacher et al. 2012](#); [Puterman et al. 2014](#); [Steptoe et al. 2001](#)).

The adjuvant-like immunoenhancing effects of short-term stress may have evolved because many stressful situations (e.g., aggression, accident) result in immune activation (e.g., wounding, infection) and vice versa ([Dhabhar 2014](#); [Puterman et al. 2014](#)). Interestingly, in modern times, many medical procedures involving immune activation (e.g., vaccination, surgery) also induce a stress response. Preclinical findings initially lent support to this hypothesis ([Dhabhar and McEwen 1996](#); [Dhabhar et al. 1995](#); [Viswanathan and Dhabhar 2005](#)) and subsequently were replicated in humans. Clinical studies have demonstrated



that patients undergoing knee surgery who show a robust and adaptive immune cell redistribution profile during the short-term stress of surgery also show significantly enhanced recovery ([Rosenberger et al. 2009](#)). Similarly, preclinical studies initially demonstrated that short-term stress that was experienced during primary ([Blecha et al. 1982](#); [Coe et al. 1989](#); [Dhabhar and Viswanathan 2005](#); [Viswanathan et al. 2005](#); [Wood et al. 1993](#)) or secondary ([Blecha et al. 1982](#); [Dhabhar and McEwen 1996, 1999](#); [Dhabhar et al. 2000](#); [Saint-Mezard et al. 2003](#)) antigen exposure significantly enhanced the ensuing immune response ([Dhabhar 2002](#)). An elegant series of clinical studies has demonstrated that the adjuvant effects of short-term psychological stress, or exercise stress, can enhance vaccine-induced immunity in human subjects ([Edwards et al. 2006, 2007, 2008](#)).

In contrast to short-term stress, chronic or long-term stress can be harmful ([Dhabhar and McEwen 1997](#)). Chronic stress suppresses or dysregulates innate and adaptive immune responses by altering the type 1-type 2 cytokine balance, inducing low-grade chronic inflammation and suppressing the numbers, trafficking, and function of immunoprotective cells ([Dhabhar 2009a, 2009b, 2014](#)). Chronic stress has been shown to increase susceptibility to infections, reduce antibody responses to vaccination, and delay wound healing ([Cohen et al. 1991](#); [Fagundes et al. 2013](#); [Glaser and Kiecolt-Glaser 2005](#); [Irwin 2008](#); [Kiecolt-Glaser et al. 1995](#); [Padro and Sanders 2014](#); [Sanders and Straub 2002](#); [Solomon 1969](#); [Straub et al. 2013](#); [Vitlic et al. 2014](#); [Webster Marketon and Glaser 2008](#)). Chronic stress also has been linked to increased morbidity and mortality in neoplastic diseases (including breast cancer and malignant melanoma), diabetes, and cardiovascular disease ([Antoni et](#)

al. 2006; Ben-Eliyahu et al. 2007; Dhabhar 2014; Evans et al. 2005; Fenton and Stover 2006; Leserman et al. 1999; Lutgendorf and Sood 2011; Raison and Miller 2003a; Saul et al. 2005). In addition to significant personal and health-related costs of chronic stress, the annual economic cost to industry arising from work-related stress in the United States is estimated at more than \$300 billion ([American Psychological Association 2007](#)). Dysregulation of the circadian cortisol rhythm is an important marker that coincides with the deleterious effects of chronic stress ([Dhabhar 2014](#); [Dhabhar and McEwen 1997](#); [Saul et al. 2005](#); [Sephton and Spiegel 2003](#)).

Key factors that determine whether stress enhances or suppresses immune function include the following (for a review, see [Dhabhar 2009a, 2009b; 2014](#)):

1. The effects of stress on immune cell distribution in the body
2. The duration (short [minutes to hours] versus long [weeks to months to years]) of changes in stress-related factors
3. The differential effects of physiological versus pharmacological concentrations of stress hormones and the differential effects of endogenous (e.g., cortisol, corticosterone) versus synthetic (e.g., dexamethasone) hormones
4. The timing of stressor or stress hormone exposure relative to the time of activation and ensuing time course of the immune response

It is important to recognize that factors such as gender, genetics, age, route of administration and nature of the immunizing antigen, and time during the circadian cycle additionally affect immune function and could also affect

the nature of the relationship between stress and immune function. It is also important to bear in mind that it is not the effect of a particular stressor in enhancing or suppressing immune function, but rather the end effect on the immune response, that determines whether stress-immune system interactions have beneficial or harmful effects on health.

## Effects of Depression on Immune Function

Numerous studies have investigated the effects of stress-related disorders, especially major depressive disorder, on immune function ([Antonioli et al. 2012](#); [Blume et al. 2011](#); [Irwin and Miller 2007](#); [Miller and Raison 2016](#)). Despite a significant degree of heterogeneity across individual studies, evidence suggests that patients with major depressive disorder demonstrate a number of immune changes similar to those seen in individuals undergoing chronic and/or severe stress ([Herbert and Cohen 1993](#); [Zorrilla et al. 2001](#)). This is hardly surprising, given the many indices of stress system hyperactivity that are apparent in patients with major depressive disorder, including increased CRH and cortisol production ([Pariante et al. 1995](#)) and augmented sympathetic nervous system activity as manifested in part by increased peripheral blood catecholamines ([Veith et al. 1994](#); [Wong et al. 2000](#)). Enumerative immune changes shared by major depressive disorder and chronic or severe stress include decreases in lymphocytes, B cells, and T cells and increases in the ratio of CD4 to CD8 T cell subsets ([Herbert and Cohen 1993](#)). Shared functional changes include decreases in natural

killer (NK) cell activity and lymphocyte proliferation in response to nonspecific mitogens (Table 5-1) (Herbert and Cohen 1993; Zorrilla et al. 2001). It is important to note, however, that major depressive disorder is a heterogeneous condition, and immune changes are not uniform across all patients. Indeed, inhibited lymphocyte responses tend to be most striking in patients who are older, are hospitalized, or have more severe and/or melancholic types of depression (Miller 1998; Schleifer et al. 1989). In addition, the sleep changes common in depression are known to alter lymphocyte responses, especially NK cell activity (NKCA), even in the absence of other depressive symptoms (Irwin 2015; Irwin et al. 1996). Nonetheless, it does not appear that these factors completely account for the association between major depressive disorder and alterations in measures of the number and function of lymphocyte subsets (Herbert and Cohen 1993; Irwin and Miller 2007).

---

**TABLE 5-1. Immune alterations in major depressive disorder**

---

Increased white blood cells
Increased neutrophil percentage
Decreased lymphocyte percentage
Increased CD4-to-CD8 ratio
Decreased natural killer cell activity
Decreased mitogen-induced lymphocyte proliferation
Increased circulating interleukin-6
Decreased circulating interleukin-10
Increased haptoglobin
Increased prostaglandin E <sub>2</sub>

---

Evidence suggests that depression, like chronic stress, may impair T cell function in ways that are relevant to disease vulnerability. For example, one study reported that patients with major depressive disorder have a marked decrease in the ability to generate lymphocytes that respond to the herpes zoster virus ([Irwin et al. 1998](#)). Also consistent with impaired T cell function in depression is the observation that depressed patients, especially those with melancholia, demonstrate impaired cell-mediated immunity (CMI), as measured by the delayed-type hypersensitivity response ([Hickie et al. 1993, 1995](#)).

A growing database suggests that depression in both medically healthy and medically ill patients is associated with increased immunopathological proinflammatory responses ([Andrei et al. 2007](#); [Kim et al. 2007](#); [Lespérance et al. 2004](#); [Maes 1999](#); [Miller and Raison 2016](#); [Musselman et al. 2001b](#); [Raison et al. 2006](#)). Findings consistent with inflammatory activation in depression include increased plasma and cerebrospinal fluid (CSF) concentrations of inflammatory cytokines, increased in vitro production of proinflammatory cytokines from stimulated peripheral blood mononuclear cells, increased acute-phase proteins (and decreased negative acute-phase proteins), increased chemokines and adhesion molecules, and increased production of prostaglandins ([Kim et al. 2007](#); [Maes 1999](#); [Raison et al. 2006](#)).

On the basis of meta-analyses, increases in peripheral blood IL-6 and C-reactive protein are two of the most reliable inflammatory biomarkers associated with depression ([Zorrilla et al. 2001](#)). Indeed, careful studies examining IL-6 across the circadian cycle have found that in comparison with control subjects, depressed patients show a reverse circadian pattern of IL-6, with markedly elevated

levels of this cytokine during the morning hours ([Alesci et al. 2005](#)). Of interest, given the role of IL-6 and C-reactive protein in predicting disease outcome in both cardiovascular disorders and diabetes ([Ridker et al. 2000a, 2000b](#)), as well as data indicating that inflammation may play a role in cancer ([Aggarwal et al. 2006](#)), the relationship between depression and activation of the proinflammatory response may provide a mechanism that explains the negative impact of depression on a number of illnesses ([Evans et al. 2005](#)). Moreover, immune activation in major depressive disorder may be involved in several of the pathophysiological changes that are common in the context of depression, including bone loss, insulin resistance, cachexia, increased body temperature, and hippocampal volume loss ([Raison et al. 2006](#)).

It is important to recognize that in the absence of chronic infection, cancer, or immunodeficiency disease, modest elevations in anti-inflammatory cytokines may exert salubrious or health-protective effects by mediating the resolution of inflammatory processes and preventing or antagonizing the damaging effects of prolonged inflammation. In contrast to the attention focused on proinflammatory cytokines, considerably less attention has been accorded to the potential role of anti-inflammatory/immunomodulatory cytokines such as IL-10 in depression. In healthy individuals, there is a regulated balance between pro- and anti-inflammatory cytokines: for example, IL-6 mediates the early phase of the inflammatory process and induces the release of IL-10, which exerts immunoregulatory effects and resolves inflammation ([Daftarian et al. 1996](#); [Fang et al. 2008](#); [Ogawa et al. 2008](#)). The net result of such regulatory relationships is that the immune system can quickly respond to a challenge and

subsequently return to homeostasis once the challenge has ended. Short-term inflammatory reactions in response to immune challenges such as wounding or infection are adaptive and essential for survival, but chronic inflammation is harmful. Interestingly, depression is associated with numerous disorders that are thought to involve chronic inflammation ([Dantzer et al. 2008](#); [Evans et al. 2005](#); [Kiecolt-Glaser and Glaser 2002](#)). These include cardiovascular disease ([Frasure-Smith et al. 2007](#); [McCaffery et al. 2006](#); [Musselman and Nemeroff 2000](#); [Whooley et al. 2007](#)), obesity ([Onyike et al. 2003](#)), rheumatoid arthritis ([Bruce 2008](#); [Zautra et al. 2004](#)), multiple sclerosis ([Triantafyllou et al. 2008](#)), and cancer ([Currier and Nemeroff 2014](#)).

A number of potential factors may contribute to increased proinflammatory responses in depressed patients. One factor that has received special attention is body mass index (BMI). BMI has been reliably correlated with peripheral markers of inflammation, including IL-6, in part related to the capacity of adipocytes to produce inflammatory cytokines ([Schäffler et al. 2007](#)). Of relevance in this regard, an analysis of data from the Third National Health and Nutrition Examination Survey revealed that after adjustment for a multitude of variables, including BMI, there was a strong association between major depressive disorder and elevated levels of C-reactive protein in men but not in women ([Ford and Erlinger 2004](#)). Early life stress is another factor that may be involved. For example, males with current major depressive disorder and a history of high early life stress exhibited significantly greater increases in IL-6 and nuclear factor (NF)- $\kappa$ B DNA binding following a psychosocial stressor compared with nondepressed male control subjects ([Pace et al. 2006](#)).

It has been suggested that an important and relatively underappreciated mechanism for the link between depression and inflammatory disorders may be disruption of the immunoregulatory balance between pro- and anti-inflammatory cytokines ([Dhabhar et al. 2009](#)). The cytokine balance can be tilted toward a proinflammatory milieu because of elevated concentrations of proinflammatory cytokines such as IL-6, lowered concentrations of anti-inflammatory/immunomodulatory cytokines such as IL-10, or a combination of the two. Therefore, in addition to the absolute concentrations of these cytokines, the relative concentrations of pro- and anti-inflammatory cytokines can provide a useful index of the net inflammatory milieu and of immune dysregulation. In keeping with this hypothesis, it has been demonstrated that in comparison with control subjects, depressed subjects manifest significantly lower serum IL-10 concentrations, nonsignificantly higher IL-6 concentrations, and significantly higher IL-6 to IL-10 ratios ([Dhabhar et al. 2009](#)). Furthermore, higher levels of depressive symptoms were significantly related to lower IL-10 concentrations and tended to be related to higher IL-6 to IL-10 ratios but were not significantly related to IL-6 concentrations across the total sample of participants ([Dhabhar et al. 2009](#)). Moreover, control subjects showed a strong positive correlation between serum IL-6 and IL-10 concentrations, which was completely absent (near-zero effect size) in depressed subjects. Although depressed subjects had significantly higher BMIs than did the controls, covarying for BMI (or controlling for BMI) did not alter this finding ([Dhabhar et al. 2009](#)).

Given the anti-inflammatory properties of glucocorticoids ([Rhen and Cidlowski 2005](#)), it might be expected that patients with depression who have decreased



glucocorticoid sensitivity, as manifested by nonsuppression of cortisol on the dexamethasone suppression test (DST), would be especially likely to show signs of immune activation. Some evidence suggests that this is indeed the case. Compared with patients with depression who have normal in vivo glucocorticoid sensitivity, patients who are DST nonsuppressors show increased plasma concentrations of the acute-phase reactant  $\alpha_1$ -glycoprotein, as well as increased in vitro mitogen-stimulated IL-6 production ([Sluzewska 1999](#)). Glucocorticoid resistance, as assessed by the DST, has been associated with poor response to antidepressant treatment ([Holsboer 2000](#)). Of interest in light of the relationship between DST nonsuppression and increased inflammatory activity, study findings suggest that patients with treatment-resistant depression are more likely than patients whose depression is responsive to treatment to show evidence of increased inflammatory activity, including increased plasma concentrations of acute-phase proteins, IL-6, and the soluble receptor for IL-6 (sIL-6r), which synergistically enhances IL-6 activity ([Raison et al. 2006](#); [Sluzewska 1999](#)). Moreover, depressed patients who show reductions in unstimulated tumor necrosis factor alpha (TNF- $\alpha$ ) during antidepressant treatment are more likely to respond than those whose TNF- $\alpha$  remains elevated ([Lanquillon et al. 2000](#)).

## Other Psychiatric Disorders and Immune Function

Some evidence suggests that other stress-related neuropsychiatric conditions—including posttraumatic stress disorder (PTSD), chronic fatigue syndrome (CFS), seasonal

affective disorder, and fibromyalgia—may be associated with immune activation, although these conditions have been less well characterized than major depressive disorder. Patients with combat-related PTSD have been reported to demonstrate increased plasma concentrations of IL-1, increased CSF concentrations of IL-6, and increased expression of genes related to inflammation and NF- $\kappa$ B systems ([Baker et al. 2001](#); [Guardado et al. 2016](#); [Spivak et al. 1997](#)). PTSD following civilian disasters appears to be associated with elevated plasma concentrations of IL-6 and its soluble receptor ([Maes et al. 1999b](#)). PTSD following childhood abuse is associated with enhanced CMI responses ([Altemus et al. 2003](#)). Although not found consistently ([Maes et al. 1999b](#)), both severity of symptoms and duration of illness have been reported to correlate positively with indices of immune activation in PTSD ([R.J. Miller et al. 2001](#); [Spivak et al. 1997](#)).

A growing body of literature suggests that patients exposed to early life trauma may be especially vulnerable to the development of psychophysical disorders (e.g., CFS, fibromyalgia) that are characterized by complaints of chronic pain, fatigue, and cognitive difficulties of unknown etiology ([Heim et al. 1997](#)). Consistent with this vulnerability, these disorders have also been associated with evidence of increased inflammatory activity. For example, it has been reported that both CFS and fibromyalgia are accompanied by an increase in acute-phase reactants and increased plasma concentrations and/or peripheral blood mononuclear cell production of proinflammatory cytokines, including IL-1, IL-6, and TNF- $\alpha$  ([Borish et al. 1998](#); [Cannon et al. 1999](#); [Gupta et al. 1997](#); [Maes et al. 1999a](#)). Of note, one report indicates that seasonal affective disorder, a condition with significant

symptom overlap with CFS and fibromyalgia, may be characterized by increased plasma concentrations of IL-6 ([Leu et al. 2001](#)).

Finally, although the picture is far less clear, there has been speculation that immune system activation may contribute to the pathophysiology of psychotic disorders, including schizophrenia, possibly related to an autoimmune diathesis ([Pearce 2001](#); [Rothermundt et al. 2001](#)). Elevated levels of cytokines and their receptors, including IL-2, sIL-2, and IL-6, have been reported in the blood and CSF of patients with schizophrenia, and a high level of CSF IL-2 has been found to predict subsequent schizophrenic relapse ([Rothermundt et al. 2001](#)). In a related fashion, on the basis of seasonal birth patterns that have been reliably replicated in large epidemiological studies of patients with schizophrenia, consideration has been given to the role of viral infection early in development ([Pearce 2001](#)). These findings are consistent with in utero infections of relevant brain structures, including the hippocampus, during critical periods of development (especially during the second trimester) ([Pearce 2001](#)). Moreover, cross-reactivity between brain antigens and antigens of infectious agents may contribute not only to schizophrenia but also to the neurological and psychiatric complications associated with streptococcal infection (i.e., pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections [PANDAS]) ([Snider and Swedo 2000](#)).

---

## Mediating Pathways

---

Underlying the ability of the central nervous system (CNS) to affect the immune system is a host of connections between autonomic nervous system (ANS) and neuroendocrine pathways and immune system elements. Immune cells are able to directly respond to brain outflow pathways via receptors for small-molecule neurotransmitters, adrenal and gonadal steroids, hypothalamic-releasing factors, and other neuropeptides ([Raison et al. 2002](#)). Specific receptor densities vary among immune cell types, and these variations correlate with cell sensitivity to a given ligand.

## Autonomic Nervous System

It is well known that sympathetic and parasympathetic pathways within the ANS interact to maintain homeostasis in a variety of physiological states, including regulation of the immune response. In addition to expressing receptors for autonomic and neuroendocrine signaling molecules, immune cells and tissues are innervated by fibers derived from the ANS, together comprising a neural pathway that can reflexively regulate the immune response ([Czura et al. 2007](#); [Downing and Miyan 2000](#); [Miller 1998](#); [Raison et al. 2002](#); [Sanders and Kavelaars 2007](#); [Tracey 2002](#)). The sympathetic branch of the ANS appears able to influence the immune system either by changing the vascular tone and blood flow into lymphoid organs or by directly influencing immune cell function via locally released neurotransmitters, especially norepinephrine, and neuropeptides such as neuropeptide Y, substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and CRH, which, in turn, interact with specific

receptors on nearby immune cells ([Bellinger et al. 1997](#); [Czura et al. 2007](#)).

In addition to immune regulation by the sympathetic branch, the parasympathetic branch of the ANS has been shown to contribute to the regulation of innate immune responses via an efferent neural signaling pathway referred to as the *cholinergic anti-inflammatory pathway* ([Tracey 2002](#)). The existence of this pathway was initially identified in studies showing that stimulation of the vagus nerve attenuates immune system activation and the physiological signs of septic shock in response to lipopolysaccharide, a key component of gram-negative bacterial cell walls ([Borovikova et al. 2000](#)). Follow-up studies have determined that vagal release of acetylcholine, which in turn interacts with the  $\alpha 7$  subunit of the acetylcholine receptor ( $\alpha 7$ nAChR) on relevant immune cells, is capable of suppressing production of cytokines, including TNF- $\alpha$ , via inhibitory effects on nuclear translocation of NF- $\kappa$ B ([Altavilla et al. 2006](#); [Guarini et al. 2003](#)) and activation of Janus kinase 2 signal transducers and activators of transcriptions (STAT) 3 ([de Jonge et al. 2005](#); [Pavlov and Tracey 2005](#)).

Subsequent studies have established that cytokine production is inhibited by efferent vagal pathways in the context of a variety of inflammatory processes, including myocardial ischemia, hemorrhagic shock, ischemia/reperfusion, and pancreatitis ([Altavilla et al. 2006](#); [Guarini et al. 2003](#); [Mioni et al. 2005](#); [van Westerloo et al. 2006](#); [H. Wang et al. 2004](#)). It also has been shown that both vagus nerve stimulation and  $\alpha 7$ nAChR agonists inhibit production of a number of proinflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and high-mobility group box 1 ([H. Wang et al. 2004](#)). Of note, a specific  $\alpha$ nAChR-

dependent vagus nerve pathway to the spleen has been identified that inhibits proinflammatory cytokine production during endotoxemia and polymicrobial sepsis. Furthermore, both splenectomy and vagotomy interrupt the cholinergic anti-inflammatory response ([Huston et al. 2006](#)). Taken together, these findings suggest that in addition to effects on cellular signaling, there are anatomical and hard-wired components of the cholinergic anti-inflammatory pathway.

## Hypothalamic-Pituitary-Adrenal Axis

In concert with the ANS, the HPA axis serves as a central component of the mammalian stress response system. Although glucocorticoids, which represent the final product of HPA axis activation, have long been viewed as immunosuppressive because of their well-documented ability to suppress inflammation (largely through protein-protein interactions between the glucocorticoid receptor and NF- $\kappa$ B) ([Rhen and Cidlowski 2005](#)), it is increasingly recognized that HPA axis effects on immunity are complex ([Dhabhar 2009a, 2009b, 2014](#); [Dhabhar et al. 1995](#)). This complexity arises from the fact that HPA axis effects on the immune system depend on numerous factors, including the immune compartment that is being assessed, the element of the HPA axis being evaluated (i.e., CRH vs. cortisol), and the duration and timing relative to the immune response and stressor application. Thus, for example, glucocorticoids are known to mediate immune cell redistribution in the body ([Dhabhar et al. 1996, 2012](#)) and to enhance CMI in vivo ([Dhabhar and McEwen 1996](#)) through their effects on lymphocyte trafficking ([Dhabhar 1998, 2009, 2014](#)). Moreover, different HPA axis elements demonstrate

divergent immune system effects. For example, the end result of CRH-induced HPA axis activation is proinflammatory cytokine suppression, yet studies demonstrate that the direct effect of CRH on proinflammatory cytokine production may be stimulatory ([Labeur et al. 1995](#); [Paez Pereda et al. 1995](#)).

Finally, the effect of glucocorticoids on naturalistic measures of immunity, such as cutaneous CMI, depends on both the concentration and the duration of glucocorticoids within the immune compartment under consideration. Thus, low doses of glucocorticoids applied for brief periods have been shown in rodents to stimulate CMI, whereas higher (or more protracted) glucocorticoid exposure suppresses CMI ([Dhabhar 2009a, 2009b, 2014](#); [Dhabhar and McEwen 1999](#)).

CRH applied within the CNS suppresses several measures of immunity, including splenic NKCA, mitogen-stimulated lymphocyte proliferation, and in vivo and in vitro antibody formation, as well as T cell responses to T cell receptor antibody ([Caroleo et al. 1993](#); [Irwin et al. 1988](#); [Labeur et al. 1995](#); [Rassnick et al. 1994](#)). CRH-overproducing mice demonstrate a profound decrease in the number of B cells and severely diminished primary and memory antibody responses ([Stenzel-Poore et al. 1994](#)). These immunosuppressive effects appear to be mediated by stress response outflow pathways activated by CRH, given that blockade of the sympathetic nervous system abolishes CRH effects on NKCA and adrenalectomy obviates CRH effects on lymphocyte proliferation ([Irwin et al. 1988](#); [Labeur et al. 1995](#)). In addition, the B cell decreases in CRH-overproducing mice are consistent with the marked reduction in rodent B cells observed after chronic glucocorticoid exposure ([Miller et al. 1994](#)).

In contrast to its immunosuppressive properties, CRH has also been shown to enhance proinflammatory cytokine production in rodents and humans when administered peripherally or within the CNS. Chronic intracerebroventricular administration of CRH to rats leads to induction of IL-1 $\beta$  messenger RNA (mRNA) in splenocytes, and acute intravenous administration in humans has been reported to cause a fourfold increase in the induction of IL-1 $\alpha$  ([Labeur et al. 1995](#); [Schulte et al. 1994](#)). Similarly, the addition of CRH to in vitro mononuclear cell preparations induces the release of IL-1 and IL-6 ([Leu and Singh 1992](#); [Paez Pereda et al. 1995](#)). Both chronic and acute CRH infusion have also been reported to increase production of the immunoregulatory cytokine IL-2 in humans and rodents ([Labeur et al. 1995](#); [Schulte et al. 1994](#)). In addition to potential proinflammatory activities of CRH within the CNS, peripheral production of CRH has been demonstrated in inflammatory diseases such as ulcerative colitis and arthritis, in which it appears to act as a local proinflammatory agent ([Karalis et al. 1997](#); [Nishioka et al. 1996](#)).

Of all neurotransmitters or hormones known to modulate immune functioning, the actions of glucocorticoids, although complicated, are probably the best understood ([Raison et al. 2002](#)). Identified effects of glucocorticoids on the immune (and inflammatory) system include the following:

- Modulation of immune cell trafficking throughout the body ([Dhabhar et al. 1995](#))
- Enhancement of CMI by physiological concentrations of endogenous glucocorticoids ([Dhabhar and McEwen 1999](#);



[Dhabhar 2009a, 2009b, 2014](#))

- Promotion of Th2 (antibody) responses ([Elenkov and Chrousos 1999](#))
- Modulation of cell death (i.e., apoptosis) pathways ([McEwen et al. 1997](#))
- Inhibition of arachidonic acid pathway products (e.g., prostaglandins) that mediate inflammation and illness symptoms (e.g., fever) ([Goldstein et al. 1992](#))
- Inhibition of T cell- and NK cell-mediated cytotoxicity ([Raison et al. 2002](#))
- Inhibition of cytokine production and function through interaction of glucocorticoid receptors with transcription factors (NF- $\kappa$ B in particular), which in turn regulate the expression of cytokine genes and/or cytokine-inducible genes ([McKay and Cidlowski 1999](#))

Although glucocorticoids may actually enhance certain aspects of naturalistic immune functioning when produced for brief periods at low to moderate doses in the context of acute and/or mild stress, glucocorticoids in general play a primary role in restraining excessive or prolonged inflammatory activation ([Munck 1989](#)). This property has long been exploited by modern medicine for the treatment of autoimmune and other chronic inflammatory conditions, with the result that glucocorticoids remain a cornerstone of our anti-inflammatory armamentarium. Consistent with their pharmacological uses, glucocorticoids have been shown to be essential for inflammatory regulation in response to immune system activation. For example, neutralization of endogenous glucocorticoid function results in increased pathology and mortality in rodents exposed to lipopolysaccharide or to other inflammatory stimulators such as streptococcal cell wall antigen or myelin basic

protein ([Bertini et al. 1988](#); [Sternberg et al. 1989](#)). Similarly, rodents that have been rendered glucocorticoid deficient by adrenalectomy have markedly increased death rates following infection with murine cytomegalovirus, an effect that arises from unrestrained activity of the proinflammatory cytokine TNF- $\alpha$  ([Ruzek et al. 1999](#)).

---

## Effects of the Immune System on the Brain and Behavior

---

### Immune System-to-Brain Signaling Pathways

The field of psychoneuroimmunology is based on the existence of bidirectional communication pathways between the nervous, endocrine, and immune systems ([Ader 2007](#); [Miller et al. 2000](#)). This implies that just as the CNS is capable of modulating immunity, the immune system can alter functioning within the CNS. Although researchers historically were first interested in pathways by which the brain affects immunity, the past 10–15 years have seen a groundswell of interest in the ways in which the immune system contributes to the development of psychopathology ([Capuron and Miller 2011](#); [Steinberg et al. 2015](#)).

Underpinning this growing interest is an increasing appreciation for the multiple ways in which proinflammatory cytokines are able to signal the brain and change CNS function ([Table 5-2](#)). Although the brain was historically considered an “immune privileged” organ,

protected from immune system activity by the blood-brain barrier, it is now clear that cytokines released in the periphery rapidly affect CNS functioning via at least four pathways that are not mutually exclusive (see [Table 5-2](#)) ([Banks 2006](#); [Banks et al. 1995](#); [Maier et al. 1998](#); [Plotkin et al. 1996](#); [Quan 2006, 2014](#); [Raison et al. 2002](#); [Rivest et al. 2000](#)).

---

**TABLE 5-2. Evidence that cytokines can alter central nervous system function**

---

1. Cytokines released peripherally have access to the brain.
    - Passage through leaky regions in the blood-brain barrier (e.g., circumventricular organs)
    - Active transport
    - Activation of intermediary cell types (e.g., endothelial cells) that produce relevant second messengers (e.g., prostaglandins, nitric oxide)
    - Transmission of cytokine signals through afferent nerve fibers (e.g., vagus)
  2. A cytokine network exists within the brain.
    - Glia (especially microglia) and neurons express/produce cytokines and express cytokine receptors
  3. Cytokines have effects on neurotransmitter turnover, neuroendocrine function, synaptic plasticity, and behavior (sickness behavior).
- 

Once proinflammatory cytokines have gained access to the CNS through any of the routes outlined in [Table 5-2](#), the inflammatory signal appears to be amplified by a cytokine network within the brain itself ([Quan et al. 1999](#)).

It has already been noted that cytokines produced in the periphery stimulate the production of proinflammatory cytokines, such as IL-1, IL-6, and TNF- $\alpha$ , in a number of brain regions ([Dantzer and Kelley 2007](#); [Gatti and Bartfai 1993](#); [Layé et al. 1994](#); [Quan 2006, 2014](#); [Quan et al. 1999](#)). Receptors for proinflammatory cytokines are found in the brain, especially in areas of particular importance to homeostatic and emotional regulation, such as the hypothalamus and hippocampus ([Benveniste 1998](#)). Among neural cells, activated microglia are capable of producing significant numbers of proinflammatory cytokines, which in turn are potent activators of glial cells ([Schöbitz et al. 1994](#)). Of interest, growing evidence suggests that nonimmunological stressors can induce cytokine expression in the brain, an effect likely mediated by stress-induced activation of microglia ([Frank et al. 2007](#)). These data suggest that CNS cytokine pathways may participate in an organism's response to a wide variety of environmental perturbations. Consistent with this finding, proinflammatory cytokines have been implicated in the modulation of circadian functioning, especially the sleep-wake cycle ([Hohagen et al. 1993](#); [Opp 2005](#)).

## Sickness Behavior and the Development of Depression in the Medically Ill

It has long been known that major depressive disorder, as well as milder forms of mood disturbance, is many times more common in people with medical illness than in the general population ([Evans et al. 1999](#)). Although this higher

incidence is often ascribed to the overwhelming psychological stress that serious illness engenders, more recent theories have suggested that the immune system activation that typically accompanies medical illness may itself biologically predispose these patients to depression ([Dantzer et al. 2008, 2011](#); [Raison and Nemeroff 2000](#); [Udina et al. 2014](#)). Evidence for this theory comes from the observation that rates of depression are significantly elevated in a wide variety of medical conditions, including inflammatory and autoimmune disorders such as multiple sclerosis and rheumatoid arthritis, as well as in illnesses such as cardiovascular disease, diabetes, and cancer, which are increasingly being recognized as having an important inflammatory component ([Aggarwal et al. 2006](#); [Blake and Ridker 2002](#); [Currier and Nemeroff 2014](#); [Dantzer et al. 2008, 2011](#); [Evans et al. 2005](#)). Moreover, prospective studies of conditions characterized by episodic immune dysregulation, such as multiple sclerosis or herpes infection, typically find that depression immediately precedes, rather than follows, episodes of disease exacerbation, suggesting that depressive symptoms associated with these conditions may result from underlying immune system activity rather than from a psychological reaction to exacerbation of the illness ([Foley et al. 1992](#); [Hickie and Lloyd 1995](#)). Finally, as noted in the subsection “Effects of Depression on Immune Function,” numerous researchers have shown that plasma concentrations of proinflammatory cytokines are significantly higher in medically ill patients with major depressive disorder compared with similar patients without a mood disorder ([Raison et al. 2006](#)). For example, depressed patients with cancer show elevations in IL-6 ([Currier and Nemeroff 2014](#); [Musselman et al. 2001b](#)), and depressed patients with

acute coronary syndromes or chronic heart failure show elevations in C-reactive protein ([Andrei et al. 2007](#); [Lespérance et al. 2004](#)).

More direct evidence that inflammatory processes may contribute to psychopathology, especially in the context of medical illness, comes from many studies in humans and animals demonstrating that administration of proinflammatory cytokines reliably induces changes in mood, cognition, and behavior similar to those commonly observed in patients with mood and anxiety disorders, as well as in psychophysical conditions such as CFS and fibromyalgia ([Dantzer and Kelley 2007](#); [Raison et al. 2006](#)). This constellation of immune-induced changes, referred to as *sickness syndrome* or *sickness behavior*, consists of dysphoria, anhedonia, fatigue, social withdrawal, hyperalgesia, and cognitive and sleep disturbances, as well as decreased appetite and libido ([Dantzer et al. 2008, 2011](#); [Kent et al. 1992](#)). Although seen in response to infection, the full syndrome can be reproduced in animals and humans by administration of innate immune cytokines, such as interferon-alpha (IFN- $\alpha$ ), IL-1, TNF- $\alpha$ , and IL-6, as well as IL-2, even in the absence of infection ([Raison et al. 2002](#)).

Blocking cytokine activity with an IL-1 receptor antagonist,  $\alpha$ -melanocyte-stimulating hormone, or IL-10 diminishes or prevents sickness behavior in laboratory animals, even when such behavior develops as a result of psychological stress ([Milligan et al. 1998](#)). Similarly, etanercept, a novel agent that blocks TNF- $\alpha$  activity, has been reported to improve energy and overall emotional functioning in patients with rheumatoid arthritis, a condition characterized by increased proinflammatory cytokine activity ([Bortolato et al. 2015](#); [Mathias et al. 2000](#);

[Schmidt et al. 2014](#)). TNF antagonists have recently been shown to reduce depressive symptoms in patients with various autoimmune conditions ([Fleming et al. 2015](#); [Persoons et al. 2005](#); [Tyring et al. 2006](#)). Further evidence that cytokine-induced behavioral toxicity is related to major depressive disorder comes from studies showing that in humans and animals, antidepressants are able to abolish or attenuate the development of sickness behavior in response to cytokine administration ([Musselman et al. 2001a](#); [Yirmiya et al. 2001](#)).

## Pathways by Which Inflammatory Cytokines Produce Neuropsychiatric Disturbance

In keeping with the observation that antidepressants mitigate emotional and behavioral symptoms resulting from immune system activation, significant evidence demonstrates that inflammatory cytokines affect neurotransmitters and neuroendocrine pathways that are regulated by currently available antidepressants and that have been implicated in the pathophysiology of depression and other stress-related neuropsychiatric disorders. It is increasingly recognized that these effects on the CNS and its outflow pathways may provide a physiological basis for the observation that immune activation frequently produces neuropsychiatric disturbance ([Miller and Raison 2016](#)) ([Table 5-3](#)).

---

**TABLE 5-3. Potential mechanisms by which cytokines may influence behavior**

---

Activation of corticotropin-releasing hormone pathways  
Alteration of monoamine metabolism  
Induction of the euthyroid sick syndrome  
Disruption of glucocorticoid receptor signaling  
Alteration of regional brain activity  
Inhibition of relevant growth factors

---

## **Effects of Inflammatory Cytokines on Monoamine Neurotransmitters**

In laboratory animals, acute intracerebral administration of IL-1 produces a rapid and significant increase in norepinephrine and serotonin (5-hydroxytryptamine [5-HT]) turnover in several brain regions ([Linthorst et al. 1995a, 1995b](#)). Very little is known about the effect of chronic proinflammatory cytokine exposure on the functioning of monoamine systems in either animals or humans. However, cytokines, including IFN- $\alpha$ , have been shown to diminish 5-HT availability as a result of cytokine-mediated enhancement of the activity of indoleamine 2,3-dioxygenase (IDO), an enzyme that shunts tryptophan metabolism away from 5-HT and toward kynurenine and quinolinic acid, which are known to have neurotoxic properties ([Dantzer and Kelley 2007](#); [Raison et al. 2006](#)). Tryptophan is the primary precursor of 5-HT, and tryptophan depletion has been associated with the precipitation of mood disturbances in vulnerable patients ([Moore et al. 2000](#)). Moreover, significant evidence suggests that serotonergic neurotransmission is decreased in many patients with depression ([Owens and Nemeroff 1998](#)). It has also been shown that proinflammatory cytokines, via p38 mitogen-activated protein kinase



(MAPK)-linked pathways, can increase the expression and function of synaptic reuptake pumps for serotonin (and norepinephrine), potentially further contributing to reduced synaptic availability of mood-relevant monoamines (Zhu et al. 2005, 2006).

Of interest, the development of major depressive disorder in the context of chronic IFN- $\alpha$  treatment has been shown to correlate closely with decreased plasma concentrations of tryptophan, possibly as a result of increased IDO activity, consistent with the idea that cytokine-induced decrements in 5-HT availability may contribute to the development of depression (Capuron et al. 2002b). Furthermore, treatment with the selective serotonin reuptake inhibitor (SSRI) paroxetine attenuates the behavioral consequences of IFN- $\alpha$ -mediated tryptophan depletion (Capuron et al. 2003a). In addition to the effects of chronic cytokine exposure on serotonergic transmission, both IL-2 and IFN- $\alpha$ , when they are administered chronically, have been reported to alter dopamine metabolism, and IFN- $\alpha$  has been shown to lead to altered metabolic activity in brain regions high in dopaminergic neurocircuits, including the basal ganglia (Capuron et al. 2007; Lacosta et al. 2000; Shuto et al. 1997).

## Effects of Inflammatory Cytokines on the Thyroid Axis

Medical illness is often associated with a state of functional thyroid deficiency known as *euthyroid sick syndrome* (Papanicolaou 2000). In its early stages, euthyroid sick syndrome is characterized by normal thyroid-stimulating hormone and thyroxine (T<sub>4</sub>) levels but reduced levels of triiodothyronine (T<sub>3</sub>), which is the more biologically active

form of thyroid hormone. In later stages of euthyroid sick syndrome,  $T_4$  levels are also reduced. Evidence suggests that proinflammatory cytokines promote this condition through direct effects on the thyroid gland, as well as through inhibition of enzymes responsible for peripheral conversion of  $T_4$  to  $T_3$ , especially in the liver ([Papanicolaou 2000](#)). It is well known that decreased thyroid functioning is associated with emergence of depressive symptoms, and functional abnormalities of the thyroid axis are found in many patients with major depressive disorder who do not have clinically obvious thyroid disease ([Musselman and Nemeroff 1996](#)).

### **Effects of Inflammatory Cytokines on the Hypothalamic-Pituitary-Adrenal Axis**

Inflammatory cytokines have well-described effects on the HPA axis that are consistent with changes frequently seen in patients with major depressive disorder, including increased production of CRH and cortisol and decreased tissue sensitivity to glucocorticoid hormones ([Capuron et al. 2003a](#); [Hasler et al. 2004](#); [Pace et al. 2007](#); Silverman et al. 2005). Although cytokines have been shown to be capable of activating the HPA axis at multiple levels, with a resultant increase in glucocorticoid release, significant evidence suggests that a major final common pathway for cytokine activation involves stimulation of CRH production in the paraventricular nucleus of the hypothalamus ([Besedovsky and del Rey 1996](#)). Several lines of evidence suggest that this increase in CRH activity may contribute to cytokine-induced depression or sickness behavior ([Miller and Raison 2016](#)). CRH has behavioral effects in laboratory animals that are similar to those seen in patients with depression

and/or sickness behavior, including alterations in appetite, activity, and sleep ([Owens and Nemeroff 1991](#)). Patients with major depressive disorder frequently demonstrate increased CRH production, as assessed by increased CRH in CSF, increased mRNA in the paraventricular nucleus, downregulated frontal CRH receptors, and a blunted adrenocorticotrophic hormone response to CRH challenge (likely reflecting downregulation of pituitary CRH receptors) ([Owens and Nemeroff 1993](#)).

Agents that block the CRH type I receptor have been shown to have antidepressant and anxiolytic effects in humans ([Zobel et al. 2000](#)). In laboratory animals, blocking CRH reverses some of the behavioral sequelae of proinflammatory cytokine administration ([Dantzer 2001](#)). Indirect evidence for a role of CRH in cytokine-induced depression in humans comes from a study in which individuals who subsequently developed depression during IFN- $\alpha$  administration exhibited significantly higher adrenocorticotrophic hormone and cortisol responses to the first injection of IFN- $\alpha$  compared with control subjects ([Capuron et al. 2003b](#)). These findings suggest that sensitized CRH pathways may serve as a vulnerability factor for cytokine-induced behavioral changes.

In addition to direct stimulatory effects on CRH within the CNS, in vivo and in vitro studies suggest that inflammation may induce resistance to circulating glucocorticoids in nervous, endocrine, and immune system tissues ([Miller and Raison 2016](#); [Pariante and Miller 2001](#); [Raison and Miller 2003b](#)). This effect is of great potential relevance, given the high rates of relative glucocorticoid resistance in HPA axis tissues (as assessed in vivo with the DST or the dexamethasone-CRH stimulation test) and the immune system (as measured in vitro) found in patients with major

depressive disorder as well as in rodents and humans exposed to chronic and/or severe stressors ([Holsboer 2000](#)). Also supporting a role for cytokines in the induction of glucocorticoid resistance is the observation that many chronic inflammatory conditions, including steroid-resistant asthma, rheumatoid arthritis, multiple sclerosis, and HIV infection, are characterized by a decrease in sensitivity to glucocorticoids ([Raison et al. 2002](#)). In HIV infection, glucocorticoid resistance has been shown to correlate with increased IFN- $\alpha$  plasma levels ([Norbiato et al. 1998](#)).

There are several mechanisms by which proinflammatory cytokines might disrupt glucocorticoid receptor (GR) function and contribute to glucocorticoid resistance. In addition to downregulating the expression of GR protein, proinflammatory cytokines have been found to increase the expression of the inert  $\beta$  isoform of the GR ([Oakley et al. 1996](#)). Exposure of cells that constitutively express both GR- $\alpha$  (the active isoform) and GR- $\beta$  to either TNF- $\alpha$  or IL-1 $\beta$  in vitro results in a marked increase in GR- $\beta$  production, which is associated with the development of glucocorticoid resistance, as evidenced by a significant reduction in dexamethasone-stimulated activity of a GR-sensitive reporter gene in cytokine-treated cells ([Webster et al. 2001](#)). That overproduction of the negative GR- $\beta$  isoform has a clinically relevant effect on glucocorticoid sensitivity is suggested by several studies documenting that patients with a variety of inflammatory and immune system disorders, including asthma, ulcerative colitis, and chronic lymphocytic leukemia, whose conditions are resistant to steroid treatment demonstrate a significantly increased GR- $\beta$  to GR- $\alpha$  ratio ([Honda et al. 2000](#); [Leung 1997](#); [Shahidi et al. 1999](#); [Sousa et al. 2000](#)).

Another mechanism by which inflammatory cytokines may attenuate GR signal transduction and thereby cause glucocorticoid resistance is through induction of inflammatory signaling pathways that directly influence GR function ([Pace et al. 2007](#)). For example, adding IL-1 $\alpha$  to an in vitro preparation of mouse fibroblast cells has been shown to suppress the ability of dexamethasone to induce translocation of the GR from the cytoplasm to its site of action in the nucleus ([Pariente et al. 1999](#)). This IL-1 $\alpha$ -mediated blockade of GR translocation from the cytoplasm to the cellular nucleus inhibits GR activity, as indicated by a decrease in the ability of dexamethasone to activate a glucocorticoid-sensitive reporter gene construct. One of the signaling pathways involved in this effect is p38 MAPK, which has been shown to phosphorylate the GR ([X. Wang et al. 2004](#)). Other inflammatory signaling pathways—including NF- $\kappa$ B, Jun N-terminal kinase (JNK), and STAT5—have also been shown to alter GR function ([Pace et al. 2007](#)).

## Effects of Anti-Inflammatory Agents on Depression

Given that inflammatory factors have been shown to contribute to depression, it has been proposed that anti-inflammatory agents may also have antidepressant actions. It appears that this is the case for patients with inflammatory disorders (e.g., psoriasis, ankylosing spondylitis) who also show increased levels of depression ([Arisoy et al. 2013](#); [Fleming et al. 2015](#); [Krishnan et al. 2007](#); [Tyring et al. 2006](#)) and patients with depression who also show increased levels of proinflammatory markers

([Köhler et al. 2014](#); [Raison et al. 2013](#)). However, anti-inflammatory medications do not appear to have antidepressant effects for patients who do not show increased levels of inflammation. Indeed, the use of anti-inflammatory agents in such patients may actually impair the placebo effect that is thought to be important for antidepressant effectiveness ([Miller and Raison 2016](#); [Raison et al. 2013](#)). Given these findings, insightful reviews have highlighted the need for elucidating markers to identify subgroups of depressed patients in whom anti-inflammatory agents might have antidepressant activity ([Miller and Raison 2016](#); [Schmidt et al. 2016](#)).

## Antidepressants and the Immune System

The term *antidepressant* has been depicted more than once as a misnomer, given the wide spectrum of activity evinced by these pharmacological agents. Adding to this activity spectrum are findings that antidepressants have clear immunomodulatory effects in animals and humans. In general, antidepressants have been found to decrease immune responsiveness ([Eyre et al. 2016](#); [Kenis and Maes 2002](#); [Schmidt et al. 2016](#)). Because of this effect, antidepressant agents may be of benefit for a wide range of symptoms that arise in the context of immune activation. Of special interest, given the ability of inflammatory cytokines to induce sickness behavior and/or major depressive disorder, a number of antidepressants have been reported to attenuate proinflammatory cytokine production, not just from peripheral immune cells ([Maes 1999](#)) but also from within the CNS, where the tricyclic antidepressant

desipramine has been reported to diminish TNF- $\alpha$  release within the locus coeruleus ([Ignatowski and Spengler 1994](#)). Also of interest in this regard, the antidepressant efficacy of desipramine in rats during the forced-swim test has been shown to be dependent on reductions in neuronal production of TNF- $\alpha$  and can be reversed by coadministration of exogenous TNF- $\alpha$  with the antidepressant ([Reynolds et al. 2004](#)). Desipramine has also been shown to reduce peripheral TNF- $\alpha$  production in response to lipopolysaccharide administration—an effect that was associated with abrogation of the depressive-like behavioral effects of lipopolysaccharide ([Shen et al. 1999](#)). The heterocyclic antidepressant bupropion has similarly been noted to markedly diminish TNF- $\alpha$  production following lipopolysaccharide administration in mice ([Brustolim et al. 2006](#)). Of note, concomitant with attenuating proinflammatory cytokine production, antidepressants enhance production of the anti-inflammatory cytokine IL-10 ([Maes et al. 1999d](#)).

In addition to potential direct effects on cytokine production, antidepressants affect neuroendocrine and neurotransmitter systems in ways known to diminish inflammatory activity. For example, all antidepressants appear to downregulate the overproduction of CRH and cortisol that frequently occurs in the context of major depressive disorder. Much evidence suggests that this downregulation results from the ability of antidepressants to enhance glucocorticoid signaling via increased glucocorticoid receptor functioning, which in turn leads to restoration of glucocorticoid-mediated inhibitory control of the HPA axis ([Pariante and Miller 2001](#)). Because CRH has been shown to directly stimulate proinflammatory cytokine production, antidepressants may modulate inflammatory

activity in part by diminishing CRH production. Glucocorticoid receptors, in addition to inhibiting CRH release in the hypothalamus, also mediate the well-characterized anti-inflammatory properties of glucocorticoids. It is likely that antidepressants decrease inflammatory activity in part via their ability to potentiate glucocorticoid receptor functioning ([Pariente and Miller 2001](#)). Antidepressants also normalize the hyperactivity of the locus coeruleus and sympathetic nervous system frequently seen in major depressive disorder ([Ressler and Nemeroff 1999](#)). Because catecholamines have been shown to enhance proinflammatory activity, the normalizing effect of antidepressants on catecholaminergic functioning would be expected to result in diminished inflammatory activity. Finally, antidepressants are known to enhance functioning in intracellular second-messenger systems (such as the cyclic adenosine monophosphate cascade) known to suppress the activation of genes that encode for the production of proinflammatory cytokines ([Duman et al. 2001](#)).

It is clear from studies in laboratory animals and humans that antidepressants effectively diminish many physical, emotional, cognitive, and behavioral symptoms that arise in the context of immune system activation ([Capuron et al. 2002a](#)). In rodents, pretreatment with antidepressants has been shown to prevent the development or reduce the severity of sickness behavior in response to pathogen or cytokine exposure ([Yirmiya et al. 2001](#)). In humans, pretreatment with an antidepressant has been shown in a double-blind, placebo-controlled trial to significantly reduce the development of major depressive disorder among patients receiving high doses of the proinflammatory cytokine IFN- $\alpha$  for the treatment of malignant melanoma



([Musselman et al. 2001a](#)). In this study, 45% of patients receiving placebo developed major depressive disorder within 3 months of starting IFN- $\alpha$ , compared with only 11% of those receiving the SSRI paroxetine. Of interest, however, paroxetine was not equally efficacious for all of the symptoms associated with sickness behavior. Specifically, paroxetine significantly reduced the symptoms of depressed mood, anxiety, and poor cognitive functioning but was no more effective than placebo in reducing somatic or neurovegetative symptoms, such as fatigue and anorexia, suggesting that these symptom domains may have nonoverlapping etiologies ([Capuron et al. 2002a](#)). Consistent with this finding, neurovegetative symptoms tended to develop early (and to persist) in the course of IFN- $\alpha$  treatment in the majority of patients, whereas symptoms of depressed mood, anxiety, and cognitive disturbance tended to develop insidiously over weeks or months of treatment in a smaller percentage of patients ([Trask et al. 2000](#)). The success of pretreatment strategies in preventing the development of neuropsychiatric disorders in medically ill patients at high risk for mood disorders is intriguing and suggests that the use of prophylactic antidepressants should be considered in other medical contexts, such as for patients about to undergo treatment with radiation and/or chemotherapy, as well as for patients about to undergo major surgery.

There are also data to suggest that antipsychotics, although not as well studied as antidepressants, may have immunological effects relevant to their mechanism of action. Intriguing in this regard is a study demonstrating increased antipsychotic efficacy in patients with schizophrenia treated with the combination of the cyclooxygenase-2 inhibitor celecoxib (an anti-inflammatory drug)

and risperidone versus risperidone alone ([Müller et al. 2002](#)). It has also been suggested that proinflammatory factors are elevated in the systemic circulation during the first episode of schizophrenia and that antipsychotic treatment induces a decrease in these factors ([Stefanović et al. 2015](#)). However, other studies have not observed anti-inflammatory effects of antipsychotics ([Fernandes et al. 2016](#)).

---

## Conclusion

---

It is important to appreciate that mental and physical health are maintained through multidirectional interactions among psychological factors and the nervous, endocrine, and immune systems and other physiological systems of the body. Thus, it should come as no surprise that dysregulated multisystem interactions are often involved in mediating the underlying pathology of numerous diseases. In this chapter we have reviewed a few important examples of ways in which the nervous and endocrine systems affect immune function and the ways in which the immune system in turn affects the endocrine and nervous systems and behavior in the context of health and disease. Much work remains to be done to further elucidate mechanisms and translate findings from bench to bedside. However, elucidation of psychoneuroendocrine-immune pathways and mechanisms is likely to be critically useful for restoring health in the presence of disease or promoting health in the absence of disease.

---

# References

---

- Ader R: Psychoneuroimmunology, 4th Edition. Burlington, MA, Elsevier Academic Press, 2007
- Ader R, Cohen N: Behaviorally conditioned immunosuppression. *Psychosom Med* 37(4):333-340, 1975 1162023
- Aggarwal BB, Shishodia S, Sandur SK, et al: Inflammation and cancer: how hot is the link? *Biochem Pharmacol* 72(11):1605-1621, 2006 16889756
- Alesci S, Martinez PE, Kelkar S, et al: Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab* 90(5):2522-2530, 2005 15705924
- Altavilla D, Guarini S, Bitto A, et al: Activation of the cholinergic anti-inflammatory pathway reduces NF-kappaB activation, blunts TNF-alpha production, and protects against splanchnic artery occlusion shock. *Shock* 25(5):500-506, 2006 16680015
- Altemus M, Cloitre M, Dhabhar FS: Enhanced cellular immune response in women with PTSD related to childhood abuse. *Am J Psychiatry* 160(9):1705-1707, 2003 12944352
- American Psychological Association: Stress in America. Washington, DC, American Psychological Association, 2007, pp 1-19
- Andrei AM, Fraguas R Jr, Telles RM, et al: Major depressive disorder and inflammatory markers in elderly patients with heart failure. *Psychosomatics* 48(4):319-324, 2007 17600168
- Antoni MH, Lutgendorf SK, Cole SW, et al: The influence of bio-behavioural factors on tumour biology: pathways and

- mechanisms. *Nat Rev Cancer* 6(3):240-248, 2006 16498446
- Antonioli M, Rybka J, Carvalho LA: Neuroimmune endocrine effects of antidepressants. *Neuropsychiatr Dis Treat* 8:65-83, 2012 22347798
- Arisoy O, Bes C, Cifci C, et al: The effect of TNF-alpha blockers on psychometric measures in ankylosing spondylitis patients: a preliminary observation. *Rheumatol Int* 33(7):1855-1864, 2013 23334426
- Aschbacher K, Epel E, Wolkowitz OM, et al: Maintenance of a positive outlook during acute stress protects against pro-inflammatory reactivity and future depressive symptoms. *Brain Behav Immun* 26(2):346-352, 2012 22119400
- Baker DG, Ekhtor NN, Kasckow JW, et al: Plasma and cerebrospinal fluid interleukin-6 concentrations in posttraumatic stress disorder. *Neuroimmunomodulation* 9(4):209-217, 2001 11847483
- Banks WA: The blood-brain barrier in psychoneuroimmunology. *Neurol Clin* 24(3):413-419, 2006 16877115
- Banks WA, Kastin AJ, Broadwell RD: Passage of cytokines across the blood-brain barrier. *Neuroimmunomodulation* 2(4):241-248, 1995 8963753
- Bellinger D, Felten SY, Lorton D, et al: Innervation of the lymphoid organs and neurotransmitter-lymphocyte interactions, in *Immunology of the Nervous System*. Edited by Keane RW, Hickey WF. New York, Oxford University Press, 1997, pp 226-332
- Ben-Eliyahu S, Page GG, Schleifer SJ: Stress, NK cells, and cancer: Still a promissory note. *Brain Behav Immun* 21(7):881-887, 2007 17662574
- Benveniste EN: Cytokine actions in the central nervous system. *Cytokine Growth Factor Rev* 9(3-4):259-275, 1998 9918124

- Bertini R, Bianchi M, Ghezzi P: Adrenalectomy sensitizes mice to the lethal effects of interleukin 1 and tumor necrosis factor. *J Exp Med* 167(5):1708-1712, 1988 3259257
- Besedovsky HO, del Rey A: Immune-neuro-endocrine interactions: facts and hypotheses. *Endocr Rev* 17(1):64-102, 1996 8641224
- Blake GJ, Ridker PM: Tumour necrosis factor-alpha, inflammatory biomarkers, and atherogenesis. *Eur Heart J* 23(5):345-347, 2002 11846489
- Blecha F, Barry RA, Kelley KW: Stress-induced alterations in delayed-type hypersensitivity to SRBC and contact sensitivity to DNFB in mice. *Proc Soc Exp Biol Med* 169(2):239-246, 1982 7063505
- Bluestone JA, Tang Q: How do CD4+ CD25+ regulatory T cells control autoimmunity? *Curr Opin Immunol* 17(6):638-642, 2005 16209918
- Blume J, Douglas SD, Evans DL: Immune suppression and immune activation in depression. *Brain Behav Immun* 25(2):221-229, 2011 20955778
- Borish L, Schmalting K, DiClementi JD, et al: Chronic fatigue syndrome: identification of distinct subgroups on the basis of allergy and psychologic variables. *J Allergy Clin Immunol* 102(2):222-230, 1998 9723665
- Borovikova LV, Ivanova S, Zhang M, et al: Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 405(6785):458-462, 2000 10839541
- Bortolato B, Carvalho AF, Soczynska JK, et al: The involvement of TNF-alpha in cognitive dysfunction associated with major depressive disorder: an opportunity for domain specific treatments. *Curr Neuropsychopharmacol* 13(5):558-576, 2015 26467407
- Bower JE, Irwin MR: Mind-body therapies and control of inflammatory biology: a descriptive review. *Brain Behav Immun* 51:1-11, 2016 26116436

- Bruce TO: Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. *Curr Psychiatry Rep* 10(3):258-264, 2008 18652795
- Brustolim D, Ribeiro-dos-Santos R, Kast RE, et al: A new chapter opens in anti-inflammatory treatments: the antidepressant bupropion lowers production of tumor necrosis factor-alpha and interferon-gamma in mice. *Int Immunopharmacol* 6(6):903-907, 2006 16644475
- Cannon JG, Angel JB, Ball RW, et al: Acute phase responses and cytokine secretion in chronic fatigue syndrome. *J Clin Immunol* 19(6):414-421, 1999 10634215
- Capuron L, Miller AH: Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* 130(2):226-238, 2011 21334376
- Capuron L, Gunnick JF, Musselman DL, et al: Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 26(5):643-652, 2002a 11927189
- Capuron L, Ravaud A, Neveu PJ, et al: Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol Psychiatry* 7(5):468-473, 2002b 12082564
- Capuron L, Neirauter G, Musselman DL, et al: Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. *Biol Psychiatry* 54(9):906-914, 2003a 14573318
- Capuron L, Raison CL, Musselman DL, et al: Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am J Psychiatry* 160(7):1342-1345, 2003b 12832253
- Capuron L, Pagnoni G, Demetrashvili MF, et al: Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy.

Neuropsychopharmacology 32(11):2384-2392, 2007  
17327884

Caroleo MC, Pulvirenti L, Arbitrio M, et al: Evidence that CRH microinfused into the locus coeruleus decreases cell-mediated immune response in rats. *Funct Neurol* 8(4):271-277, 1993 8314119

Coe CL, Lubach G, Ershler WB: Immunological consequences of maternal separation in infant primates, in *Infant Stress and Coping*. Edited by Lewis M, Worobey J. New York, Jossey-Bass, 1989, pp 64-91

Cohen S, Tyrrell DA, Smith AP: Psychological stress and susceptibility to the common cold. *N Engl J Med* 325(9):606-612, 1991 1713648

Currier MB, Nemeroff CB: Depression as a risk factor for cancer: from pathophysiological advances to treatment implications. *Annu Rev Med* 65:203-221, 2014 24215332

Czura CJ, Rosas-Ballina M, Tracey KJ: Cholinergic regulation of inflammation, in *Psychoneuroimmunology*, 4th Edition. Edited by Ader R. Burlington, MA, Elsevier Academic Press, 2007, pp 85-96

Daftarian PM, Kumar A, Kryworuchko M, et al: IL-10 production is enhanced in human T cells by IL-12 and IL-6 and in monocytes by tumor necrosis factor-alpha. *J Immunol* 157(1):12-20, 1996 8683105

Dantzer R: Cytokine-induced sickness behavior: where do we stand? *Brain Behav Immun* 15(1):7-24, 2001 11259077

Dantzer R, Kelley KW: Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 21(2):153-160, 2007 17088043

Dantzer R, O'Connor JC, Freund GG, et al: From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9(1):46-56, 2008 18073775

- Dantzer R, O'Connor JC, Lawson MA, et al: Inflammation-associated depression: from serotonin to kynurenine. *Psychoneuroendocrinology* 36(3):426-436, 2011 21041030
- de Jonge WJ, van der Zanden EP, The FO, et al: Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat Immunol* 6(8):844-851, 2005 16025117
- Dhabhar FS: Stress-induced enhancement of cell-mediated immunity. *Ann N Y Acad Sci* 840:359-372, 1998 9629263
- Dhabhar FS: Stress-induced augmentation of immune function—the role of stress hormones, leukocyte trafficking, and cytokines. *Brain Behav Immun* 16(6):785-798, 2002 12480507
- Dhabhar FS: Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. *Neuroimmunomodulation* 16(5):300-317, 2009a 19571591
- Dhabhar FS: A hassle a day may keep the pathogens away: the fight-or-flight stress response and the augmentation of immune function. *Integr Comp Biol* 49(3):215-236, 2009b 21665815
- Dhabhar FS: Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res* 58(2-3):193-210, 2014 24798553
- Dhabhar FS, McEwen BS: Stress-induced enhancement of antigen-specific cell-mediated immunity. *J Immunol* 156(7):2608-2615, 1996 8786326
- Dhabhar FS, McEwen BS: Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. *Brain Behav Immun* 11(4):286-306, 1997 9512816
- Dhabhar FS, McEwen BS: Enhancing versus suppressive effects of stress hormones on skin immune function. *Proc Natl Acad Sci U S A* 96(3):1059-1064, 1999 9927693



- Dhabhar FS, Viswanathan K: Short-term stress experienced at time of immunization induces a long-lasting increase in immunologic memory. *Am J Physiol Regul Integr Comp Physiol* 289(3):R738–R744, 2005 15890793
- Dhabhar FS, Miller AH, McEwen BS, et al: Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms. *J Immunol* 154(10):5511–5527, 1995 7730652
- Dhabhar FS, Miller AH, McEwen BS, et al: Stress-induced changes in blood leukocyte distribution. Role of adrenal steroid hormones. *J Immunol* 157(4):1638–1644, 1996 8759750
- Dhabhar FS, Satoskar AR, Bluethmann H, et al: Stress-induced enhancement of skin immune function: a role for gamma interferon. *Proc Natl Acad Sci U S A* 97(6): 2846–2851, 2000 10706626
- Dhabhar FS, Burke HM, Epel ES, et al: Low serum IL-10 concentrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. *J Psychiatr Res* 43(11):962–969, 2009 19552919
- Dhabhar FS, Malarkey WB, Neri E, et al: Stress-induced redistribution of immune cells—from barracks to boulevards to battlefields: a tale of three hormones—Curt Richter Award winner. *Psychoneuroendocrinology* 37(9):1345–1368, 2012 22727761
- Downing JE, Miyan JA: Neural immunoregulation: emerging roles for nerves in immune homeostasis and disease. *Immunol Today* 21(6):281–289, 2000 10825740
- Duman RS, Nakagawa S, Malberg J: Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology* 25(6):836–844, 2001 11750177
- Edwards KM, Burns VE, Reynolds T, et al: Acute stress exposure prior to influenza vaccination enhances antibody response in women. *Brain Behav Immun* 20(2):159–168, 2006 16102936

- Edwards KM, Burns VE, Carroll D, et al: The acute stress-induced immunoenhancement hypothesis. *Exerc Sport Sci Rev* 35(3):150-155, 2007 17620934
- Edwards KM, Burns VE, Adkins AE, et al: Meningococcal A vaccination response is enhanced by acute stress in men. *Psychosom Med* 70(2):147-151, 2008 18256346
- Elenkov IJ, Chrousos GP: Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends Endocrinol Metab* 10(9):359-368, 1999 10511695
- Evans DL, Staab JP, Petitto JM, et al: Depression in the medical setting: biopsychological interactions and treatment considerations. *J Clin Psychiatry* 60 (suppl 4):40-55, discussion 56, 1999 10086482
- Evans DL, Charney DS, Lewis L, et al: Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 58(3):175-189, 2005 16084838
- Eyre HA, Lavretsky H, Kartika J, et al: Modulatory effects of antidepressant classes on the innate and adaptive immune system in depression. *Pharmacopsychiatry* 49(3):85-96, 2016 26951496
- Fagundes CP, Glaser R, Kiecolt-Glaser JK: Stressful early life experiences and immune dysregulation across the lifespan. *Brain Behav Immun* 27(1):8-12, 2013 22771426
- Fang Y, Sharp GC, Braley-Mullen H: Interleukin-10 promotes resolution of granulomatous experimental autoimmune thyroiditis. *Am J Pathol* 172(6):1591-1602, 2008 18467701
- Fenton WS, Stover ES: Mood disorders: cardiovascular and diabetes comorbidity. *Curr Opin Psychiatry* 19(4):421-427, 2006 16721175
- Fernandes BS, Steiner J, Bernstein HG, et al: C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. *Mol Psychiatry* 21(4):554-564, 2016 26169974

- Finn OJ: Cancer immunology. *N Engl J Med* 358(25):2704-2715, 2008 18565863
- Fleming P, Roubille C, Richer V, et al: Effect of biologics on depressive symptoms in patients with psoriasis: a systematic review. *J Eur Acad Dermatol Venereol* 29(6):1063-1070, 2015 25490866
- Foley FW, Traugott U, LaRocca NG, et al: A prospective study of depression and immune dysregulation in multiple sclerosis. *Arch Neurol* 49(3):238-244, 1992 1536625
- Ford DE, Erlinger TP: Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 164(9):1010-1014, 2004 15136311
- Frank MG, Baratta MV, Sprunger DB, et al: Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. *Brain Behav Immun* 21(1):47-59, 2007 16647243
- Fraser-Smith N, Lespérance F, Irwin MR, et al: Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes. *Biol Psychiatry* 62(4):302-308, 2007 17210140
- Gatti S, Bartfai T: Induction of tumor necrosis factor-alpha mRNA in the brain after peripheral endotoxin treatment: comparison with interleukin-1 family and interleukin-6. *Brain Res* 624(1-2):291-294, 1993 8252403
- Glaser R, Kiecolt-Glaser JK: Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol* 5(3):243-251, 2005 15738954
- Goldstein DS, McEwen B: Allostasis, homeostats, and the nature of stress. *Stress* 5(1):55-58, 2002 12171767
- Goldstein R, Bowen DL, Fauci AS: Adrenal corticosteroids, in *Inflammation: Basic Principles and Clinical Correlates*.

- Edited by Gallin JI, Goldstein IM, Snyderman R. New York, Raven, 1992, pp 1061-1082
- Guardado P, Olivera A, Rusch HL, et al: Altered gene expression of the innate immune, neuroendocrine, and nuclear factor-kappa B (NF-kappaB) systems is associated with posttraumatic stress disorder in military personnel. *J Anxiety Disord* 38:9-20, 2016 26751122
- Guarini S, Altavilla D, Cainazzo MM, et al: Efferent vagal fibre stimulation blunts nuclear factor-kappaB activation and protects against hypovolemic hemorrhagic shock. *Circulation* 107(8):1189-1194, 2003 12615800
- Gupta S, Aggarwal S, See D, Starr A: Cytokine production by adherent and non-adherent mononuclear cells in chronic fatigue syndrome. *J Psychiatr Res* 31(1):149-156, 1997 9201656
- Hasler G, Drevets WC, Manji HK, et al: Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29(10):1765-1781, 2004 15213704
- Heim C, Owens MJ, Plotsky PM, et al: The role of early adverse life events in the etiology of depression and posttraumatic stress disorder. Focus on corticotropin-releasing factor. *Ann N Y Acad Sci* 821:194-207, 1997 9238204
- Herbert TB, Cohen S: Depression and immunity: a meta-analytic review. *Psychol Bull* 113(3):472-486, 1993 8316610
- Hickie I, Lloyd A: Are cytokines associated with neuropsychiatric syndromes in humans? *Int J Immunopharmacol* 17(8):677-683, 1995 8847162
- Hickie I, Hickie C, Lloyd A, et al: Impaired in vivo immune responses in patients with melancholia. *Br J Psychiatry* 162:651-657, 1993 8149117
- Hickie I, Hickie C, Bennett B, et al: Biochemical correlates of in vivo cell-mediated immune dysfunction in patients

- with depression: a preliminary report. *Int J Immunopharmacol* 17(8):685-690, 1995 8847163
- Hohagen F, Timmer J, Weyerbrock A, et al: Cytokine production during sleep and wakefulness and its relationship to cortisol in healthy humans. *Neuropsychobiology* 28(1-2):9-16, 1993 8255417
- Holsboer F: The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23(5):477-501, 2000 11027914
- Honda M, Orii F, Ayabe T, et al: Expression of glucocorticoid receptor beta in lymphocytes of patients with glucocorticoid-resistant ulcerative colitis. *Gastroenterology* 118(5):859-866, 2000 10784585
- Huston JM, Ochani M, Rosas-Ballina M, et al: Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. *J Exp Med* 203(7):1623-1628, 2006 16785311
- Ignatowski TA, Spengler RN: Tumor necrosis factor-alpha: presynaptic sensitivity is modified after antidepressant drug administration. *Brain Res* 665(2):293-299, 1994 7895065
- Irwin MR: Human psychoneuroimmunology: 20 years of discovery. *Brain Behav Immun* 22(2):129-139, 2008 17911004
- Irwin MR: Why sleep is important for health: a psychoneuroimmunology perspective. *Annu Rev Psychol* 66:143-172, 2015 25061767
- Irwin MR, Miller AH: Depressive disorders and immunity: 20 years of progress and discovery. *Brain Behav Immun* 21(4):374-383, 2007 17360153
- Irwin MR, Rothmundt M: Clinical psychoneuroimmunology. *Handb Clin Neurol* 106:211-225, 2012 22608623
- Irwin M, Hauger RL, Brown M, et al: CRF activates autonomic nervous system and reduces natural killer

- cytotoxicity. *Am J Physiol* 255(5 Pt 2):R744–R747, 1988 2847561
- Irwin M, McClintick J, Costlow C, et al: Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB J* 10(5):643–653, 1996 8621064
- Irwin M, Costlow C, Williams H, et al: Cellular immunity to varicella-zoster virus in patients with major depression. *J Infect Dis* 178 (suppl 1):S104–S108, 1998 9852986
- Karalis K, Muglia LJ, Bae D, et al: CRH and the immune system. *J Neuroimmunol* 72(2):131–136, 1997 9042104
- Kelley KW, McCusker RH: Getting nervous about immunity. *Semin Immunol* 26(5): 389–393, 2014 24556600
- Kenis G, Maes M: Effects of antidepressants on the production of cytokines. *Int J Neuropsychopharmacol* 5(4):401–412, 2002 12466038
- Kent S, Bluthé RM, Kelley KW, et al: Sickness behavior as a new target for drug development. *Trends Pharmacol Sci* 13(1):24–28, 1992 1542935
- Kiecolt-Glaser JK, Glaser R: Depression and immune function: central pathways to morbidity and mortality. *J Psychosom Res* 53(4):873–876, 2002 12377296
- Kiecolt-Glaser JK, Marucha PT, Malarkey WB, et al: Slowing of wound healing by psychological stress. *Lancet* 346(8984):1194–1196, 1995 7475659
- Kim YK, Na KS, Shin KH, et al: Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 31(5):1044–1053, 2007 17433516
- Köhler O, Benros ME, Nordentoft M, et al: Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71(12):1381–1391, 2014 25322082
- Krishnan R, Cella D, Leonardi C, et al: Effects of etanercept therapy on fatigue and symptoms of depression in

subjects treated for moderate to severe plaque psoriasis for up to 96 weeks. *Br J Dermatol* 157(6):1275-1277, 2007 17916204

Labeur MS, Arzt E, Wiegers GJ, et al: Long-term intracerebroventricular corticotropin-releasing hormone administration induces distinct changes in rat splenocyte activation and cytokine expression. *Endocrinology* 136(6):2678-2688, 1995 7750492

Lacosta S, Merali Z, Anisman H: Central monoamine activity following acute and repeated systemic interleukin-2 administration. *Neuroimmunomodulation* 8(2):83-90, 2000 10965233

Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H: Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology* 22(4):370-379, 2000 10700656

Layé S, Parnet P, Goujon E, Dantzer R: Peripheral administration of lipopolysaccharide induces the expression of cytokine transcripts in the brain and pituitary of mice. *Brain Res Mol Brain Res* 27(1):157-162, 1994 7877446

Leserman J, Jackson ED, Petitto JM, et al: Progression to AIDS: the effects of stress, depressive symptoms, and social support. *Psychosom Med* 61(3):397-406, 1999 10367622

Lespérance F, Frasure-Smith N, Thérioux P, et al: The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. *Am J Psychiatry* 161(2):271-277, 2004 14754776

Leu SJ, Singh VK: Stimulation of interleukin-6 production by corticotropin-releasing factor. *Cell Immunol* 143(1):220-227, 1992 1623564

Leu SJ, Shiah IS, Yatham LN, et al: Immune-inflammatory markers in patients with seasonal affective disorder:

- effects of light therapy. *J Affect Disord* 63(1-3):27-34, 2001 11246077
- Leung DY: Atopic dermatitis: immunobiology and treatment with immune modulators. *Clin Exp Immunol* 107 (suppl 1):25-30, 1997 9020932
- Linthorst AC, Flachskamm C, Holsboer F, et al: Intraperitoneal administration of bacterial endotoxin enhances noradrenergic neurotransmission in the rat preoptic area: relationship with body temperature and hypothalamic-pituitary-adrenocortical axis activity. *Eur J Neurosci* 7(12):2418-2430, 1995a 8845947
- Linthorst AC, Flachskamm C, Müller-Preuss P, et al: Effect of bacterial endotoxin and interleukin-1 beta on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: an in vivo microdialysis study. *J Neurosci* 15(4):2920-2934, 1995b 7536823
- Lutgendorf SK, Sood AK: Biobehavioral factors and cancer progression: physiological pathways and mechanisms. *Psychosom Med* 73(9):724-730, 2011 22021459
- Maes M: A review on the acute phase response in major depression. *Rev Neurosci* 4(4):407-416, 1993 7506108
- Maes M: Major depression and activation of the inflammatory response system. *Adv Exp Med Biol* 461:25-46, 1999 10442165
- Maes M, Libbrecht I, Van Hunsel F, et al: The immune-inflammatory pathophysiology of fibromyalgia: increased serum soluble gp130, the common signal transducer protein of various neurotrophic cytokines. *Psychoneuroendocrinology* 24(4):371-383, 1999a 10341365
- Maes M, Lin AH, Delmeire L, et al: Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. *Biol Psychiatry* 45(7):833-839, 1999b 10202570



- Maes M, Song C, Lin AH, et al: Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacology* 20(4):370-379, 1999d 10088138
- Maier SF, Goehler LE, Fleshner M, et al: The role of the vagus nerve in cytokine-to-brain communication. *Ann N Y Acad Sci* 840:289-300, 1998 9629257
- Mathias SD, Colwell HH, Miller DP, et al: Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. *Clin Ther* 22(1):128-139, 2000 10688396
- McCaffery JM, Frasurre-Smith N, Dubé M-P, et al: Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation and serotonin. *Psychosom Med* 68(2):187-200, 2006 16554382
- McEwen BS: *The End of Stress as We Know It*. Washington, DC, Dana Press, 2002
- McEwen BS, Biron CA, Brunson KW, et al: The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. *Brain Res Brain Res Rev* 23(1-2):79-133, 1997 9063588
- McKay LI, Cidlowski JA: Molecular control of immune/inflammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. *Endocr Rev* 20(4):435-459, 1999 10453354
- Miller AH: Neuroendocrine and immune system interactions in stress and depression. *Psychiatr Clin North Am* 21(2):443-463, 1998 9670236
- Miller AH, Raison CL: The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 16(1):22-34, 2016 26711676

- Miller AH, Spencer RL, Hassett J, et al: Effects of selective type I and II adrenal steroid agonists on immune cell distribution. *Endocrinology* 135(5):1934-1944, 1994 7956914
- Miller AH, Pearce B, Pariante C: Immune system and central nervous system interactions, in Kaplan and Sadock's *Comprehensive Textbook of Psychiatry*, Vol 1. Philadelphia, PA, Lippincott Williams & Wilkins, 2000, pp 113-133
- Miller RJ, Sutherland AG, Hutchison JD, et al: C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study. *Cytokine* 13(4):253-255, 2001 11237435
- Milligan ED, Nguyen KT, Deak T, et al: The long term acute phase-like responses that follow acute stressor exposure are blocked by alpha-melanocyte stimulating hormone. *Brain Res* 810(1-2):48-58, 1998 9813238
- Mioni C, Bazzani C, Giuliani D, et al: Activation of an efferent cholinergic pathway produces strong protection against myocardial ischemia/reperfusion injury in rats. *Crit Care Med* 33(11):2621-2628, 2005 16276189
- Moore P, Landolt HP, Seifritz E, et al: Clinical and physiological consequences of rapid tryptophan depletion (comment). *Neuropsychopharmacology* 23(6):601-622, 2000 11063917
- Müller N, Riedel M, Scheppach C, et al: Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. *Am J Psychiatry* 159(6):1029-1034, 2002 12042193
- Munck A: Glucocorticoid physiology and homeostasis in relation to anti-inflammatory actions, in *Anti-Inflammatory Steroid Action: Basic and Clinical Aspects*. New York, Academic Press, 1989, pp 30-47
- Musselman DL, Nemeroff CB: Depression and endocrine disorders: focus on the thyroid and adrenal system. *Br J Psychiatry Suppl* (30):123-128, 1996 8864158

- Musselman DL, Nemeroff CB: Depression really does hurt your heart: stress, depression, and cardiovascular disease. *Prog Brain Res* 122:43-59, 2000 10737050
- Musselman DL, Lawson DH, Gumnick JF, et al: Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 344(13):961-966, 2001a 11274622
- Musselman DL, Miller AH, Porter MR, et al: Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *Am J Psychiatry* 158(8):1252-1257, 2001b 11481159
- Nemeroff CB: Psychoneuroimmunoendocrinology: the biological basis of mind-body physiology and pathophysiology. *Depress Anxiety* 30(4):285-287, 2013 23576236
- Nishioka T, Kurokawa H, Takao T, et al: Differential changes of corticotropin releasing hormone (CRH) concentrations in plasma and synovial fluids of patients with rheumatoid arthritis (RA). *Endocr J* 43(2):241-247, 1996 9026271
- Norbiato G, Bevilacqua M, Vago T, Clerici M: Glucocorticoid resistance and the immune function in the immunodeficiency syndrome. *Ann N Y Acad Sci* 840:835-847, 1998 9629309
- Oakley RH, Sar M, Cidlowski JA: The human glucocorticoid receptor beta isoform: expression, biochemical properties, and putative function. *J Biol Chem* 271(16):9550-9559, 1996 8621628
- Ogawa Y, Duru EA, Ameredes BT: Role of IL-10 in the resolution of airway inflammation. *Curr Mol Med* 8(5):437-445, 2008 18691071
- Olson BM, McNeel DG: Monitoring regulatory immune responses in tumor immunotherapy clinical trials. *Front Oncol* 3:109, 2013 23653893
- Onyike CU, Crum RM, Lee HB, et al: Is obesity associated with major depression? Results from the Third National

- Health and Nutrition Examination Survey. *Am J Epidemiol* 158(12):1139–1147, 2003 14652298
- Opp MR: Cytokines and sleep. *Sleep Med Rev* 9(5):355–364, 2005 16102986
- Owens MJ, Nemeroff CB: Physiology and pharmacology of corticotropin-releasing factor. *Pharmacol Rev* 43(4):425–473, 1991 1775506
- Owens MJ, Nemeroff CB: The role of corticotropin-releasing factor in the pathophysiology of affective and anxiety disorders: laboratory and clinical studies. *Ciba Found Symp* 172:296–308; discussion 308–316, 1993 8491091
- Owens MJ, Nemeroff CB: The serotonin transporter and depression. *Depress Anxiety* 8 (suppl 1):5–12, 1998 9809208
- Pace TW, Mletzko TC, Alagbe O, et al: Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry* 163(9):1630–1633, 2006 16946190
- Pace TW, Hu F, Miller AH: Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain Behav Immun* 21(1):9–19, 2007 17070667
- Padro CJ, Sanders VM: Neuroendocrine regulation of inflammation. *Semin Immunol* 26(5):357–368, 2014 24486056
- Paez Pereda M, Sauer J, Perez Castro C, et al: Corticotropin-releasing hormone differentially modulates the interleukin-1 system according to the level of monocyte activation by endotoxin. *Endocrinology* 136(12):5504–5510, 1995 7588301
- Papanicolaou DA: Euthyroid Sick Syndrome and the role of cytokines. *Rev Endocr Metab Disord* 1(1–2):43–48, 2000 11704991
- Pariente CM, Miller AH: Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment.

- Biol Psychiatry 49(5):391–404, 2001 11274650
- Pariente CM, Nemeroff CB, Miller AH: Glucocorticoid receptors in depression. *Isr J Med Sci* 31(12):705–712, 1995 8543464
- Pariente CM, Pearce BD, Pisell TL, et al: The proinflammatory cytokine, interleukin-1alpha, reduces glucocorticoid receptor translocation and function. *Endocrinology* 140(9):4359–4366, 1999 10465310
- Pavlov VA, Tracey KJ: The cholinergic anti-inflammatory pathway. *Brain Behav Immun* 19(6):493–499, 2005 15922555
- Pearce BD: Schizophrenia and viral infection during neurodevelopment: a focus on mechanisms. *Mol Psychiatry* 6(6):634–646, 2001 11673791
- Persoons P, Vermeire S, Demyttenaere K, et al: The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. *Aliment Pharmacol Ther* 22(2):101–110, 2005 16011668
- Piccirillo CA: Regulatory T cells in health and disease. *Cytokine* 43(3):395–401, 2008 18722786
- Plotkin SR, Banks WA, Kastin AJ: Comparison of saturable transport and extracellular pathways in the passage of interleukin-1 alpha across the blood-brain barrier. *J Neuroimmunol* 67(1):41–47, 1996 8707929
- Puterman E, Epel ES, O'Donovan A, et al: Anger is associated with increased IL-6 stress reactivity in women, but only among those low in social support. *Int J Behav Med* 21(6):936–945, 2014 24357433
- Quan N: Brain's firewall: blood-brain barrier actively regulates neuroimmune information flow. *Brain Behav Immun* 20(5):447–448, 2006 16621441
- Quan N: In-depth conversation: spectrum and kinetics of neuroimmune afferent pathways. *Brain Behav Immun* 40:1–8, 2014 24566385
- Quan N, Stern EL, Whiteside MB, et al: Induction of pro-inflammatory cytokine mRNAs in the brain after

peripheral injection of subseptic doses of lipopolysaccharide in the rat. *J Neuroimmunol* 93(1-2):72-80, 1999 10378870

Raison CL, Miller AH: Depression in cancer: new developments regarding diagnosis and treatment. *Biol Psychiatry* 54(3):283-294, 2003a 12893104

Raison CL, Miller AH: When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry* 160(9):1554-1565, 2003b 12944327

Raison CL, Nemeroff CB: Cancer and depression: prevalence, diagnosis, and treatment. *Home Health Care Consultant* 7(9):34-41, 2000

Raison CL, Gummick JF, Miller AH: Neuroendocrine-immune interactions: implications for health and behavior, in *Hormones, Brain and Behavior*, Vol 5. San Diego, CA, Academic Press, 2002, pp 209-261

Raison CL, Capuron L, Miller AH: Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 27(1):24-31, 2006 16316783

Raison CL, Rutherford RE, Woolwine BJ, et al: A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 70(1):31-41, 2013 22945416

Rassnick S, Sved AF, Rabin BS: Locus coeruleus stimulation by corticotropin-releasing hormone suppresses in vitro cellular immune responses. *J Neurosci* 14(10): 6033-6040, 1994 7931560

Ressler KJ, Nemeroff CB: Role of norepinephrine in the pathophysiology and treatment of mood disorders. *Biol Psychiatry* 46(9):1219-1233, 1999 10560027

Reynolds JL, Ignatowski TA, Sud R, et al: Brain-derived tumor necrosis factor-alpha and its involvement in noradrenergic neuron functioning involved in the

- mechanism of action of an antidepressant. *J Pharmacol Exp Ther* 310(3):1216–1225, 2004 15082752
- Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med* 353(16):1711–1723, 2005 16236742
- Ridker PM, Hennekens CH, Buring JE, et al: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 342(12):836–843, 2000a 10733371
- Ridker PM, Rifai N, Stampfer MJ, et al: Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 101(15):1767–1772, 2000b 10769275
- Rivest S, Lacroix S, Vallières L, et al: How the blood talks to the brain parenchyma and the paraventricular nucleus of the hypothalamus during systemic inflammatory and infectious stimuli. *Proc Soc Exp Biol Med* 223(1):22–38, 2000 10632958
- Rosenberger PH, Ickovics JR, Epel E, et al: Surgical stress-induced immune cell redistribution profiles predict short-term and long-term postsurgical recovery. A prospective study. *J Bone Joint Surg Am* 91(12):2783–2794, 2009 19952239
- Rothermundt M, Arolt V, Bayer TA: Review of immunological and immunopathological findings in schizophrenia. *Brain Behav Immun* 15(4):319–339, 2001 11782102
- Ruzek MC, Pearce BD, Miller AH, et al: Endogenous glucocorticoids protect against cytokine-mediated lethality during viral infection. *J Immunol* 162(6):3527–3533, 1999 10092810
- Saint-Mezard P, Chavagnac C, Bosset S, et al: Psychological stress exerts an adjuvant effect on skin dendritic cell functions in vivo. *J Immunol* 171(8):4073–4080, 2003 14530328
- Sanders V, Kavelaars A: Adrenergic regulation of immunity, in *Psychoneuroimmunology*, 4th Edition. Edited by Ader

- R. Burlington, MA, Elsevier Academic Press, 2007, pp 63–84
- Sanders VM, Straub RH: Norepinephrine, the beta-adrenergic receptor, and immunity. *Brain Behav Immun* 16(4):290–332, 2002 12096881
- Sapolsky RM: The influence of social hierarchy on primate health. *Science* 308(5722): 648–652, 2005 15860617
- Saul AN, Oberyszyn TM, Daugherty C, et al: Chronic stress and susceptibility to skin cancer. *J Natl Cancer Inst* 97(23):1760–1767, 2005 16333031
- Schäffler A, Schölmerich J, Salzberger B: Adipose tissue as an immunological organ: Toll-like receptors, C1q/TNFs and CTRPs. *Trends Immunol* 28(9):393–399, 2007 17681884
- Schedlowski M, Engler H, Grigoleit JS: Endotoxin-induced experimental systemic inflammation in humans: a model to disentangle immune-to-brain communication. *Brain Behav Immun* 35:1–8, 2014 24491305
- Schleifer SJ, Keller SE, Bond RN, et al: Major depressive disorder and immunity. Role of age, sex, severity, and hospitalization. *Arch Gen Psychiatry* 46(1):81–87, 1989 2562915
- Schmidt FM, Kirkby KC, Himmerich H: The TNF-alpha inhibitor etanercept as monotherapy in treatment-resistant depression—report of two cases. *Psychiatr Danub* 26(3):288–290, 2014 25191779
- Schmidt FM, Kirkby KC, Lichtblau N: Inflammation and immune regulation as potential drug targets in antidepressant treatment. *Curr Neuropharmacol* 14(7):674–687, 2016 26769225
- Schöbitz B, De Kloet ER, Holsboer F: Gene expression and function of interleukin 1, interleukin 6 and tumor necrosis factor in the brain. *Prog Neurobiol* 44(4):397–432, 1994 7886232
- Schulte HM, Bamberger CM, Elsen H, et al: Systemic interleukin-1 alpha and interleukin-2 secretion in



- response to acute stress and to corticotropin-releasing hormone in humans. *Eur J Clin Invest* 24(11): 773–777, 1994 7890016
- Sephton S, Spiegel D: Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease? *Brain Behav Immun* 17(5):321–328, 2003 12946654
- Shahidi H, Vottero A, Stratakis CA, et al: Imbalanced expression of the glucocorticoid receptor isoforms in cultured lymphocytes from a patient with systemic glucocorticoid resistance and chronic lymphocytic leukemia. *Biochem Biophys Res Commun* 254(3):559–565, 1999 9920778
- Shen Y, Connor TJ, Nolan Y, et al: Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat. *Life Sci* 65(17):1773–1786, 1999 10576557
- Shuto H, Kataoka Y, Horikawa T, et al: Repeated interferon-alpha administration inhibits dopaminergic neural activity in the mouse brain. *Brain Res* 747(2):348–351, 1997 9046014
- Silverman MN, Pearce BD, Biron CA, et al: Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol* 18(1):41–78, 2005 15802953
- Simpson E: Special regulatory T-cell review: Regulation of immune responses—examining the role of T cells. *Immunology* 123(1):13–16, 2008 18154613
- Sluzewska A: Indicators of immune activation in depressed patients. *Adv Exp Med Biol* 461:59–73, 1999 10442167
- Snider LA, Swedo SE: Pediatric obsessive-compulsive disorder. *JAMA* 284(24): 3104–3106, 2000 11135753
- Solomon GF: Emotions, stress, the central nervous system, and immunity. *Ann N Y Acad Sci* 164(2):335–343, 1969 5260533

- Sousa AR, Lane SJ, Cidlowski JA, et al: Glucocorticoid resistance in asthma is associated with elevated in vivo expression of the glucocorticoid receptor beta-isoform. *J Allergy Clin Immunol* 105(5):943–950, 2000 10808175
- Spivak B, Shohat B, Mester R, et al: Elevated levels of serum interleukin-1 beta in combat-related posttraumatic stress disorder. *Biol Psychiatry* 42(5):345–348, 1997 9276074
- Stefanović V, Mihajlović G, Nenadović M, et al: The effect of antipsychotic drugs on nonspecific inflammation markers in the first episode of schizophrenia. *Vojnosanit Pregl* 72(12):1085–1092, 2015 26898032
- Steinberg H, Kirkby KC, Himmerich H: The historical development of immunoendocrine concepts of psychiatric disorders and their therapy. *Int J Mol Sci* 16(12):28841–28869, 2015 26690116
- Stenzel-Poore MP, Heinrichs SC, Rivest S, et al: Overproduction of corticotropin-releasing factor in transgenic mice: a genetic model of anxiogenic behavior. *J Neurosci* 14(5 Pt 1):2579–2584, 1994 8182429
- Steptoe A, Willemsen G, Owen N, et al: Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. *Clin Sci (Lond)* 101(2):185–192, 2001 11473494
- Sternberg EM, Hill JM, Chrousos GP, et al: Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. *Proc Natl Acad Sci U S A* 86(7):2374–2378, 1989 2538840
- Straub RH: Interaction of the endocrine system with inflammation: a function of energy and volume regulation. *Arthritis Res Ther* 16(1):203, 2014 24524669
- Straub RH, Bijlsma JW, Masi A, et al: Role of neuroendocrine and neuroimmune mechanisms in chronic inflammatory rheumatic diseases—the 10-year

- update. *Semin Arthritis Rheum* 43(3):392-404, 2013 23731531
- Tracey KJ: The inflammatory reflex. *Nature* 420(6917):853-859, 2002 12490958
- Trask PC, Esper P, Riba M, et al: Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. *J Clin Oncol* 18(11):2316-2326, 2000 10829053
- Triantafyllou N, Evangelopoulos ME, Kimiskidis VK, et al: Increased plasma homocysteine levels in patients with multiple sclerosis and depression. *Ann Gen Psychiatry* 7:17, 2008 18782433
- Tyring S, Gottlieb A, Papp K, et al: Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 367(9504):29-35, 2006 16399150
- Udina M, Moreno-España J, Capuron L, et al: Cytokine-induced depression: current status and novel targets for depression therapy. *CNS Neurol Disord Drug Targets* 13(6):1066-1074, 2014 24923336
- Van Gaal LF, Mertens IL, De Block CE: Mechanisms linking obesity with cardiovascular disease. *Nature* 444(7121):875-880, 2006 17167476
- van Westerloo DJ, Giebelen IA, Florquin S, et al: The vagus nerve and nicotinic receptors modulate experimental pancreatitis severity in mice. *Gastroenterology* 130(6):1822-1830, 2006 16697744
- Veith RC, Lewis N, Linares OA, et al: Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch Gen Psychiatry* 51(5):411-422, 1994 8179465
- Viswanathan K, Dhabhar FS: Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. *Proc Natl Acad Sci U S A* 102(16): 5808-5813, 2005 15817686

- Viswanathan K, Daugherty C, Dhabhar FS: Stress as an endogenous adjuvant: augmentation of the immunization phase of cell-mediated immunity. *Int Immunol* 17(8):1059-1069, 2005 16000327
- Vitlic A, Lord JM, Phillips AC: Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system. *Age (Dordr)* 36(3):9631, 2014 24562499
- Wang H, Liao H, Ochani M, et al: Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat Med* 10(11):1216-1221, 2004 15502843
- Wang X, Wu H, Miller AH: Interleukin1 alpha (IL-1alpha) induced activation of p38 mitogen-activated protein kinase inhibits glucocorticoid receptor function. *Mol Psychiatry* 9(1):65-75, 2004 14699442
- Webster JC, Oakley RH, Jewell CM, et al: Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci U S A* 98(12):6865-6870, 2001 11381138
- Webster Marketon JI, Glaser R: Stress hormones and immune function. *Cell Immunol* 252(1-2):16-26, 2008 18279846
- Whiteside TL: Regulatory T cell subsets in human cancer: are they regulating for or against tumor progression? *Cancer Immunol Immunother* 63(1):67-72, 2014 24213679
- Whooley MA, Caska CM, Hendrickson BE, et al: Depression and inflammation in patients with coronary heart disease: findings from the Heart and Soul Study. *Biol Psychiatry* 62(4):314-320, 2007 17434456
- Wing K, Sakaguchi S: Regulatory T cells exert checks and balances on self tolerance and autoimmunity. *Nat Immunol* 11(1):7-13, 2010 20016504

- Wong ML, Kling MA, Munson PJ, et al: Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc Natl Acad Sci U S A* 97(1):325-330, 2000 10618417
- Wood PG, Karol MH, Kusnecov AW, et al: Enhancement of antigen-specific humoral and cell-mediated immunity by electric footshock stress in rats. *Brain Behav Immun* 7(2):121-134, 1993 8347894
- Yirmiya R, Pollak Y, Barak O, et al: Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacology* 24(5):531-544, 2001 11282253
- Zautra AJ, Yocum DC, Villanueva I, et al: Immune activation and depression in women with rheumatoid arthritis. *J Rheumatol* 31(3):457-463, 2004 14994388
- Zhu CB, Carneiro AM, Dostmann WR, et al: p38 MAPK activation elevates serotonin transport activity via a trafficking-independent, protein phosphatase 2A-dependent process. *J Biol Chem* 280(16): 15649-15658, 2005 15728187
- Zhu CB, Blakely RD, Hewlett WA: The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology* 31(10):2121-2131, 2006 16452991
- Zobel AW, Nickel T, Kunzel HE, et al: Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res* 34(3):171-181, 2000 10867111
- Zorrilla EP, Luborsky L, McKay JR, et al: The relationship of depression and stressors to immunological assays: a

meta-analytic review. Brain Behav Immun 15(3):199-226, 2001 11566046

## CHAPTER 6

# Principles of Pharmacokinetics and Pharmacodynamics

C. Lindsay DeVane, Pharm.D.

Drugs may be taken as single doses on an occasional basis to mitigate a temporary condition. Alternatively, drugs may be taken by patients daily for the rest of their lives to prevent or treat chronic disease. The usual duration of drug therapy is somewhere between these extremes. The amount of drug and the frequency with which it is taken define a dosage regimen. When a new drug or formulation is marketed, dosing guidelines accompanying the product are based on results from a variety of experimental and clinical studies. An integral component of drug development is the investigation of pharmacokinetic and pharmacodynamic properties. An understanding of basic pharmacokinetic/pharmacodynamic principles can aid the investigator in designing studies to

gain the optimal insight from collected data. Understanding these principles also benefits the clinician in helping to develop precision drug dosage regimens to achieve therapeutic goals for individual patients.

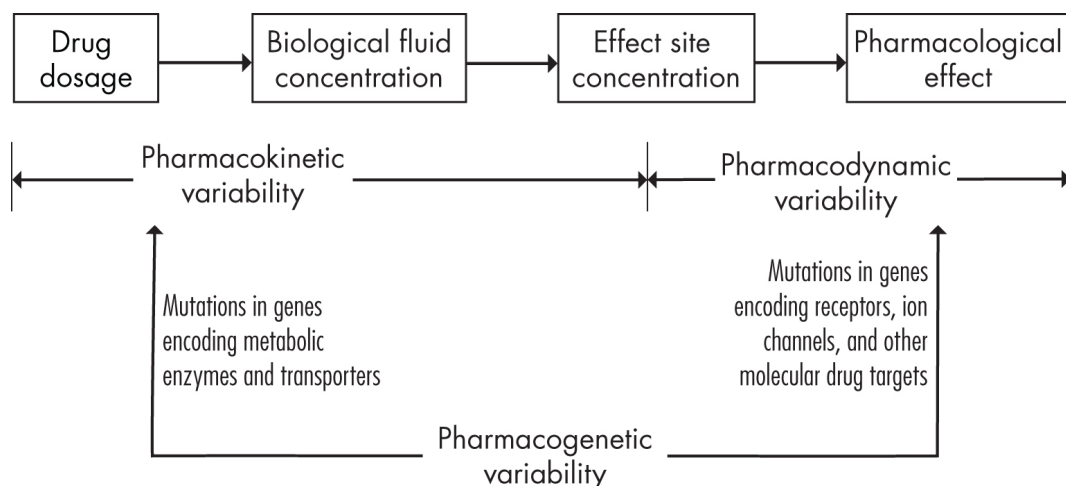
*Pharmacokinetics* is defined as the study of the time course of drugs and their metabolites through the body. A typical human study samples blood for laboratory determination of drug concentration in plasma at multiple timed intervals following administration of an oral drug dose. Computer analyses of these data generate estimates of the fundamental pharmacokinetic parameters, including absorption rate, elimination rate, area under the plasma drug concentration versus time curve (AUC), and drug clearance. These estimates can then be used to predict the plasma drug concentration that would be achieved in that individual from various dosage regimens using different-sized doses administered at selected intervals. The results from rigorously studying a small number of individuals are applied to larger populations by assuming that the drug disposition characteristics of the intensively studied population are representative of the larger patient population who will eventually receive the drug. Such data are useful to achieve a minimum plasma drug concentration with multiple-dose regimens when a threshold for pharmacological effects can be defined, or for avoiding excessive drug plasma concentrations that may be associated with adverse events. However, the results of a pharmacokinetic study per se have only limited utility unless they are paired with pharmacodynamic data.

*Pharmacodynamics* is defined as the study of the time course and intensity of the pharmacological effects of drugs. Although pharmacodynamic effects can be recorded following a drug administration, the most useful data will be



derived from studies that record both the drug concentration in a biological fluid (blood, urine, or cerebrospinal fluid [CSF]) and simultaneous measures of a pharmacological effect of interest. With these data, the relationship between drug concentration and effect can be defined so that drug dosage regimens can be designed to achieve a target concentration associated with a desired outcome. Thus, the goal of pharmacokinetic/pharmacodynamic studies is to inform dosing to achieve specific degrees of desired pharmacological effects while avoiding undesirable effects.

The dose and the frequency of dosing necessary to produce the desired pharmacological response from psychoactive drugs differ widely among patients. This variability in the drug dose-effect relationship is not surprising, given the large differences in patients' physiology, ages, range of severity of illness, activity of drug metabolizing enzymes and transporters, renal function, and other variables. The sources of variability can be characterized as pharmacokinetic, pharmacodynamic, or pharmacogenomic. Genetic variability in the form of polymorphic genes controlling the transcription of proteins involved in drug-metabolizing enzymes, drug transporters, and drug targets is a substantial determinant of pharmacokinetic/pharmacodynamic variability. An integrated relationship among these sources of variability is shown as [Figure 6-1](#). An understanding of the relative contribution of each of these sources of variability to the overall dose-effect relationship is an overarching goal in the drug development process for individualizing dosage regimens for specific patients.



**FIGURE 6-1.** Pharmacokinetic, pharmacodynamic, and pharmacogenomic variability as determinants of the dose-effect relationship.

The interface between pharmacokinetics and pharmacodynamics, where drugs interact with molecular targets at an effect site (see [Figure 6-1](#)), is a focus of research. Experimental approaches that separate pharmacokinetic and pharmacodynamic components of the dose-effect relationship have shown that pharmacodynamic variability is a significant contributor in drug response. Identifiable sources of variability include sex, age, body temperature (fever), pregnancy, blood volume, fluid or electrolyte balance, and drug-drug interactions. The ability to link drug concentrations with pharmacodynamic effects using mathematical models has improved greatly in recent years. Population pharmacokinetic/pharmacodynamic modeling enables the relationship between drug concentration and effect to be defined in individuals from vulnerable populations such as children, pregnant women, and the elderly, where only sparse data may be available ([Akil et al. 2016](#); [Bies et al. 2004](#)). Covariants such as age,

gender, genotype of drug-metabolizing enzymes and transporters, and concomitant treatment with other drugs can be easily incorporated into these models and tested for their significance in influencing drug concentration and effects ([DeVane et al. 2006](#)). The mechanisms whereby pharmacodynamic variation occurs have been elusive. It is increasingly accepted that differences in the expression of multiple genes involved in drug targets is a contributor to pharmacodynamic variability.

In this chapter I present basic principles of pharmacokinetics and explain how they interface with pharmacodynamics to provide insight into observed dose-effect relationships. The interface of pharmacokinetics/pharmacodynamics with pharmacogenomics is an essential component of variability in drug dose-effect relationships in psychopharmacology (see [Figure 6-1](#)). Specific pharmacogenomic data are discussed in detail elsewhere in this volume (see [Chapter 1, “Basic Principles of Molecular Biology and Genomics,”](#) by [Yu and Rasenick](#), as well as individual chapters on specific drugs or drug classes).

---

## Pharmacokinetics

---

The mathematical models and their accompanying differential equations that describe the time course of drugs and metabolites in the body were developed in the late 1960s and 1970s ([Gibaldi and Perrier 1975](#); [Wagner 1971](#)). These models were used to explain observational data as chromatographic techniques became available to measure nanogram quantities of drugs in animals and

humans. Unfortunately, the mathematical expertise required for development of these models makes them incomprehensible to most clinicians treating patients with drugs. The principles in this chapter have been validated with substantial experimental and observational data. However, these principles continue to be reexamined and refined. At the time pharmacokinetic models were first conceived, there was no knowledge of drug transporters. This rapidly evolving area of research is reshaping many of the tenets of drug disposition.

## Significance of Drug Transporters

Since the last update of this chapter, advances in the understanding of pharmacokinetics and pharmacodynamics of drugs have led to an investigative focus on the role of membrane-bound transporters in influencing drug distribution to various tissues ([Giacomini et al. 2010](#)). It is now recognized that multiple transporters present in the cerebral capillaries that form the blood-brain barrier (BBB) influence drug access to and accumulation in the central nervous system (CNS). Initial studies focused on the *ABCB1* gene product P-glycoprotein (P-gp) and revealed a role for this protein in altering the efflux of its substrates through the gastrointestinal tract, the BBB, and the placenta and in influencing drug elimination through the biliary tract and renal tubules. The amount of drug in various tissues correlated with the presence of transporters and their genetically determined activity. It soon became apparent that multiple transporters functioned at these sites, opposing each other in direction of transport and having overlapping substrate specificity. This complexity became

problematic for discerning the role of any single transporter in regulating CNS drug concentration. Much as with the genes that influence disease expression, it is unlikely that any single transporter polymorphism will be identified that could serve as a biomarker for pharmacokinetic/pharmacodynamic predictability. Other transporters in the brain capillary endothelial cells contributing to the function of the BBB include the uptake transporters organic anion transporting polypeptides 1A2 and 2B1 (OATP1A2, OATP2B1) and the efflux pumps P-gp, breast cancer resistance protein (BCRP), and multidrug resistance proteins 4 and 5 (MRP4, MRP5) ([Nigam 2015](#)).

Some provocative results have stimulated this field of research. When P-gp activity was lowered through use of a specific inhibitor, risperidone was found to have an increased drug concentration in the brain of rats that correlated with enhanced pharmacological effects that were surrogates for antipsychotic activity ([Pacchioni et al. 2010](#)). The translational application of this research is the possibility that use of specific inhibitors might increase CNS drug concentration and enhance central effects without causing an increase in peripheral drug concentration that relates to the development of adverse effects. The research supporting these types of investigations is built on a foundation of basic pharmacokinetic principles. The fundamental description of drug disposition begins with studies of single drug doses.

## Single-Dose Drug Disposition

### Absorption

The route of administration is a major determinant of the onset and duration of a drug's pharmacological effects. Intravenous injection ensures that all of the administered drug is available to the circulation. The rate of drug injection or infusion can be used to control completely the rate of drug availability. However, few psychopharmacological drugs are administered intravenously. Intramuscular administration is commonly thought to produce a rapid onset of effect, but exceptions have been documented. For example, drug absorption by this route was found to be slow and erratic with chlordiazepoxide ([Greenblatt et al. 1974](#)). The recent availability of intramuscular forms of some atypical antipsychotics will be advantageous for treating psychotic states when rapid tranquilization is desired and oral administration is impractical. For drugs that are equally well absorbed by the intramuscular and oral routes of administration, the total systemic exposure as reflected by the AUC from the two routes should be similar, as should the elimination half-life. A major difference is that the rate of absorption from the intramuscular route may be more rapid. Most psychoactive drugs are highly lipophilic compounds, which are well absorbed when taken orally.

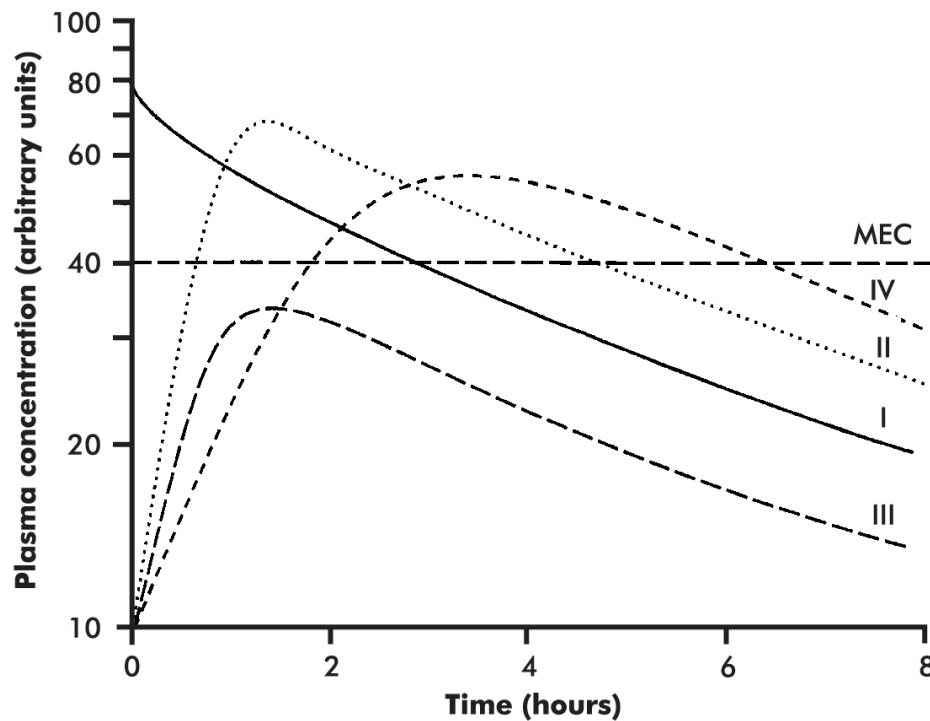
Drug absorption is usually a passive process occurring in the small intestine. The efficiency of oral absorption is influenced by the physiological state of the patient, by formulation factors, and by the timing of administration around meals. Most drugs are best absorbed on an empty stomach. The presence of food or antacids in the stomach usually decreases the rate of drug absorption. Consistency in drug availability to the systemic circulation from oral absorption is promoted by administering each drug dose at a similar time in relation to meals. Normally, the presence

of food can be expected to reduce the peak drug concentration achieved in blood or plasma and to prolong the time required following an oral dose to reach the maximum plasma concentration. The absolute amount of drug absorbed may or may not be affected. Acute drug effects are facilitated by administration apart from meals. Sedative-hypnotic drugs are examples of drugs for which the rate of absorption is clinically meaningful ([Greenblatt et al. 1978](#)). Zolpidem's effectiveness in reducing the time to onset of sleep is considerably reduced if the drug is taken at bedtime in close proximity to food.

In recent years, the use of alternative routes of administration has increased. Buccal, sublingual, and transdermal routes of administration have the advantage of avoiding presystemic elimination, as absorption directly into the circulation avoids an initial pass through the liver before some drug is distributed to tissues. Hepatic elimination is dependent on the amount of drug extracted from blood as drug enters the liver, a function that is independent of the route of administration. Thus, the terminal elimination phase reflected by elimination half-life should not differ from one route of administration to another.

Formulation factors are especially meaningful when a drug effect is associated with achieving a minimal effective concentration (MEC) in plasma. [Figure 6-2](#) shows the predicted plasma concentration-time curves of a drug following a rapid intravenous injection (I), an oral formulation that is completely absorbed with no presystemic elimination (II), an incompletely absorbed oral formulation (III), and an extended-release formulation that results in slow absorption of drug (IV). A formulation with poor bioavailability (III) may never achieve a plasma

concentration above the MEC, whereas a drug whose absorption is delayed (IV) may retard the onset of effect but maintain an effective concentration for a period similar to that for the more rapidly available formulations (I, II). The principle of an MEC may apply in antipsychotic therapy, where minimal occupancy of dopamine  $D_2$  or other receptors during a dosage interval may be needed for optimal therapeutic benefit.



**FIGURE 6-2.** Predicted plasma concentration curves following single doses of a drug by rapid intravenous injection (I), a dosage form with complete bioavailability (II), a dosage form with reduced bioavailability (III), and an extended-release dosage



form that reduces the rate but not the completeness of absorption (IV).

MEC=minimal effective concentration.

Research in pharmaceutical science continues to produce new systems for controlling the release of oral drugs. These include coated systems, with a core of active drug surrounded by a slow-releasing film, and matrix systems, with active drug distributed in erodible gel matrices, and other hydrophilic, swellable, or erodible polymers, to slowly dissolve and release the drug at predictable rates to produce one or more peak concentrations during a dosage interval. Bupropion, paroxetine, venlafaxine, and the psychostimulants used to treat attention-deficit/hyperactivity disorder (ADHD) are examples of drugs whose clinical utility has been improved by reformulation as controlled-release dosage forms. Recently, a controlled-release oral suspension was developed for delivery of methylphenidate. Among the immediate-release dosage formulations, a general rank order of products providing the most rapid to the slowest rate of drug release for oral absorption is solutions, suspensions, tablets, enteric- or film-coated tablets, and capsules. Regardless of the dosage formulation selected, the last several hours of declining drug concentration in plasma occur in parallel, because the drug's rate of elimination is unaffected by its rate or extent of absorption (see [Figure 6-2](#)). The time at which a terminal elimination phase is clearly observable following a single dose may be delayed, but the terminal elimination half-life is unchanged. Formulation as controlled-release tablets or capsules may allow drugs with short elimination half-lives, which must be given multiple times per day to maintain an

effective concentration, to be effective when administered only once or twice daily.

## Presystemic Elimination

Many drugs undergo extensive metabolism as they move from the gastrointestinal tract to the systemic circulation (i.e., as they pass through the gastrointestinal membranes and hepatic circulation during absorption). This process is known as the *first-pass effect* or *presystemic elimination* and is an important determinant of drug bioavailability after oral administration. Several factors are potentially important in influencing the degree of first-pass effect. Food has been mentioned previously as one factor. A first-pass effect is usually indicated by either a decreased amount of parent drug reaching the systemic circulation or an increased quantity of metabolites after oral administration compared with parenteral dosing. This process is important in the formation of active metabolites for psychoactive drugs and is a major source of pharmacokinetic variability ([George et al. 1982](#)).

Presystemic metabolism of drugs is extensively accomplished by cytochrome P450 (CYP) enzymes located both in the liver and in the luminal epithelium of the small intestine ([Kolars et al. 1992](#)). CYP3A4 represents approximately 70% of total CYP in the human intestine. Many useful psychopharmacological drugs are CYP3A4 substrates, inhibitors, and/or inducers. The liver contains about two- to fivefold greater amounts of CYP3A protein (nmol/mg protein) compared with the intestine ([de Waziers et al. 1990](#)). Nevertheless, intestinal CYP3A4 has a profound effect on presystemic drug metabolism. Up to 43% of orally administered midazolam, for example, is metabolized as it passes through the intestinal mucosa

([Paine et al. 1996](#)). The exposure of drugs to gut CYP3A4 is not limited by binding to plasma proteins, as can occur with hepatic metabolism. Slower blood flow may also contribute to intestinal metabolism, thereby compensating for the lower quantity of CYP3A4 in the gut compared with the liver.

Certain foods, such as grapefruit juice, can substantially alter the bioavailability of some drugs. Components in grapefruit juice—which contains a variety of suspect candidates, including naringin, other flavonoids, bergamottin, and other furanocoumarins—inhibit intestinal CYP3A4-mediated first-pass metabolism ([Paine et al. 2005](#)). The maximal effect can occur within 30 minutes of ingestion of juice. Grapefruit juice may also inhibit the efflux transport of drugs by P-gp and MRP2. In the gut, P-gp works in concert with CYP3A4 to limit the intestinal absorption of drugs that are common substrates for both proteins. Efflux transporters minimize drug absorption by recycling drug that has escaped metabolism back to the gastrointestinal tract for further exposure to enzymatic elimination before absorption. Current research aims to develop nonabsorbable inhibitors of drug transporters to increase drug bioavailability. Such compounds would be useful for coadministration with drugs having poor bioavailability or excessive costs.

Changing the route of administration to avoid presystemic metabolism can have a therapeutic advantage. When given orally, selegiline, an irreversible inhibitor of monoamine oxidase (MAO), is substantially converted to several metabolites through extensive first-pass metabolism. Transdermal dosing with drug contained in a removable patch adhering to the skin results in higher systemic exposure to selegiline and lower exposure to

metabolites. This allows greater CNS exposure to selegiline from a given dose to inhibit MAO relative to the required dose from oral administration ([Azzaro et al. 2007](#)).

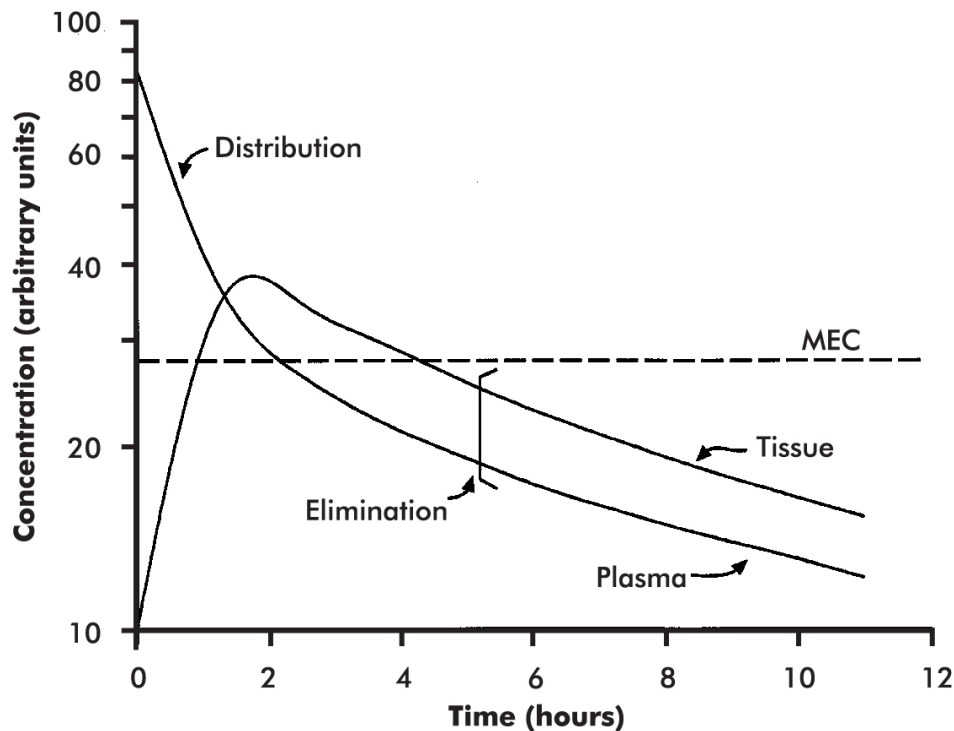
In summary, an important pharmacokinetic principle is that the choice of drug formulation and the route of administration can determine the rate at which the drug and metabolites appear in the systemic circulation. This rate may be manipulated to retard the magnitude of the peak plasma drug concentration when a high peak concentration is related to the occurrence of adverse effects. For example, slow-release formulations of lithium and paroxetine reduce gastrointestinal side effects ([DeVane 2003](#)). Alternatively, rapid absorption may be desirable to achieve immediate pharmacological effects.

## **Distribution**

Drug distribution to tissues begins almost simultaneously with absorption into the systemic circulation. The rate at which distribution occurs will partially influence the onset of pharmacological response. Access to effect sites depends on membrane permeability, the patient's state of hydration, regional blood flow, and other physiological variables. Physicochemical properties influencing the rate of drug distribution to effect sites include lipid solubility, ionizability, and affinity for plasma proteins and tissue components. Diazepam is highly lipophilic, and its onset of effect is rapid as a result of its entry into the brain within minutes after oral administration ([Greenblatt et al. 1980](#)). The concentration of diazepam at its effect site may fall so precipitously as a result of redistribution that diazepam's duration of action after an initial dose is shorter than would be expected based on its elimination half-life.

Frequently, the intensity and duration of the pharmacological effect of a second drug dose, taken immediately after cessation of the effect of the first dose, are greater and longer, respectively, than the intensity and duration of the effect of the first dose. This is known as the *second-dose effect* in pharmacokinetics (DeVane and Liston 2001). When dosing is repeated before the previous dose has been eliminated from the body, the second and subsequent doses produce a greater effect than the initial dose, but the relative intensity of subsequent doses diminishes. This second-dose effect occurs, regardless of the half-life of the drug, when dosing is repeated in response to the observed effect. Common examples of this phenomenon include the self-administration of caffeine and the administration of certain anesthetics.

The predicted time course of drug concentration in plasma and in tissue following a single intravenous drug injection is shown in Figure 6-3. Drug concentration in plasma rapidly declines in a manner consistent with the extensive distribution of the compound out of the systemic circulation. Drug concentration in tissue rapidly increases during this time. Pharmacological effects may not occur immediately but may be delayed until the tissue concentration at the effect site rises above an MEC. An equilibrium eventually occurs between drug in plasma and drug in tissue. Concentrations from this time forth decline in parallel during a terminal elimination phase.



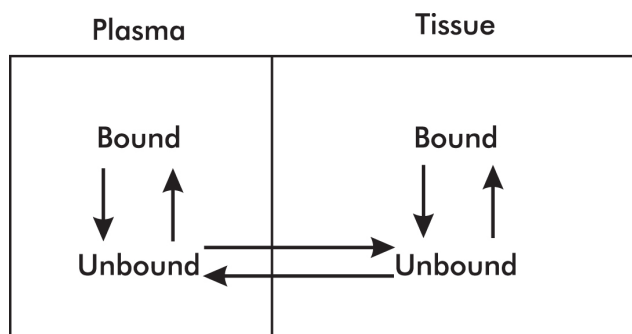
**FIGURE 6-3.** Predicted concentration of a drug in plasma and tissue following a rapid intravenous injection.

MEC=minimal effective concentration.

The observed time course of drug concentration changes in plasma has frequently been considered in the pharmacokinetic literature to confer the characteristics on the body of a two-compartment mathematical model (Gibaldi and Perrier 1975). Physiological systems are so complex that a complete mathematical model of drug transit through the body cannot be achieved. Therefore, it is necessary to reduce a mathematical description of the real system with a series of simplifying assumptions regarding drug behavior in the body. Many drugs appear to

be first absorbed into a central compartment (composed of the circulation and rapidly equilibrating tissues) and then distributed to less accessible tissues (which collectively form a peripheral compartment). This compartmentalization of drug concentration greatly aids mathematical analysis of pharmacokinetic data.

Even though the drug concentration can vary widely among tissues, equilibrium eventually occurs between drug concentration in plasma and in tissue (see [Figure 6-3](#)). The concentration of drug in brain tissue may be substantially different—higher or lower—from that in plasma, but reduction of the plasma drug concentration through renal and hepatic elimination of drug from the central compartment should be mirrored by a proportional reduction of drug concentration from the brain or other tissues. For this reason, an MEC determined from plasma data may reflect an MEC at the effect site. The distribution of a drug in the body largely depends on the drug's relative binding affinity to plasma proteins and tissue components and the capacity of tissues for drug binding. This pharmacokinetic principle is illustrated in [Figure 6-4](#). Only unbound drug is capable of distributing between plasma and tissues. Different degrees of plasma protein binding among antidepressants, for example, cannot be used to draw valid conclusions about the availability of drug to exert pharmacological effects at the site of action ([DeVane 1994](#)). The nonspecific binding of drugs to tissue components complicates the interpretation of the significance of plasma protein-binding differences among drugs. Drug binding in tissues cannot be measured directly in vivo and must be inferred using mathematical models and/or in vitro methods.



**FIGURE 6-4.** Effect of protein binding on distribution of drug between plasma and tissue.

Most drugs circulate in the blood bound to plasma proteins, principally albumin or alpha-1-acid glycoprotein. Many psychotropic drugs are highly protein bound, frequently to a degree greater than 90%. Displacement of drug from plasma protein-binding sites may result from drug-drug interactions. This situation should lead to more unbound drug being available for distribution to peripheral tissues and interaction with receptor sites (see [Figure 6-4](#)). As a result, potentially greater pharmacological effects, either beneficial or detrimental, may be expected. However, there are few documented examples in which the above events occurred with psychoactive drugs and led to significant clinical consequences. Compensatory changes occur in the body to buffer the impact of drug-binding interactions ([DeVane 2002](#)). When plasma protein binding is restrictive regarding the drug's hepatic and/or renal elimination, the increased free drug concentration in plasma will be a transient effect as more free (non-protein-bound) drug becomes available to routes of elimination. Total (bound plus free) drug concentration in plasma will eventually return to a predisplacement value. The conclusion of several authoritative reviews is that plasma



protein-binding displacement interactions are rarely a major source of variability in psychopharmacology (DeVane 2002; Greenblatt et al. 1982; Rolan 1994; Sellers 1979).

## Elimination

Drugs are eliminated or cleared from the body through renal excretion in an unchanged or conjugated form; through biotransformation, primarily in the liver, to polar metabolites; or through both of these mechanisms (see Figure 6-1).

*Clearance* is defined as the volume of blood or other fluid from which drug is irreversibly removed per unit of time. Thus, clearance units are volume per time. Drug clearance is analogous to creatinine clearance by the kidney. From the blood that delivers drug to the liver, or any other eliminating organ, an extraction occurs as blood travels through the organ. Because drug extraction by the liver and other organs is rarely 100%, the portion that escapes presystemic elimination reaches the systemic circulation intact. Plasma protein binding, as mentioned above, can restrict the organ extraction process, depending on the specific drug. If a drug were to be completely extracted, then clearance would equal the blood flow to the organ. An average hepatic blood flow is 1,500 mL/minute. When drug is eliminated by additional organs, the total clearance is an additive function of all the individual organ clearances. Clearance values in excess of 1,500 mL/minute reported for many psychopharmacological drugs are reflective of presystemic elimination (DeVane 1994). When the drug dose and bioavailability are constant, then clearance is the pharmacokinetic parameter that determines the extent of drug accumulation in the body to a steady state. By

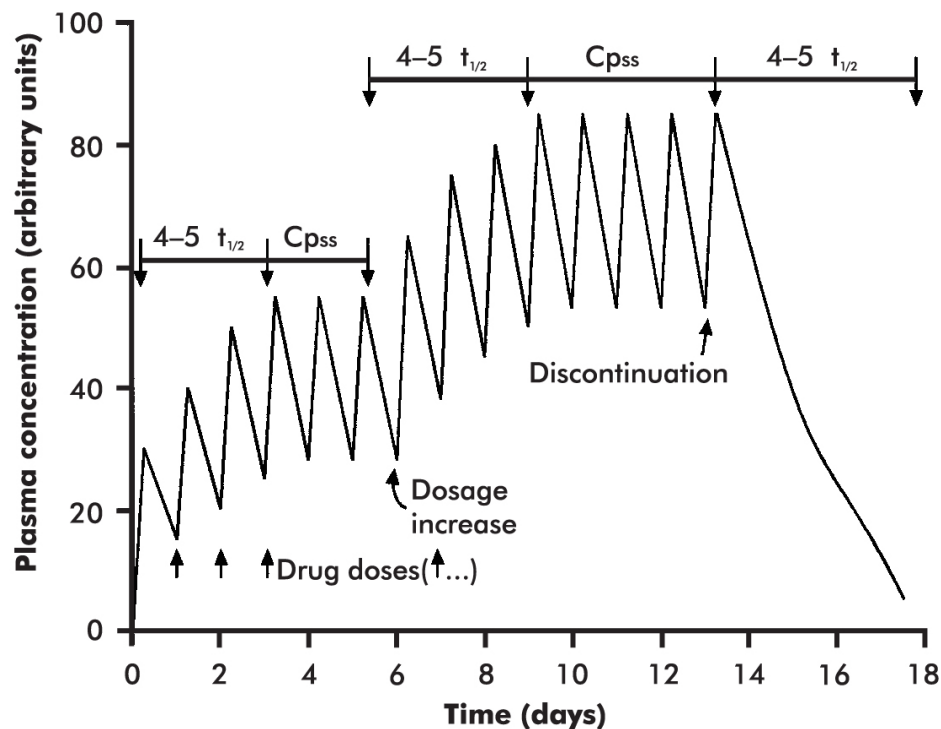
contrast, elimination half-life is useful to reflect the rate, but not the extent, of drug accumulation.

*Elimination half-life* is defined as the time required for the amount of drug in the body, or drug concentration, to decline by 50%. This parameter is commonly determined after a single-dose pharmacokinetic study or after drug discontinuation in a multiple-dose study. In either situation, drug concentration decline in plasma can be followed by multiple (serial) blood sampling. Half-life is easily determined by graphical means or by inspection, as long as data are used from the terminal log-linear portion of the elimination curve (see [Figures 6-2](#) and [6-3](#)). Knowledge of a drug's elimination half-life is particularly useful for designing multiple-dosing regimens.

## Multiple Dosing to Steady State

Multiple drug doses usually are required in the pharmacotherapy of mental illness. During a multiple-dosing regimen, second and subsequent drug doses are usually administered before sufficient time has elapsed for the initial dose to be completely eliminated from the body. This process results in drug accumulation, as illustrated in [Figure 6-5](#). When drug elimination follows a linear or first-order process, the amount of drug eliminated over time is proportional to the amount of drug available for elimination ([Gibaldi and Perrier 1975](#)). Accumulation does not occur indefinitely; rather, it reaches a steady state. A *steady state* exists when the amount of drug entering the body is equal to the amount leaving the body. From a practical standpoint, this definition means that after a period of continuous dosing, the body retains a pool of drug

molecules from several doses, and the drug eliminated each day is replaced by an equivalent amount of newly administered drug. The time required from the first administered dose to the point at which an approximate steady state occurs is equivalent to the total of four to five elimination half-lives. The same amount of time is required for a new steady state to be achieved after an increase or decrease in the daily dosing rate or for a drug to wash out of the body after dosing is discontinued (see [Figure 6-5](#)).



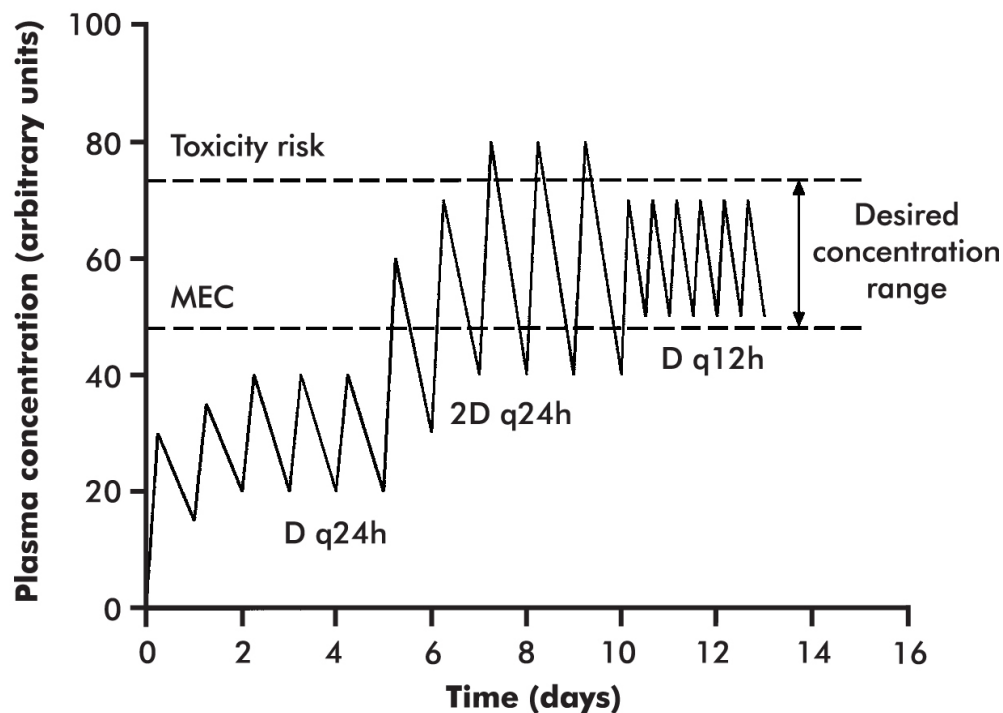
**FIGURE 6-5.** Accumulation of drug during multiple dosing.

It takes four to five half-lives ( $4-5 t_{1/2}$ ) to achieve initial steady state ( $C_{pss}$ ) on a constant dosage regimen, to achieve a new steady state after an increase in dosage, or to wash out drug from the body after

discontinuation. The average steady-state concentration lies somewhere between the peaks and troughs of drug concentration during a dosage interval.

The term *steady state* is a misnomer in that a true drug steady state occurs only with a constant-rate intravenous infusion. Because of the concurrent processes of drug absorption, distribution, and elimination, drug concentration is constantly changing in plasma and tissues during an oral dosing regimen. A peak and a trough concentration occur within each dosage interval. The average steady-state concentration occurs somewhere between these extremes and is determined by the daily dosage and the drug's total body clearance for that individual.

On reaching a steady-state concentration, the average concentration and the magnitude of the peaks and troughs may be manipulated according to established pharmacokinetic principles. [Figure 6-6](#) shows the predicted plasma concentration changes based on drug doses given every 24 hours. The selected dose does not produce a high enough average steady-state concentration to reach the desired concentration range between an MEC and a concentration threshold associated with an increased risk of toxicity. When the dose is doubled and the dosage interval is kept constant, the average steady-state concentration increases, but the magnitude of the peak and trough concentration difference also increases. These changes are consistent with the pharmacokinetic principles of superposition and linearity ([Gibaldi and Perrier 1975](#)).



**FIGURE 6-6.** Predicted plasma concentration changes from administering either a selected dose (D) every 24 hours (D q24h), twice the dose every 24 hours (2D q24h), or the original dose every 12 hours (D q12h).

MEC=minimal effective concentration.

*Linearity* refers to maintaining a stable clearance across the usual dosage range. Within the linear dose range, the magnitude of a dosage increase results in a proportional change in steady-state concentration (see [Figure 6-6](#)). The magnitude of the dose change theoretically superimposes on the new peak and trough concentration. In [Figure 6-6](#), doubling the daily dose results in an adequate average steady-state concentration, but the new peak and trough concentration values cause both an increased risk of

toxicity and an inadequate concentration, with plasma levels declining below the MEC for a portion of each dosage interval. An alternative is to increase the total daily dose and divide it into more frequent administrations. This is accomplished by administering the original dose every 12 hours instead of every 24 hours. The new average steady-state concentration remains within the desired range, and the differences between the peak and trough concentrations are reduced to an acceptable fluctuation.

Selection of a proper drug dosage regimen must consider both the amount of drug administered and the frequency of administration. Some drugs with half-lives long enough to be administered once daily may not be suitable for administration every 24 hours because toxicity may be precipitated by an excessive peak concentration from a single dose. Examples include lithium and clozapine. Once-daily dosing with lithium may produce gastrointestinal intolerance, and clozapine is dosed two or more times each day to avoid peak concentrations that might predispose to seizure activity. Bupropion was initially formulated to be dosed multiple times a day to avoid high peak concentrations in plasma for this same reason, but its reformulation as an extended-release tablet allowed for once-daily administration. When high peak concentration is tolerable, the dosage interval can theoretically be extended beyond 1 day by use of larger amounts of drug in single doses taken less frequently. This principle applies to fluoxetine, which is available as a 90-mg capsule for once-weekly administration. Drugs with elimination half-lives much longer than 24 hours, such as aripiprazole, could theoretically be administered once every several days to maintain adequate drug in the body for therapeutic effects. However, combining the dose for several days into a single

administration may increase the risk of adverse events. The development of long-acting intramuscular formulations of atypical antipsychotic drugs—such as those for risperidone or aripiprazole, which can be administered as infrequently as biweekly or monthly, respectively—offers the advantage of transparency of medication adherence.

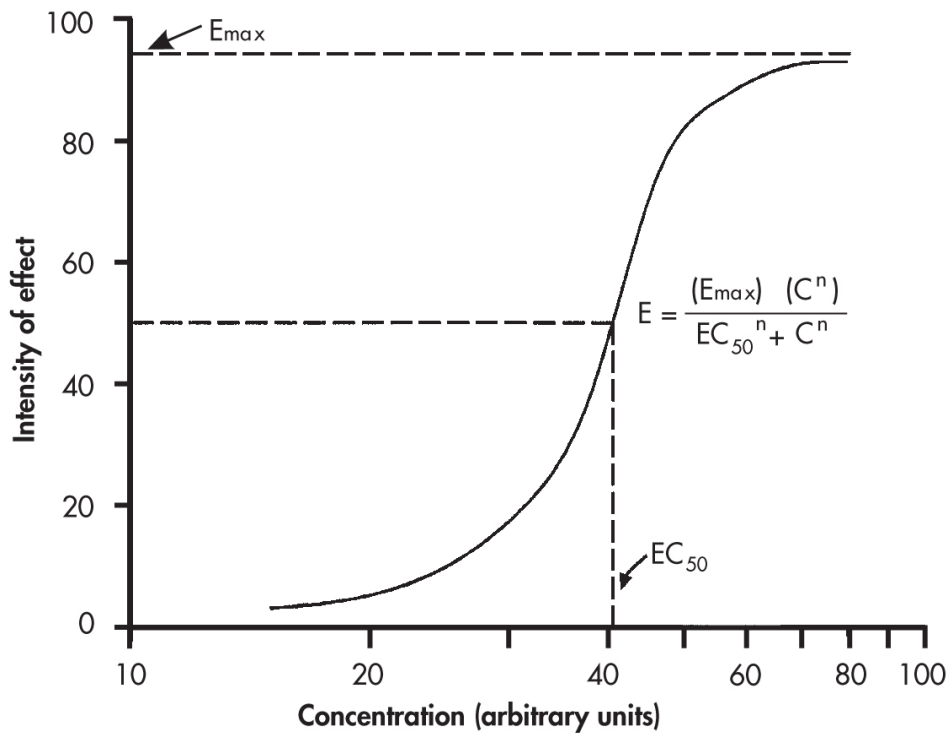
---

## Pharmacodynamics

---

Pharmacodynamic variability may exceed pharmacokinetic variability (see [Figure 6-1](#)). The drug dosage or concentration that produces a pharmacological effect differs widely among patients. Similarly, pharmacological effects can vary widely among patients with comparable plasma concentrations of drug.

The principles of dosage regimen design discussed above rely heavily on the existence of a functional relationship between the concentration at an effect site and the intensity of the response produced. Many observed processes in nature behave according to the sigmoid relationship shown in [Figure 6-7](#). At a low dosage or concentration, only a marginal effect is produced. As drug dosage or concentration increases, the intensity of effect ( $E$ ) increases until a maximum effect ( $E_{\max}$ ) is achieved. This response is observed as a plateau in the sigmoid dose-effect curve (see [Figure 6-7](#)). Further dosage increases do not produce a greater effect.



**FIGURE 6-7.** The sigmoid maximum effect ( $E_{\max}$ ) pharmacodynamic model relates concentration ( $C$ ) to intensity of effect ( $E$ ).

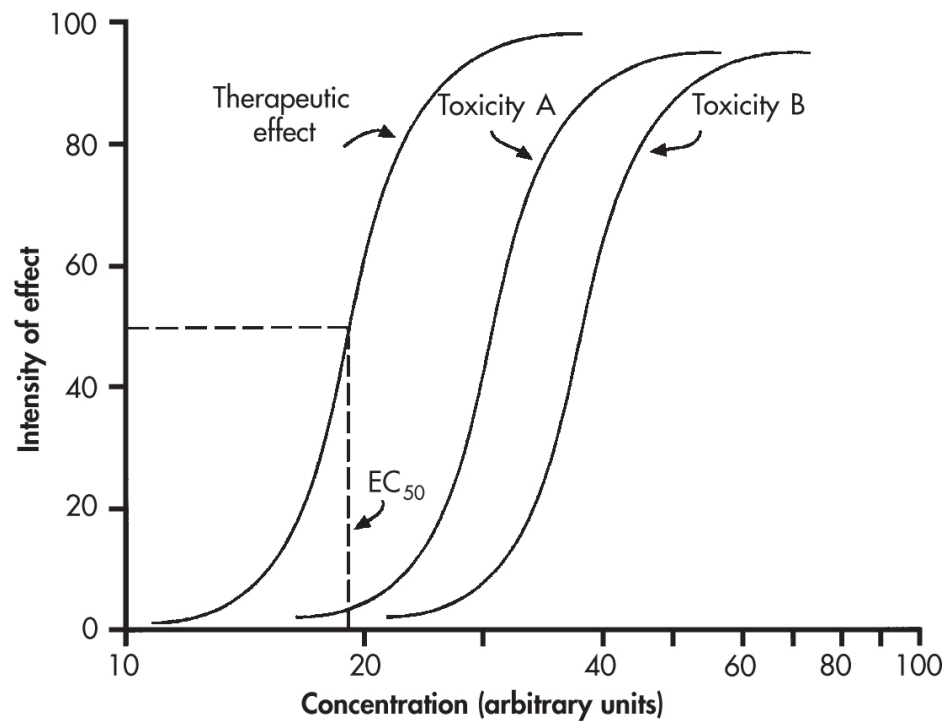
$EC_{50}$  is the concentration that produces half of the  $E_{\max}$ , and  $n$  is an exponent that relates to the shape of the curve.

The dose-effect relationship in [Figure 6-7](#) has practical applications to psychopharmacology. The increase in drug response that results from an increase in dosage depends on the shape and steepness of the theoretical dose-response curve for each patient and the starting point on the curve when a dosage is changed. At low dosages or concentrations, a substantial dose increase may be necessary to achieve an effect. In a linear part of the relationship, dosage increases should result in proportional



increases in effect. In the higher dosage or concentration range, a further increase will not produce a significant increase in effect because of diminishing returns. This phenomenon is likely caused by the saturation of molecular targets by drug molecules above a critical concentration.

Drugs rarely have a single pharmacological effect or interact with only a single receptor population or molecular target. Drugs generally have affinity for multiple receptors; therefore, several theoretical concentration-effect relationships can exist for a given drug. Dose-response curves are shown in [Figure 6-8](#) for a drug that produces a therapeutic effect and mild and severe toxicity. The greater the separation between the curves for therapeutic and toxic effects, the more safely the drug can be administered in increasing doses to achieve therapeutic goals. Estimates of these interrelationships are made in preclinical animal studies and Phase I human studies for drugs in development. In clinical practice, the degree of separation between these curves and their steepness will show both inter- and intraindividual variability. Concurrent medical illness may predispose patients to side effects by effectively causing a shift to the left in one or both of the concentration-toxicity curves. This narrows the range over which doses can be safely administered without incurring adverse effects. The  $EC_{50}$  in [Figure 6-8](#) produces negligible toxicity. Increasing the concentration with a dosage increase to gain an increased response can only be accomplished at the expense of mild toxicity. As the dosage and concentration increase, therapeutic effects approach a plateau, and small increments in concentration result in a disproportionate change in toxicity.

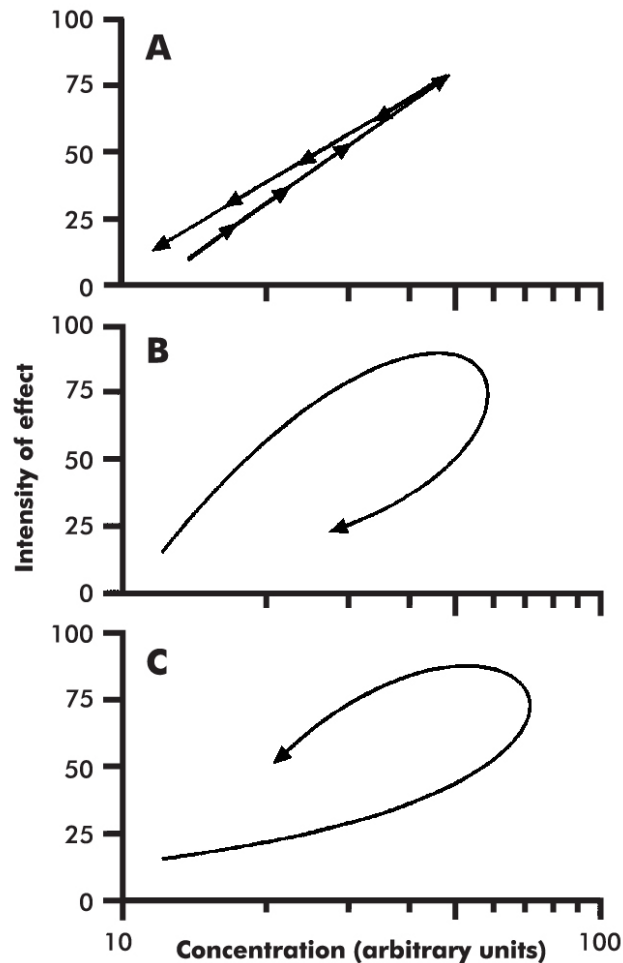


**FIGURE 6-8.** Concentration–effect curves for a drug that produces a therapeutic effect and mild (A) and severe (B) toxicity.

The concentration is shown for a therapeutic effect that produces 50% of the maximum effect ( $EC_{50}$ ).

The pharmacodynamic relationships considered above are most reproducible when pharmacological effects are direct and closely related to plasma concentration. In [Figure 6-9](#), the concentration–effect relationship is shown as a function of drug concentration changes over time. In [Figure 6-9A](#), the changes in effect are almost superimposable with the increase and decrease in concentration. This type of relationship often reflects a direct action of the drug with a single receptor. This

straightforward relationship is generally not observed in psychopharmacology.



**FIGURE 6-9.** Theoretical relationships of drug concentration versus intensity of effect.

Drug concentration changes occur in the direction of the arrow. Effects superimposable on concentration changes **(A)** suggest a direct and reversible interaction between drug and receptor, a clockwise hysteresis curve **(B)** suggests the development of

tolerance, and a counterclockwise curve **(C)** suggests an indirect effect or the presence of an active metabolite.

In [Figure 6-9B](#), the response has begun to diminish with time before concentration begins to decline. This type of plot is known as a *clockwise hysteresis curve*. The observed effect may be explained by the development of tolerance. The time course of tolerance to psychoactive drug effects varies from minutes to weeks. Acute tolerance to some euphoric effects of cocaine can occur following a single dose ([Foltin and Fischman 1991](#)). Tolerance to the sedative effects of various drugs may take weeks. The mechanisms operative in the development of tolerance include acute depletion of a neurotransmitter or cofactor, homeostatic changes in receptor sensitivity from blockade of various transporters, and receptor agonist or antagonist effects. Ultimately, cellular responses to chronic treatment with drugs can alter gene transcription factors as mediators of physical and psychological aspects of tolerance ([Nestler 1993](#)).

A time delay in response occurs when effects are increasing and are maintained despite decreasing plasma drug concentration (see [Figure 6-9C](#)). This results in a *counterclockwise hysteresis curve*. A pharmacokinetic explanation of this lag in response may involve a delay in reaching the critical drug MEC at the effect site until the plasma concentration has already begun to decline. Alternatively, response may depend on multiple “downstream” receptor effects. Response may increase despite a decreasing drug concentration when a metabolite contributes to the observed effects. To overcome these complications, kinetic dynamic models can incorporate an “effect” compartment (see [Figure 6-1](#)). The effect site

equilibrates with plasma after a finite time, which can be assigned a half-life.

---

## **Variability in the Dose-Effect Relationship**

---

A major challenge of treating mental illness with drugs is that both pharmacokinetic and pharmacodynamic variability complicate the dose-effect relationship. The presence of active metabolites, the influence of pharmacogenomics, and the effects of combining two or more drugs contribute to variability. Nonadherence to the prescribed treatment plan on the part of the patient can seriously undermine reliability in the expected effects from pharmacotherapy. Differences in sex, age, and weight and the presence of hepatic or other disease states are major factors that increase the need for individualization of therapy.

### **Active Metabolites**

With the exceptions of lithium and gabapentin, which are renally excreted, drugs used in clinical psychopharmacology are cleared partially or completely by metabolism, primarily in the liver. A general characteristic of highly lipid-soluble drugs is a likelihood of elimination involving metabolism, whereas water-soluble drugs will undergo some degree of clearance from the body by renal elimination in an unchanged form. Many psychoactive drugs produce pharmacologically active metabolites that

distribute to the effect sites (see [Figure 6-1](#)). Like their precursors, metabolites may have multiple pharmacological effects that may be similar to or different from those of the parent drug.

When pharmacotherapy is being switched from one drug or drug class to another, the presence of any active metabolites should be considered. Norfluoxetine, for example, has an average half-life of 8-9 days, much longer than the average of 2-3 days for fluoxetine, its parent drug ([DeVane 1994](#)), and it is an equipotent serotonin reuptake inhibitor. It may take several weeks for this metabolite to clear the body after discontinuation of fluoxetine ([Pato et al. 1991](#)). A similar situation applies to aripiprazole and its active metabolite dehydroaripiprazole, which have elimination half-lives approaching 75 hours and 94 hours, respectively.

Metabolites will accumulate to a steady state in the body in relation to their own elimination half-lives and not those of their parent drugs. For a drug that is nearly completely metabolized in the liver, a characteristic of numerous psychoactive drugs, the metabolites will always have an elimination half-life that is equal to or longer than the half-life of the parent drug. This is a logical conclusion of considering that a metabolite cannot be eliminated faster than it is formed. Of course, administration of the metabolite as a separate molecular entity apart from the parent drug would produce a drug concentration-time curve independent of any influence of the metabolite being formed from a precursor in vivo. For some drugs, the full expression of direct pharmacological effects may not be expected until both the drug and any important active metabolites have all attained their steady-state concentration. For drugs producing indirect effects, when

the response depends on second messengers or a cascade of receptor actions, the waiting period for fully expressed effects may be even longer.

---

## Stereochemistry

---

Stereochemistry or chirality of drug molecules is an important consideration in pharmacokinetics. Many psychoactive drugs exist as two or more stereoisomers or enantiomers with distinctly different biological properties and are marketed as the racemic (i.e., 50:50) mixtures of both isomers. Although enantiomers have identical physicochemical properties, they are often recognized as distinct entities by biological systems and may bind to transport proteins, drug-metabolizing enzymes, and pharmacological effect sites with different affinities. As a result, one enantiomer may possess a significant pharmacological effect, whereas the other stereoisomer may lack that effect or produce different effects. Enantiomers may also differ in their absorption, metabolism, protein binding, and excretion, leading to substantial differences in pharmacokinetic properties ([Darwish et al. 2009](#); [DeVane and Boulton 2002](#)). Furthermore, one isomer may modify the effects of the other. Motivation for development of individual enantiomers has been stimulated by reports that some enantiomers may antagonize or counteract the activity of the other stereoisomer.

The development of single-isomer drugs may offer advantages over use of the racemic mixture. Potential advantages include a less complex and more selective

pharmacological profile, a possibly improved therapeutic index, a more simplified pharmacokinetic profile, a reduced propensity for complex drug interactions, and a more definable relationship between plasma drug concentration and effect. Examples of racemic mixtures in current use include methadone, methylphenidate, bupropion, venlafaxine, fluoxetine, and citalopram. Clearly, each drug needs to be considered individually with regard to its development as a single stereoisomer formulation. Recent examples of successful switches to single isomers include escitalopram, dexamethylphenidate, and armodafinil.

---

## Pharmacogenomics

---

Inheritance accounts for a large part of the variations observed in the ability to eliminate drugs (see [Figure 6-1](#)) among individuals. This forms the basis of *pharmacogenetics*, which is defined as the study of the genetic contribution to the variability in drug response ([Kalow et al. 1986](#); [Price Evans 1993](#)). This term was originally applied to the effect on pharmacokinetics, whereas *pharmacogenomics* dealt specifically with genes mediating drug response. More recently, the terms have been used interchangeably. Numerous association studies have investigated genetic polymorphisms of molecular targets as predictors of disease susceptibility, specific drug response, and drug tolerability. Recent pharmacogenomic studies have yielded advances in five areas: 1) the role of serotonin pharmacogenomic targets in predicting response to antidepressants ([Lekman et al. 2008](#); [Liu et al. 2007](#); [Serretti et al. 2007](#); [Yatham et al. 1999](#)); 2) the role of



potential pharmacogenomic targets in predicting response to prophylactic lithium in bipolar disorder (Masui et al. 2006; Serrenti et al. 2002); 3) the relationship between polymorphisms in serotonin, dopamine, and glutamate receptor genes and antipsychotic response in schizophrenia (Arranz et al. 1998; Bishop et al. 2005); 4) the relationship between the pharmacogenomics of the  $\mu$ -opioid receptor and treatment response to naltrexone in alcohol use disorder (Oslin et al. 2003); and 5) the role of pharmacogenomics in the occurrence of adverse effects from psychopharmacotherapy (Murphy et al. 2003, 2004). Specific pharmacogenomic data are discussed elsewhere in this volume (see Chapter 1, “Basic Principles of Molecular Biology and Genomics,” by Yu and Rasenick).

The genetic differences in pharmacokinetics that have been identified apply mostly to drug metabolism. Renal clearance of drugs appears to be similar in age- and weight-matched healthy subjects with no defined genetic polymorphisms. Genetic polymorphisms have been identified and defined for some drug transporters and several hepatic enzymes important in the cellular transport and metabolism of many drugs used in psychopharmacology.

P-gp, as the most thoroughly studied drug transporter, appears to be significantly involved in the disposition of a variety of psychoactive drugs (Mahar Doan et al. 2002). More than 70 polymorphisms have been reported in the *ABCB1* gene that encodes for P-gp, and three single-nucleotide polymorphisms (SNPs) of P-gp have been associated with functional changes in P-gp activity. The majority of SNP-related reports focus on the silent C3435T SNP of exon 26, which has been associated with changes in expression resulting in increased serum concentrations of

digoxin and fexofenadine ([Hoffmeyer et al. 2000](#); [Kurata et al. 2002](#)). There is emerging evidence that haplotypes of P-gp SNPs may influence drug-resistant epilepsy ([Siddiqui et al. 2003](#)), access of drugs to the brain ([Brunner et al. 2005](#)), and placental transfer of psychoactive drugs ([Rahi et al. 2007](#)). Theoretically, P-gp substrates may act as competitive inhibitors of P-gp, so that drug-drug interactions may also involve P-gp ([Wang et al. 2006](#)).

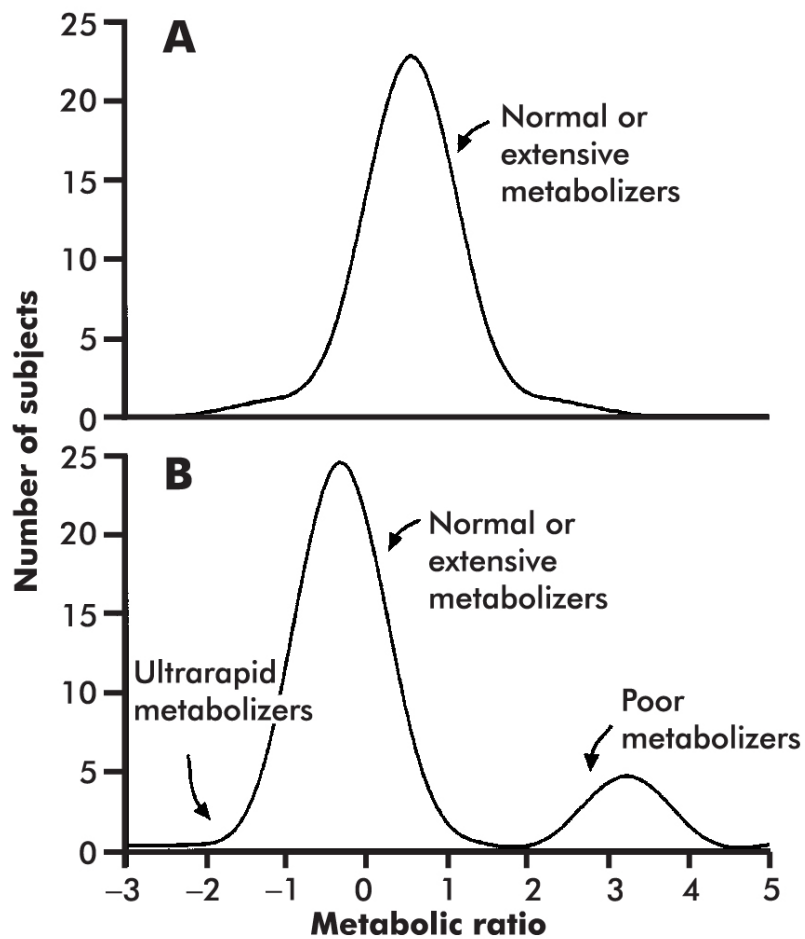
Basic research describing the functional capacity of P-gp to influence the distribution of drug substrates in several tissues, including access to the brain, has led to translational studies that demonstrated *ABCB1* genetic effects on antidepressant outcomes. In 297 depressed patients treated for 6 weeks with antidepressants, several *ABCB1* polymorphisms from 95 genotyped SNPs were associated with remission. A relationship between genotype and remission was found in patients receiving antidepressants that were P-gp substrates but not in patients receiving non-P-gp substrates ([Uhr et al. 2008](#)). This seminal observation led to a prospective study in which *ABCB1* gene test results from 58 depressed inpatients were incorporated into the clinical decision-making process ([Breitenstein et al. 2014](#)). Either increasing the drug dosage or switching to another antidepressant when patient-specific genotyping was available resulted in higher remission rates in patients whose *ABCB1* genotype was available during the hospital stay. The largest trial to date to test the value of *ABCB1* genotyping was performed as part of the prospective multicenter iSPOT antidepressant trial ([Schatzberg et al. 2015](#)). In this intent-to-treat sample of 683 depressed patients, a specific variant, rs10245483, was found to be closely correlated with medication-specific antidepressant efficacy and adverse events. Considered

together, this research affirms that drug transporters influence pharmacodynamic effects by active transport to sites containing molecular targets. Further research will define the principal polymorphisms of value for therapeutic decision making.

Genetic polymorphism in a drug-metabolizing enzyme or transporter can result in subpopulations of people who may deviate substantially from the population mean in their ability to metabolize substrates of the affected enzyme. People who are poor metabolizers constitute at least 1% of the population, but the majority of people are normal or rapid metabolizers, and some are identified as ultrarapid metabolizers due to duplicate or multiple genes. Genetic polymorphisms that define poor metabolizers have been identified for major drug-metabolizing enzymes, including CYP2D6, CYP2C9, and CYP2C19. Studies employing either single drugs or mixtures of drugs as probe compounds have been used to calculate an individual's metabolic ratio (MR)—an index of relative ability to metabolize substrates of a particular enzyme—thereby providing a phenotype identity. The MR is equal to the concentration of parent drug divided by the concentration of the major metabolite determined in the urine excreted during a timed interval following an oral dose.

Many pharmacogenetic studies yield results similar to the frequency distribution histograms shown in [Figure 6-10](#). The frequency in [Figure 6-10A](#) is expected when enzyme activity is distributed normally within a population without genetic polymorphisms. The range of values for the MR may be broad, which reflects a large variability in oxidation reaction capacity in the study population. Thus, vastly different dosages are required for many patients. The bimodal distribution in [Figure 6-10B](#) is a typical finding for

an enzyme that has a genetic polymorphism. Values above the antinode for the reference (or “probe”) drug define poor metabolizers, who are clearly differentiated from normal or extensive metabolizers. The probe drug need not be metabolized by only one enzyme (as is exemplified by the use of caffeine for phenotyping the enzyme activity of *N*-acetyltransferase and CYP1A2), but the overlap of other enzymes should be minimal in order to produce the specific metabolite of interest ([Denaro et al. 1996](#)). Comparisons of MRs across many patients of different ethnic origins have yielded measures of variability in enzyme activity in the population ([Lin et al. 1996](#)). The widespread availability of a commercial microarray chip for genotyping a small group of CYP enzymes has eliminated the need to perform phenotyping procedures in most circumstances. Although a genotypical extensive metabolizer may be phenotypically a poor metabolizer, the opposite situation does not occur.



**FIGURE 6-10.** Theoretical frequency histograms of the distribution of the metabolic ratio of a model substrate showing a unimodal distribution among a population of normal or extensive metabolizers **(A)** and a bimodal distribution among a population including poor metabolizers and ultrarapid metabolizers **(B)**.

The potential clinical consequences of being a poor metabolizer will vary according to the activity of the administered drug and any active metabolites. When the

drug is active and a pathway is affected (a situation that usually produces an inactive metabolite), higher drug concentrations can be expected. This result can lead to an exaggerated response and potential toxicity. The most serious consequences would be expected from drugs with a narrow therapeutic window. For example, when perphenazine (a drug with a narrow therapeutic window) was given to elderly patients who were poor metabolizers of CYP2D6, extrapyramidal side effects were exaggerated ([Pollock et al. 1995](#)). If the therapeutic effects depend on the formation of an active metabolite, diminished response can be expected from a lower concentration of metabolite in poor metabolizers. For example, normal doses of codeine, which is partially metabolized to the more potent morphine, may provide an inadequate analgesic effect.

For CYP2D6, the poor-metabolizer status is inherited as an autosomal recessive trait. At least 70 different alleles have been defined for the CYP2D6 gene, and many types of null mutations result in impaired CYP2D6 activity ([Gonzalez and Idle 1994](#)). Several techniques available in the field of molecular biology have a high sensitivity for detecting the mutant alleles and can establish a genotype. This procedure can be beneficial in drug development to profile test compounds for affinity to enzymes and transporters and in some forensic circumstances to help establish the cause of excessive drug concentrations. Genetic phenotyping is potentially more clinically useful than genotyping and can be done when patients are drug free to characterize their relative ability to metabolize drug substrates. About 1% of Caucasians are ultrarapid metabolizers because of an amplification of the functional CYP2D6 gene ([Johansson et al. 1993](#)). These patients have the lowest MR when phenotyped with a CYP2D6 substrate with a high urinary

concentration of metabolite and a low parent drug concentration (see [Figure 6-10B](#)). The implication is that these individuals will often require very high dosages of drugs that are CYP2D6 substrates. Research is needed to support phenotyping and genotyping as an aid in the initial selection of drugs and drug dosages for promoting precision medicine.

Of the human CYP enzymes, three families (CYP1, CYP2, and CYP3) are involved in drug metabolism ([Guengerich 1992](#); [Wrighton and Stevens 1992](#)). The enzymes most relevant to psychopharmacology are CYP enzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. Interindividual differences in the expression and catalytic activities of CYP result in a large variation in the in vivo metabolism of drugs. Average immunoquantified levels of the various specific CYP enzymes in 60 human liver microsomal samples were reported by [Shimada et al. \(1994\)](#). [Benet et al. \(1996\)](#) and [Wrighton and Stevens \(1992\)](#) estimated the participation of the liver CYP enzymes in drug metabolism based on known substrates and pathways. These values are compared in [Table 6-1](#). Among the CYP enzymes in the liver, CYP3A is present in the largest amounts and participates in the metabolism of the greatest number of drugs. Together, CYP3A and CYP2D6 participate in the metabolism of an estimated 80% of currently used drugs.

---

**TABLE 6-1. Comparison of average immunoquantified levels of the various cytochrome P450 (CYP) enzymes in liver microsomes, with their estimated participation in drug metabolism**

---

<b>CYP enzyme</b>	<b>Average immunoquantified level in human liver microsomal samples (%)<sup>a</sup></b>	<b>Estimated participation in drug metabolism (%)<sup>b</sup></b>
1A2	13	<10
2A6	4	<10
2B6	0.2	(Marginal)
2E1	7	<10
2C	18	10
2D6	1.5	30
3A	29	50
Unidentified	27.3	
Total	100	

<sup>a</sup>Shimada et al. 1994.

<sup>b</sup>Benet et al. 1996; Wrighton and Stevens 1992.

In summary, recent pharmacogenetic investigations have yielded fruitful data relating to the causes of pharmacokinetic variability in the dose-effect relationship. The polymorphism of molecular drug targets in the brain is a source of pharmacodynamic variability. Pharmacogenetic studies have extensively used metabolic phenotyping with model substrates for specific enzymes to characterize several genetic polymorphisms. The practical implications of metabolic phenotyping are most meaningful when the metabolic pathways of therapeutically administered drugs are known, when the functional significance of transporters involved in drug disposition is defined, and when drug concentration has been correlated to either therapeutic or



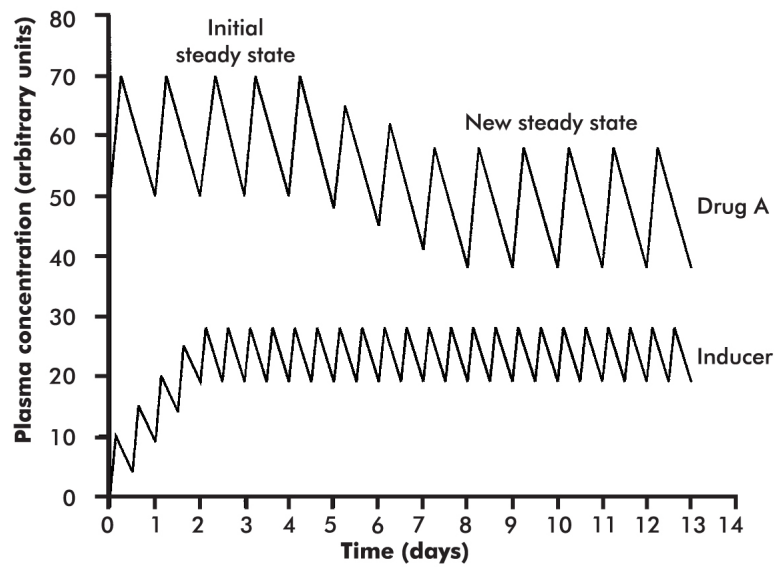
toxic effects ([Gonzalez and Idle 1994](#)). In this situation, knowledge of enzyme activity will serve as a guide to initial dosing and also allow prediction of the significance of potential drug-drug interactions.

## Drug Interactions

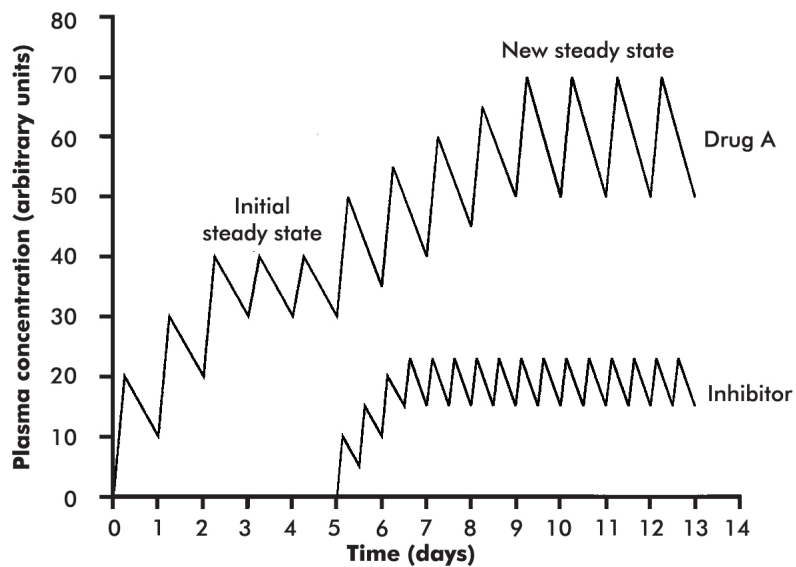
Drugs are frequently coadministered to achieve therapeutic effects from the combined actions at effect sites or to treat the adverse effects caused by one drug with another. Drug combinations routinely used include hypnotics with antidepressants, anticholinergic-antiparkinsonian drugs with antipsychotics, benzodiazepines with selective serotonin reuptake inhibitors (SSRIs), and mood stabilizers with antipsychotics. The use of more than one antidepressant or antipsychotic in combination for specific patients is increasingly encountered in clinical practice. When more than one drug is administered concurrently to a patient, the drugs may interact either in a positive manner or in a negative or undesired way because of either pharmacodynamic or pharmacokinetic mechanisms.

Pharmacodynamic interactions are likely to occur when an MAO inhibitor is combined with an SSRI (producing a serotonin syndrome) and when ethanol is combined with a benzodiazepine (leading to psychomotor impairment). Two drugs may have affinity for the same receptor sites in the brain and produce additive or synergistic effects, or their actions may oppose each other through antagonistic interactions at receptor sites. Most often, pharmacodynamic mechanisms are not such obvious causes of drug interactions and are less easily determined and investigated than pharmacokinetic interactions.

The kinetics of drug interactions has been extensively described and is a routine focus of clinical investigations as part of drug development ([Rowland and Matin 1973](#)). Two major mechanisms of drug interactions involve an alteration of metabolism through either induction or inhibition of hepatic CYP enzymes. Major differences exist in the pharmacokinetic consequences of these interactions. The expected changes are illustrated in [Figures 6-11](#) and [6-12](#). In [Figure 6-11](#), the steady-state plasma concentration of drug *A* following continuous intermittent dosing is altered by the addition of an enzyme inducer. After the inducer is started, the effects on the steady-state concentration of drug *A* do not occur for several days while additional enzyme that metabolizes drug *A* is synthesized. Ultimately, an increase in the metabolic clearance of drug *A* accompanied by a decrease in its steady-state plasma concentration occurs. The degree to which clearance is increased will depend on the relative importance of the particular induced enzymes in the overall elimination of drug *A* and the dose and potency of the inducer. A clinically significant example of this type of interaction is the loss of oral contraceptive effect as a consequence of carbamazepine induction of CYP3A4. The time required for a new steady state of drug *A* to occur following enzyme induction and the extent to which plasma concentrations decrease will depend on how marked a change in clearance occurs and the resulting change in drug half-life.



**FIGURE 6-11.** Predicted plasma concentration changes from the coadministration of an inducer of the metabolism of drug A.



---

**FIGURE 6-12.** Predicted plasma concentration changes from the coadministration of an inhibitor of the metabolism of drug A.

In contrast to the delayed effects of an inducer on drug A, the addition of an inhibitor causes an immediate increase in the plasma concentration of drug A (see [Figure 6-12](#)). This increase occurs as a result of a competitive inhibition of the relevant hepatic enzyme. Drug A's plasma concentration rises to a new steady state consistent with a change in its clearance. The time required to achieve the new steady state is greater than the time to achieve the initial steady state, because the half-life is now prolonged relative to its original value. The full effect of an inhibitory interaction may not be realized until the inhibitor also reaches a steady state, because the degree of inhibition will also depend on the concentration of the inhibitor ([Houston 1994](#); [von Moltke et al. 1994, 1995](#)).

Drug interactions are graded phenomena. The degree of interaction depends on the concentration of interacting drugs and, therefore, on the dose and timing of administration. Drug interactions are most likely to be detected when therapy with an interacting drug is initiated or discontinued. The clinical significance will depend on the particular drugs involved, the physiological state of the patient, the presence of concurrent illness, and other factors. Drugs with a narrow therapeutic window (concentration range) over which therapeutic effects are present without incurring toxicity are more likely to be involved in clinically significant drug interactions. Such drugs include theophylline, certain antiepileptic drugs, and antiarrhythmics. Sotalol and dofetilide are extensively used to treat atrial fibrillation, but drug interactions or dosages

that increase the drug concentration excessively can lead to a widening of the QTc interval sufficient to cause a potentially fatal *torsades de pointes* arrhythmia.

When a specific drug from a class of drugs is being selected to treat mental illness, its efficacy, safety, cost, and history of response are pertinent considerations. With the introduction of the SSRIs, the critical importance of potential drug interactions also became apparent. Some SSRIs have been shown in vitro and in vivo to be potent inhibitors of specific CYP isoenzymes ([Nemeroff et al. 1996](#); [von Moltke et al. 1994, 1995](#)). The rational selection of an antidepressant should include consideration of its potential CYP-mediated interactions with coprescribed drugs. Reviews (e.g., [Nemeroff et al. 1996](#)) have described the specific in vivo reports in more detail. Although numerous interactions are possible, their clinical significance depends on multiple factors in addition to a rise in drug concentration ([DeVane 2006](#); [Preskorn and Werder 2006](#)). Compensatory mechanisms and patterns of practice that minimize the expression of significant interactions include parallel pathways of drug elimination, dose dependence of inhibition and induction, initiation at lower starting doses, and careful attention to patient response ([DeVane 2006](#)). Although some interactions have an unequivocal high likelihood for adverse events (e.g., drug combinations that can result in a serotonin syndrome), severe adverse interactions appear to be rare events.

In vitro methods to predict in vivo interactions have appeared and are based on accepted pharmacokinetic principles ([Houston 1994](#); [von Moltke et al. 1994, 1995](#)). These screening techniques are now used extensively in the pharmaceutical industry in drug development. The expanding database on isoenzyme-specific metabolic

characteristics of new and established drugs holds promise for enabling a more informed approach to combination pharmacotherapy based on pharmacokinetic principles. The U.S. Food and Drug Administration now requires the results of testing for enzyme and transporter inhibition to be included in drug product labeling ([Lee et al. 2014](#)).

---

## Conclusion

---

The use of drugs in psychopharmacology can be problematic as a result of pharmacokinetic and pharmacodynamic variability in the dose-effect relationship. Some sources of variability can be controlled through application of pharmacokinetic principles in dosage regimen design and therapeutic drug monitoring. Improved understanding of pharmacodynamic principles permits greater individualization of dosage regimens. Knowledge regarding genetic contributions to drug response and to interactions between drugs is rapidly expanding. Future application of this knowledge will further enhance pharmacotherapy for mentally ill patients.

---

## References

---

- Akil A, Bies RR, Pollock BG, et al: A population pharmacokinetic model for R- and S-citalopram and desmethylocitalopram in Alzheimer's disease patients with agitation. *J Pharmacokinet Pharmacodyn* 43(1):99-109, 2016 26611790
- Arranz MJ, Munro J, Sham P, et al: Meta-analysis of studies on genetic variation in 5-HT<sub>2A</sub> receptors and clozapine

- response. *Schizophr Res* 32(2):93-99, 1998 9713904
- Azzaro AJ, Ziemniak J, Kemper E, et al: Selegiline transdermal system: an examination of the potential for CYP450-dependent pharmacokinetic interactions with 3 psychotropic medications. *J Clin Pharmacol* 47(2):146-158, 2007 17244765
- Benet LZ, Kroetz DL, Sheiner LB: Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th Edition. Edited by Hardman JG, Limbird LE. New York, McGraw-Hill, 1996, pp 3-27
- Bies RR, Feng Y, Lotrich FE, et al: Utility of sparse concentration sampling for citalopram in elderly clinical trial subjects. *J Clin Pharmacol* 44(12):1352-1359, 2004 15545305
- Bishop JR, Ellingrod VL, Moline J, Miller D: Association between the polymorphic GRM3 gene and negative symptom improvement during olanzapine treatment. *Schizophr Res* 77(2-3):253-260, 2005 15913960
- Breitenstein B, Scheuer S, Pfister H, et al: The clinical application of ABCB1 genotyping in antidepressant treatment: a pilot study. *CNS Spectr* 19(2):165-175, 2014 23880209
- Brunner M, Langer O, Sunder-Plassmann R, et al: Influence of functional haplotypes in the drug transporter gene ABCB1 on central nervous system drug distribution in humans. *Clin Pharmacol Ther* 78(2):182-190, 2005 16084852
- Darwish M, Kirby M, Hellriegel ET, et al: Armodafinil and modafinil have substantially different pharmacokinetic profiles despite having the same terminal half-lives: analysis of data from three randomized, single-dose, pharmacokinetic studies. *Clin Drug Investig* 29(9):613-623, 2009 19663523

- Denaro CP, Wilson M, Jacob P 3rd, et al: Validation of urine caffeine metabolite ratios with use of stable isotope-labeled caffeine clearance. *Clin Pharmacol Ther* 59(3):284-296, 1996 8653991
- DeVane CL: Pharmacokinetics of the newer antidepressants: clinical relevance. *Am J Med* 97(6A):13S-23S, 1994 7992822
- DeVane CL: Clinical significance of drug binding, protein binding, and binding displacement drug interactions. *Psychopharmacol Bull* 36(3):5-21, 2002 12473961
- DeVane CL: Immediate-release versus controlled-release formulations: pharmacokinetics of newer antidepressants in relation to nausea. *J Clin Psychiatry* 64 (suppl 18):14-19, 2003 14700450
- DeVane CL: Antidepressant-drug interactions are potentially but rarely clinically significant. *Neuropsychopharmacology* 31(8):1594-1604, discussion 1614-1615, 2006 16847446
- DeVane CL, Boulton DW: Great expectations in stereochemistry: focus on antidepressants. *CNS Spectr* 7 (4 suppl 1):28-33, 2002 15131490
- DeVane CL, Liston HL: An explanation of the second-dose effect in pharmacokinetics and its meaning for clinical psychopharmacology. *Psychopharmacol Bull* 35(1): 42-52, 2001 12397869
- DeVane CL, Stowe ZN, Donovan JL, et al: Therapeutic drug monitoring of psychoactive drugs during pregnancy in the genomic era: challenges and opportunities. *J Psychopharmacol* 20 (4 suppl):54-59, 2006 16785271
- de Waziers I, Cugnenc PH, Yang CS, et al: Cytochrome P 450 isoenzymes, epoxide hydrolase and glutathione transferases in rat and human hepatic and extrahepatic tissues. *J Pharmacol Exp Ther* 253(1):387-394, 1990 2329521
- Foltin RW, Fischman MW: Smoked and intravenous cocaine in humans: acute tolerance, cardiovascular and



- subjective effects. *J Pharmacol Exp Ther* 257(1):247-261, 1991 2019989
- George CF, Shand DG, Renwick AG (eds): *Presystemic Drug Elimination*. London, Butterworth Scientific, 1982
- Giacomini KM, Huang SM, Tweedie DJ, et al; International Transporter Consortium: Membrane transporters in drug development. *Nat Rev Drug Discov* 9(3):215-236, 2010 20190787
- Gibaldi M, Perrier D: *Pharmacokinetics*. New York, Marcel Dekker, 1975
- Gonzalez FJ, Idle JR: Pharmacogenetic phenotyping and genotyping. Present status and future potential. *Clin Pharmacokinet* 26(1):59-70, 1994 8137598
- Greenblatt DJ, Shader RI, Koch-Weser J: Slow absorption of intramuscular chlordiazepoxide. *N Engl J Med* 291(21):1116-1118, 1974 4416981
- Greenblatt DJ, Allen MD, MacLaughlin DS, et al: Diazepam absorption: effect of antacids and food. *Clin Pharmacol Ther* 24(5):600-609, 1978 699484
- Greenblatt DJ, Allen MD, Harmatz JS, et al: Diazepam disposition determinants. *Clin Pharmacol Ther* 27(3):301-312, 1980 7357789
- Greenblatt DJ, Sellers EM, Koch-Weser J: Importance of protein binding for the interpretation of serum or plasma drug concentrations. *J Clin Pharmacol* 22(5-6):259-263, 1982 7107972
- Guengerich FP: Human cytochrome P-450 enzymes. *Life Sci* 50(20):1471-1478, 1992 1579042
- Hoffmeyer S, Burk O, von Richter O, et al: Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc Natl Acad Sci U S A* 97(7):3473-3478, 2000 10716719
- Houston JB: Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance. *Biochem*

- Pharmacol 47(9):1469–1479, 1994 8185657
- Johansson I, Lundqvist E, Bertilsson L, et al: Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. *Proc Natl Acad Sci U S A* 90(24):11825–11829, 1993 7903454
- Kalow W, Goedde WH, Agarwal DP: *Ethnic Differences in Reactions to Drugs and Xenobiotics*. New York, Alan R Liss, 1986
- Kolars JC, Schmiedlin-Ren P, Schuetz JD, et al: Identification of rifampin-inducible P450III<sub>A4</sub> (CYP3A<sub>4</sub>) in human small bowel enterocytes. *J Clin Invest* 90(5): 1871–1878, 1992 1430211
- Kurata Y, Ieiri I, Kimura M, et al: Role of human MDR1 gene polymorphism in bioavailability and interaction of digoxin, a substrate of P-glycoprotein. *Clin Pharmacol Ther* 72(2):209–219, 2002 12189368
- Lee SC, Zhang L, Huang SM: Regulatory science perspectives on transporter studies in drug development, in *Drug Transporters: Molecular Characterization and Role in Drug Disposition*, 2nd Edition. Edited by You G, Morris ME. Hoboken, NJ, Wiley, 2014, pp 473–487
- Lekman M, Laje G, Charney D, et al: The FKBP5-gene in depression and treatment response—an association study in the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) Cohort. *Biol Psychiatry* 63(12):1103–1110, 2008 18191112
- Lin K-M, Poland RE, Wan Y-JY, et al: The evolving science of pharmacogenetics: clinical and ethnic perspectives. *Psychopharmacol Bull* 32(2):205–217, 1996 8783890
- Liu Z, Zhu F, Wang G, et al: Association study of corticotropin-releasing hormone receptor1 gene polymorphisms and antidepressant response in major depressive disorders. *Neurosci Lett* 414(2):155–158, 2007 17258395

- Mahar Doan KM, Humphreys JE, Webster LO, et al: Passive permeability and P-glycoprotein-mediated efflux differentiate central nervous system (CNS) and non-CNS marketed drugs. *J Pharmacol Exp Ther* 303(3):1029-1037, 2002 12438524
- Masui T, Hashimoto R, Kusumi I, et al: Lithium response and Val66Met polymorphism of the brain-derived neurotrophic factor gene in Japanese patients with bipolar disorder. *Psychiatr Genet* 16(2):49-50, 2006 16538178
- Murphy GM Jr, Kremer C, Rodrigues HE, et al: Pharmacogenetics of antidepressant medication intolerance. *Am J Psychiatry* 160(10):1830-1835, 2003 14514498
- Murphy GM Jr, Hollander SB, Rodrigues HE, et al: Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry* 61(11):1163-1169, 2004 15520364
- Nemeroff CB, DeVane CL, Pollock BG: Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 153(3):311-320, 1996 8610817
- Nestler EJ: Cellular responses to chronic treatment with drugs of abuse. *Crit Rev Neurobiol* 7(1):23-39, 1993 8385579
- Nigam SK: What do drug transporters really do? *Nat Rev Drug Discov* 14(1):29-44, 2015 25475361
- Oslin DW, Berrettini W, Kranzler HR, et al: A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology* 28(8):1546-1552, 2003 12813472
- Pacchioni AM, Gabriele A, Donovan JL, et al: P-glycoprotein inhibition potentiates the behavioural and neurochemical actions of risperidone in rats. *Int J*

- Neuropsychopharmacol 13(8):1067-1077, 2010  
19835667
- Paine MF, Shen DD, Kunze KL, et al: First-pass metabolism of midazolam by the human intestine. Clin Pharmacol Ther 60(1):14-24, 1996 8689807
- Paine MF, Criss AB, Watkins PB: Two major grapefruit juice components differ in time to onset of intestinal CYP3A4 inhibition. J Pharmacol Exp Ther 312(3):1151-1160, 2005 15485894
- Pato MT, Murphy DL, DeVane CL: Sustained plasma concentrations of fluoxetine and/or norfluoxetine four and eight weeks after fluoxetine discontinuation. J Clin Psychopharmacol 11(3):224-225, 1991 1741813
- Pollock BG, Mulsant BH, Sweet RA, et al: Prospective cytochrome P450 phenotyping for neuroleptic treatment in dementia. Psychopharmacol Bull 31(2):327-331, 1995 7491387
- Preskorn S, Werder S: Detrimental antidepressant drug-drug interactions: are they clinically relevant? Neuropsychopharmacology 31(8):1605-1612, discussion 1613, 2006 16847447
- Price Evans DA: Genetic Factors in Drug Therapy. Cambridge, MA, Cambridge University Press, 1993
- Rahi M, Heikkinen T, Härtter S, et al: Placental transfer of quetiapine in relation to P-glycoprotein activity. J Psychopharmacol 21(7):751-756, 2007 17259208
- Rolan PE: Plasma protein binding displacement interactions—why are they still regarded as clinically important? Br J Clin Pharmacol 37(2):125-128, 1994 8186058
- Rowland M, Matin SB: Kinetics of drug-drug interactions. Journal of Pharmacokinetics and Biopharmaceutics 1(6):553-567, 1973 doi: 10.1007/BF01059791
- Schatzberg AF, DeBattista C, Lazzeroni LC, et al: ABCB1 genetic effects on antidepressant outcomes: a report from the iSPOT-D trial. Am J Psychiatry 172(8):751-759, 2015 25815420

- Sellers EM: Plasma protein displacement interactions are rarely of clinical significance. *Pharmacology* 18(5):225-227, 1979 482342
- Serretti A, Lorenzi C, Lilli R, et al: Pharmacogenetics of lithium prophylaxis in mood disorders: analysis of COMT, MAO-A, and Gbeta3 variants. *Am J Med Genet* 114(4):370-379, 2002 11992559
- Serretti A, Kato M, De Ronchi D, et al: Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry* 12(3):247-257, 2007 17146470
- Shimada T, Yamazaki H, Mimura M, et al: Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 270(1):414-423, 1994 8035341
- Siddiqui A, Kerb R, Weale ME, et al: Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. *N Engl J Med* 348(15):1442-1448, 2003 12686700
- Uhr M, Tontsch A, Namendorf C, et al: Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. *Neuron* 57(2): 203-209, 2008 18215618
- von Moltke LL, Greenblatt DJ, Cotreau-Bibbo MM, et al: Inhibition of desipramine hydroxylation in vitro by serotonin-reuptake-inhibitor antidepressants, and by quinidine and ketoconazole: a model system to predict drug interactions in vivo. *J Pharmacol Exp Ther* 268(3):1278-1283, 1994 8138941
- von Moltke LL, Greenblatt DJ, Court MH, et al: Inhibition of alprazolam and desipramine hydroxylation in vitro by paroxetine and fluvoxamine: comparison with other

- selective serotonin reuptake inhibitor antidepressants. J Clin Psychopharmacol 15(2):125-131, 1995 7782485
- Wagner J: Biopharmaceutics and Relevant Pharmacokinetics. Hamilton, IL, Drug Intelligence Publications, 1971
- Wang JS, DeVane CL, Gibson BB, et al: Population pharmacokinetic analysis of drug-drug interactions among risperidone, bupropion, and sertraline in CF1 mice. Psychopharmacology (Berl) 183(4):490-499, 2006 16283256
- Wrighton SA, Stevens JC: The human hepatic cytochromes P450 involved in drug metabolism. Crit Rev Toxicol 22(1):1-21, 1992 1616599
- Yatham LN, Liddle PF, Dennie J, et al: Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment: a positron emission tomography study with fluorine-18-labeled setoperone. Arch Gen Psychiatry 56(8):705-711, 1999 10435604

## CHAPTER 7

# Brain Imaging in Psychopharmacology

Ebrahim Haroon, M.D.

Helen Mayberg, M.D.

The organization and content of this chapter represent a marked change from our chapter in the previous edition of this textbook. The approach has been modified to describe how brain-imaging techniques singly or in combination are currently being used to inform contemporary research in psychopharmacology and to guide treatment selection. Although a thorough, in-depth discussion of these topics is beyond the scope of this chapter, key references will be provided to guide further reading. In addition to introducing newer research, we have retained many of the older “classic” references that continue to inform our knowledge of neuroimaging to enable readers to easily locate and access these foundational papers.

---

### Neuroimaging Techniques

---

*Neuroimaging* is a generic term encompassing a number of techniques and methods aimed at detecting meaningful information through the acquisition of brain images of different kinds. A first classification of these techniques may be technology based, as follows:

- *Magnetic resonance imaging (MRI)*: Based on magnetic resonance (MR) scanning equipment
- *Positron emission tomography (PET) and single photon emission computed tomography (SPECT)*: Based on tissue labeling by radioisotopes to measure brain activity

- *Electroencephalography (EEG) and magnetoencephalography (MEG)*: Enable study of brain activity and connectivity using intrinsic electrical and magnetic properties of neural circuitry

An alternative classification might be based on the types of measurement provided, as follows:

- *Vascular (hemodynamic) effects engendered by neural activity*: PET ( $\text{H}_2^{15}\text{O}$ ), functional MRI (fMRI; blood oxygenation level-dependent [BOLD] contrast, perfusion imaging), SPECT
- *Metabolic demand*: PET ( $^{18}\text{fluorodeoxyglucose}$  [ $^{18}\text{FDG}$ ])
- *Receptor density*: PET/SPECT (radioligands)
- *Neurochemistry*: magnetic resonance spectroscopy (MRS)
- *Neural connectivity*: MRI (diffusion tensor imaging), fMRI-based functional connectivity analysis
- *Surface electrical/electromagnetic effects of brain activity*: EEG/MEG
- *Structural morphometry of brain structures*: MRI

---

## Positron Emission Tomography and Single Photon Emission Computed Tomography

---

PET and SPECT are somewhat similar techniques in that they both use injection of radioactive tracers (radiopharmaceuticals) to assess bodily functions and to diagnose and treat disease ([National Institute of Biomedical Imaging and Bioengineering 2013](#)). The path of these radioactive tracers, which emit radioactive radiation, is picked up by specialized cameras equipped with receiving counters placed on a computed tomographic scanner. SPECT techniques rely on the emission of gamma rays, whereas PET relies on the emission of positrons. Each of these techniques has specific advantages and disadvantages that render it particularly useful for certain purposes. The unique properties of gamma ray emissions and the relative inexpensiveness of the technology have made SPECT the de facto standard for obtaining key medical imaging technology data, including myocardial perfusion imaging and scans to study bone rarefaction. Although important experiments have been conducted with SPECT, its relative lack of spatial resolution has rendered SPECT techniques less useful in studying brain functions. For this reason, most of this introduction will be devoted to PET imaging.

PET was developed from in vivo autoradiographic techniques, wherein an animal is typically injected with a biologically interesting compound synthesized with a radioisotope (e.g.,  $^3\text{H}$ ). When the animal is sacrificed, the local tissue radioactivity is easily quantified. PET requires three basic technologies: the capability to produce positron-emitting compounds, the ability to detect



simultaneously emitted gamma rays, and the computational power to reconstruct the sources of emission (Haroon et al. 2009). Positrons, or positively charged electrons (antimatter), have a particular advantage over other radioactive compounds. When a positron encounters an electron, the two annihilate each other, and their collective energy is transformed into two high-energy photons that are emitted in exactly opposite directions. Because the photons travel 180° apart, it is easy to arrange a ring of detectors to determine where the annihilation occurred. When two detectors are activated simultaneously, one knows that the emission occurred somewhere along the line connecting the two detectors. By collecting the counts over a period of time, say 60 seconds, and over a full sphere surrounding the subject's head, it becomes possible to reconstruct the geometry of the source.

Positrons are synthesized indirectly, through the radioactive decay of particular isotopes. The most commonly used isotopes (carbon-11 [ $^{11}\text{C}$ ], oxygen-15 [ $^{15}\text{O}$ ], fluorine-18 [ $^{18}\text{F}$ ], nitrogen-13 [ $^{13}\text{N}$ ]) are produced in a cyclotron by the bombardment of targets with high-energy protons. This process results in a radioactive version of a biological ion (e.g.,  $^{15}\text{O}_2$ ) that can then be used in any chemical reaction (e.g., oxidation-reduction reaction with product  $\text{H}_2^{15}\text{O}$ ). After appropriate purification procedures, these compounds can be injected intravenously into a human subject. Following injection, the isotope reaches the brain in approximately 20 seconds, where it undergoes radioactive decay due to positron emission, with decay latencies dependent on the half-life of the particular isotope (e.g., 2 minutes for  $^{15}\text{O}$ ).

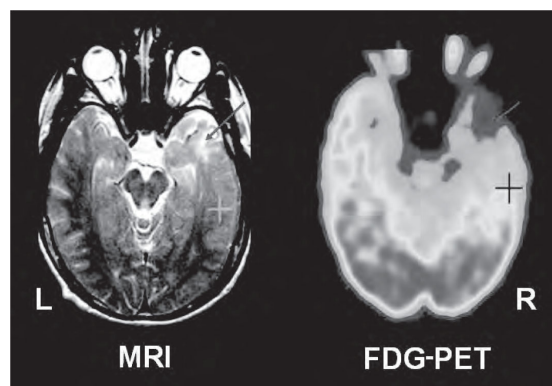
Because the photons emitted during positron decay are fairly high in energy (511-keV gamma rays), they tend to pass through matter with relative ease. A specialized detector, called a scintillation detector, is required to accurately count the decays in a directional fashion. PET scanners consist of rings of scintillation detectors arranged in parallel planes. An individual detector would be constructed from a scintillating crystal, either bismuth germanate (BGO) or lutetium oxyorthosilicate (LSO), and amplification electronics. When the ionized radiation (consisting of photons or gamma rays) enters the crystal, it loses its energy (through either the photoelectric or the Compton effect), resulting in the production of electrons. These electrons further interact with the crystal, resulting in the production of visible-wavelength photons. These photons are then detected and amplified by a photomultiplier tube and converted into an electrical pulse. A "coincidence circuit" allows for identification of the detector that picks up the 180° emitted gamma ray.

Depending on the injected molecule, a particular regional distribution will occur. In the case of  $\text{H}_2^{15}\text{O}$ , it will follow the regional cerebral blood flow (rCBF). Other compounds will cross the blood-brain barrier and bind to specific receptors, in which case the distribution of radioactivity will reflect receptor concentration.  $^{18}\text{F}$ FDG, a commonly used tracer, is metabolized by hexokinase during glycolysis, like glucose. Unlike glucose-6 phosphate,  $^{18}\text{F}$ FDG is not

metabolized further but instead accumulates intracellularly, yielding a measurement of local metabolic activity ([Kennedy et al. 1976](#); [Reivich et al. 1979](#)).

## Metabolic PET Studies

Metabolic studies use  $^{18}\text{F}$ FDG to measure regional glucose metabolism.  $^{18}\text{F}$ FDG, like all  $^{18}\text{F}$  compounds, has the advantage of a relatively long half-life (110 minutes), which allows it to be synthesized in one location and administered to a subject doing a particular task in another location remote from the PET scanner while remaining trapped in brain regions according to the local metabolic rate during scanning. The main disadvantage of  $^{18}\text{F}$ FDG PET is that the compound's long half-life results in effectively no temporal resolution. Instead, it offers a snapshot of a particular brain state, time-averaged over 20–60 minutes. [Figure 7-1](#) shows functional localization of an epileptic focus in the right temporal lobe during presurgical workup.



**FIGURE 7-1.** Functional localization of an epileptic focus in the right temporal lobe during presurgical workup using magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET).

*See [Plate 15](#) to view this figure in color.*

*Source.* Image courtesy of Carolyn C. Meltzer, M.D.

Most FDG uptake studies are based on the assumption that glucose uptake and neural activity at the synaptic level might be coupled. A caveat must be borne in mind when evaluating studies using FDG-PET. Glutamate, the main excitatory neurotransmitter in the brain, is removed from the synapse through a process of uptake by astroglial tissues, thereby terminating neural activation ([Magistretti and Pellerin 1999a, 1999b](#)). However, studies have shown that uptake of glutamate by astroglia can by itself stimulate glucose (and FDG) uptake ([Magistretti 2006](#); [Magistretti and Pellerin 1999a](#)). In fact, deactivation might actually be coupled with increased glucose uptake in a variety of

conditions ([Magistretti 2006](#)). Thus, the same problems that accompany studies of fMRI—i.e., whether the signal is actively excitatory versus actively inhibitory—are present in FDG-PET studies as well. Notwithstanding these limitations, PET studies have provided important information that helps to identify which patient will respond best to which treatment.

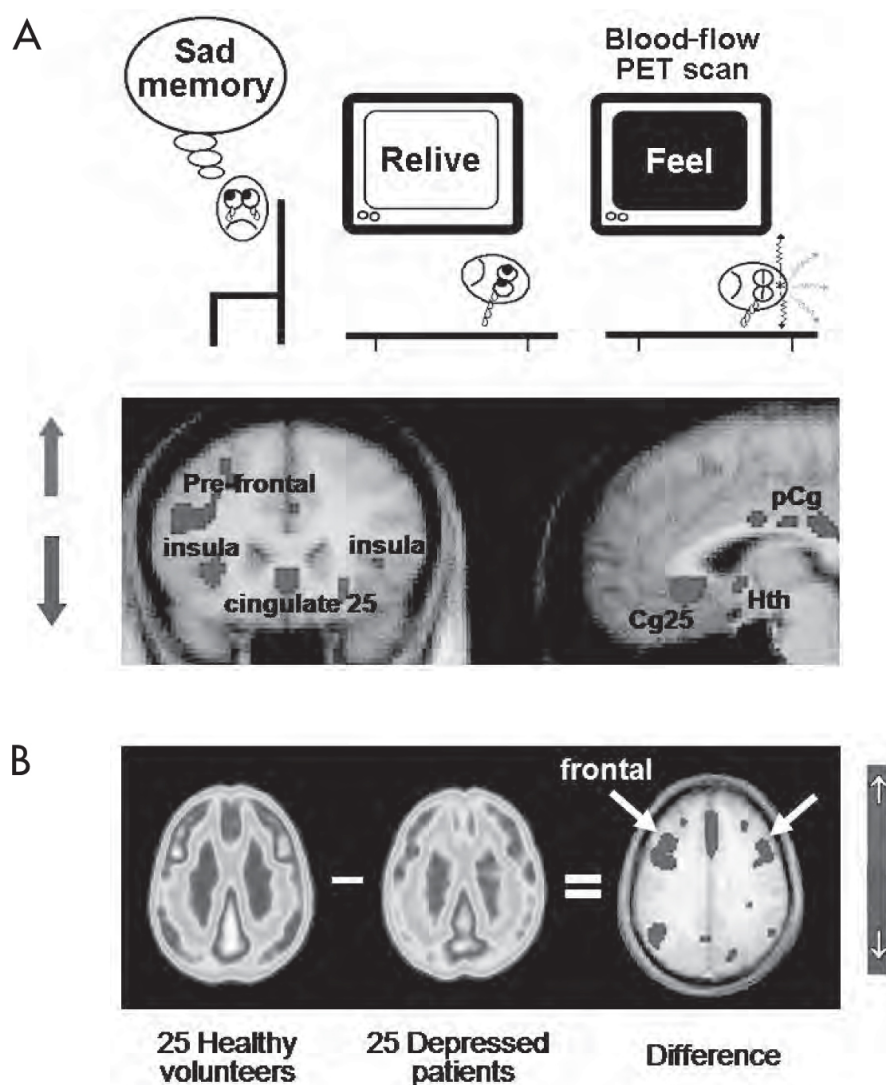
## Blood-Flow PET Studies

PET studies use  $\text{H}_2^{15}\text{O}$  to measure changes in local brain blood flow ([Herscovitch et al. 1983](#); [Mintun et al. 1984](#)). As noted earlier, blood flow is an indirect measure of local synaptic activity. Because  $^{15}\text{O}$  has a short half-life (2 minutes), several administrations can be performed during a single session. A typical  $\text{H}_2^{15}\text{O}$  study would have 8–16 injections and scans for each subject. The experimental design would manipulate the task that the subject performs during each scan. Each scan lasts about 1 minute, with 8–10 minutes between scans (5 half-lives).  $\text{H}_2^{15}\text{O}$  studies not only allow for multiple conditions to be studied but also allow for repetition of conditions, increasing the statistical power of the studies. The main disadvantage is that because of the short half-life, the  $\text{H}_2^{15}\text{O}$  must be produced reliably and in close proximity to the scanner. PET  $\text{H}_2^{15}\text{O}$  studies are increasingly being replaced by perfusion MRI studies—mostly because of the latter’s greater ease of use, decreased radiation safety concerns, and better spatial resolution.

## Metabolic and Blood-Flow PET Studies in Neuropsychiatry

PET has been used to assess functional activity of brain regions, both in the resting state and in response to various stimuli. [Figure 7-2A](#) shows a picture of increased cerebral blood flow (CBF) to paralimbic regions during a sad-mood induction task (to be described later) using  $\text{H}_2\text{O}$ -PET. In contrast, [Figure 7-2B](#) shows metabolic activity differences among depressed versus healthy patients using FDG-PET. These modalities have been effectively used to study a variety of mental phenomena and have been of considerable benefit in enhancing our understanding of psychiatric disorders. Of particular interest have been studies using PET to investigate the biological basis of schizophrenia ([Fujimoto et al. 2007](#); [Lange et al. 2005](#)), bipolar disorder ([Post et al. 2003](#)), depression ([Mayberg 2003b](#); [Neumeister et al. 2004](#)), substance abuse and craving ([Kilts et al. 2004](#)), posttraumatic stress disorder (PTSD) ([Bremner 2007](#)), attention-deficit/hyperactivity disorder (ADHD) ([Schweitzer et al. 2004](#)), and Alzheimer’s disease ([Small 1996](#)). Most PET studies of psychiatric disorders have shown generally similar patterns of resting blood flow and metabolic abnormalities.

That said, such identified patterns have not yet proved adequately consistent to warrant use of PET as a diagnostic procedure in individual patients. Notably, only resting-state FDG-PET scanning has undergone sufficient repeated sensitivity and specificity testing to be considered useful and reliable for the diagnosis of Alzheimer's disease in patients with progressive neurocognitive disturbance and presumed dementia (Silverman et al. 2002). Nonetheless, research studies using these methods have provided many new insights into the pathophysiology of the disease and the mechanisms mediating treatment response (Erritzoe et al. 2003; Evans et al. 2006; Mayberg 2003a; Roffman et al. 2005). In a similar manner, functional imaging techniques have been combined with neurosurgical treatments such as deep brain stimulation (DBS) to study brain-imaging biomarkers of treatment response (Carbon and Eidelberg 2002).



**FIGURE 7-2.** PET studies of regional functional activity in the brain.

See [Plate 16](#) to view this figure in color.

**(A)** Task-induced increased cerebral blood flow using H<sub>2</sub>O-PET. **(B)** FDG-PET resting-state contrasts among depressed patients versus healthy control subjects. FDG=fluorodeoxyglucose; PET=positron emission tomography; Cg25=subgenual cingulate; pCg=posterior cingulate; Hth=hypothalamus.

*Source.* **(A)** Adapted from Mayberg HS, Liotti M, Brannan SK, et al.: "Reciprocal Limbic-Cortical Function and Negative Mood: Converging PET Findings in Depression and Normal Sadness." *American Journal of Psychiatry* 156:675-682, 1999. Copyright 1999, American Psychiatric Association. Used with permission. **(B)** Image courtesy of Helen Mayberg, M.D.

## Receptor-Labeling PET Studies

PET-based receptor imaging has provided a window for viewing the complex functioning of brain systems that mediate treatment response to psychopharmacological agents (Gunn et al. 2015). A snapshot of available radionuclide-binding modalities is provided in Table 7-1. With use of PET-based radioligands, it has been possible to visualize density, distribution, and occupancy of neural receptors and transporters before, during, and after drug therapy (Gunn et al. 2015; Talbot and Laruelle 2002). Receptor studies use radioligands—chemicals incorporating a positron-emitting isotope into a molecule whose pharmacokinetics are already known (Gunn et al. 2015). Ideally, these ligands bind specifically to one receptor type. Most of these studies are of the mapping type, which shows the distribution of a particular receptor in the brain (e.g., dopamine type 2 [D<sub>2</sub>] receptor). Here, the measured radioactivity reflects both the local concentration of receptors ( $B_{\max}$ ) and the affinity of the ligand for the receptor (measured by  $K_D$ , the equilibrium dissociation constant). If the ligand acts as a competitive antagonist, then the *apparent* affinity is also affected by the concentration of the endogenous neurotransmitter. The analysis can be simplified by considering the ratio of  $B_{\max}$  to  $K_D$ , termed the *binding potential*. Ligands undergo both specific and nonspecific binding. Typically, one is interested only in the specific binding (i.e., to the receptor of interest). Use of a reference tissue that is known to have a low receptor concentration allows one to subtract out the nonspecific binding (e.g., the cerebellum has a low concentration of D<sub>2</sub> receptors). In this case, the difference in distribution for the two tissues is directly proportional to the binding potential. Ligands require a more involved synthesis than either water or <sup>18</sup>F-DG, and their use is a race against the clock as the isotope decays. The end product must meet several requirements: high specific activity (amount of radioactivity per mole), high radiochemical purity, and sterility. <sup>18</sup>F ligands are easier to synthesize because of their long half-life, but <sup>11</sup>C ligands (20-minute half-life) have a higher potential for biological relevance. Appropriate availability of neurotransmitters and neuromodulators is essential to normal neurological and psychological function. Dysfunction or degeneration of neurons that synthesize these substances can lead to various disorders. In the following sections, specific examples will be

provided to illustrate the use of imaging methods to answer pertinent questions of relevance to psychopharmacology.

**TABLE 7-1. Pharmacoinaging in psychiatry**

<b>Imaging modality</b>	<b>Labeling agent</b>	<b>Binding site</b>	<b>Clinical focus and type of pharmacological probe</b>
<b>Dopamine</b>			
PET	[ <sup>18</sup> F] DOPA, [ <sup>18</sup> F] FMT	Aromatic L-amino acid decarboxylase	Viability of dopamine-synthesizing neurons Probe type: enzyme labeling ligand
PET	[ <sup>11</sup> C] altropane, [ <sup>11</sup> C] CFT, [ <sup>11</sup> C] PE21, [ <sup>18</sup> F] CFT	Dopamine (D) uptake receptor	Synaptic dopamine availability and correlation with cognition Probe type: reuptake transporter ligand
PET	[ <sup>11</sup> C] raclopride, [ <sup>11</sup> C] FLB 457, [ <sup>11</sup> C] NPA, [ <sup>18</sup> F] fallipiride	D <sub>2</sub> receptor	Binding and affinity and occupancy of D <sub>2</sub> receptors by antipsychotics Probe type: postsynaptic (PS) receptor ligand
PET	[ <sup>11</sup> C] NNC-112, [ <sup>11</sup> C] SCH 23390	D <sub>1</sub> receptor	Role of dopamine in cognition Probe type: PS receptor ligand
SPECT	[ <sup>123</sup> I] iodobenzamide, β-CIT	D <sub>2</sub> receptor	Hyperresponse of dopamine secretion in schizophrenia Probe type: PS receptor ligand

## Serotonin

*Note.* 5-HT=serotonin (5-hydroxytryptamine); GABA=γ-aminobutyric acid; MRS=magnetic resonance spectroscopy; PET=positron emission tomography; SERT=serotonin transporter; SPECT=single photon emission computed tomography; TSPO=translocator protein.

<b>Imaging modality</b>	<b>Labeling agent</b>	<b>Binding site</b>	<b>Clinical focus and type of pharmacological probe</b>
PET	[ <sup>11</sup> C] methyl-L-tryptophan	5-HT synthesis	A marker of 5-HT biosynthesis Probe type: precursor ligand
PET	[ <sup>11</sup> C] MDL100907, [ <sup>11</sup> C] CIMBI-36, [ <sup>18</sup> F] altanserin	5-HT <sub>2A</sub> receptor	Serotonin turnover among suicidal and depressed patients Probe type: PS receptor ligand
PET	[ <sup>11</sup> C-carbonyl] WAY 100635, [ <sup>11</sup> C] CUMI 101, [ <sup>18</sup> F] FCWAY, [ <sup>18</sup> F] MPPF	5-HT <sub>1A</sub> receptor	Antidepressant efficacy studies Probe type: autoreceptor ligand
PET	[ <sup>11</sup> C] P943, [ <sup>11</sup> C] AZ10419369	5-HT <sub>1B</sub> receptor	Antidepressant efficacy studies Probe type: PS receptor ligand
PET	[ <sup>11</sup> C] McN-5652, [ <sup>11</sup> C] DASB, [ <sup>11</sup> C] AFM, [ <sup>11</sup> C] HOMADAM	SERT	Antidepressant binding efficacy Probe type: reuptake site ligand
SPECT	[ <sup>123</sup> I] β-CIT, [ <sup>123</sup> I] ADAM	SERT; type: same as above	Antidepressant binding efficacy Probe type: reuptake site ligand
SPECT	[ <sup>123</sup> I] 5-I-R91150	5-HT <sub>2A</sub> receptor	Serotonin turnover Probe type: PS receptor ligand

#### **Amino acid transmitters: GABA/glutamate**

---

*Note.* 5-HT=serotonin (5-hydroxytryptamine); GABA=γ-aminobutyric acid; MRS=magnetic resonance spectroscopy; PET=positron emission tomography; SERT=serotonin transporter; SPECT=single photon emission computed tomography; TSPO=translocator protein.

<b>Imaging modality</b>	<b>Labeling agent</b>	<b>Binding site</b>	<b>Clinical focus and type of pharmacological probe</b>
Glutamate	[ <sup>11</sup> C] ABP688, [ <sup>18</sup> F] FPEB	Metabotropic glutamate receptor	Glutamate turnover Probe type: Glutamate regulation presynaptic and astrocytic
PET	[ <sup>11</sup> C] flumazenil	Benzodiazepine receptor	GABA levels in anxiety states Probe type: PS receptor ligand
SPECT	[ <sup>123</sup> I] iomazenil	Benzodiazepine receptor	GABA levels in anxiety states Probe type: PS receptor ligand
MRS	None	None	Concentrations of GABA, glutamate Probe type: metabolomic approach
<b>Neurodegeneration imaging</b>			
PET	[ <sup>11</sup> C] PIB, [ <sup>11</sup> C] AZD2184, [ <sup>11</sup> C] AZD4694, [ <sup>11</sup> C] SB13, [ <sup>18</sup> F] AV45, [ <sup>18</sup> F] BAY94-9172, [ <sup>18</sup> F] GE067	Beta-amyloid plaque	Progression of senile plaques in Alzheimer's disease Probe type: ligand of pathological deposit in senile plaques (beta amyloid)
PET	[ <sup>11</sup> C] PBB3, [ <sup>18</sup> F] AV-1451, [ <sup>18</sup> F] FDDNP, [ <sup>18</sup> F] THK5117, [ <sup>18</sup> F] THK 5351	Tau deposition	Progression of senile plaques in Alzheimer's disease Probe type: ligand of pathological deposit in neurofibrillary tangles (tau)
<b>Other targets</b>			

*Note.* 5-HT=serotonin (5-hydroxytryptamine); GABA=γ-aminobutyric acid; MRS=magnetic resonance spectroscopy; PET=positron emission tomography; SERT=serotonin transporter; SPECT=single photon emission computed tomography; TSPO=translocator protein.



<b>Imaging modality</b>	<b>Labeling agent</b>	<b>Binding site</b>	<b>Clinical focus and type of pharmacological probe</b>
PET	[ <sup>11</sup> C] carfentanil, [ <sup>11</sup> C] diprenorphine, [ <sup>11</sup> C] LY2795050	Opioid receptors	Pain perception and placebo response Probe type: opioid receptors
PET	[ <sup>11</sup> C] PK11195, [ <sup>11</sup> C] PBR28, [ <sup>18</sup> F] FEPPA, [ <sup>18</sup> F] PBR06, [ <sup>18</sup> F] PBR111	Microglial labeling: TSPO binding site	Pain perception and placebo response Probe type: opioid receptors
PET	[ <sup>11</sup> C] OMAR, [ <sup>18</sup> F] MK9470	Cannabinoid receptors	Pain perception and placebo response Probe type: cannabinoid type 1 receptors

*Note.* 5-HT=serotonin (5-hydroxytryptamine); GABA=γ-aminobutyric acid; MRS=magnetic resonance spectroscopy; PET=positron emission tomography; SERT=serotonin transporter; SPECT=single photon emission computed tomography; TSPO=translocator protein.

### **Dopamine PET Imaging**

Parkinson's disease is caused by selective degeneration of the dopamine-synthesizing neurons of the nigrostriatal system. Uptake of 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine ([<sup>18</sup>F] DOPA), which selectively labels aromatic L-amino acid decarboxylase (AADC), a critical enzyme in the synthesis of dopamine, has been used to estimate both the number of surviving cells and AADC activity among nigral neurons, thus providing a tool to understand the connection between dopamine dysfunction and clinical symptom evolution ([Cropley et al. 2006](#); [Ravina et al. 2005](#)). PET imaging has been used to identify binding sites of neurotransmitters of relevance to psychiatric disorders, in order to characterize patients and inform treatment decisions based on mechanisms of drug action. For instance, studies with ligands that bind to D<sub>2</sub> receptors have informed us that lower binding affinity, faster dissociation, and optimal occupancy at usually prescribed doses of D<sub>2</sub> receptor antagonists might form the basis of atypical antipsychotic drug action ([Kapur and Remington 2001](#)). Dopamine transporter (DAT)-labeling PET ligands have also been used to study cognitive and motor dysfunction in Parkinson's disease ([Cropley et al. 2006](#); [Ravina et al. 2005](#)) and are currently being used to investigate psychiatric disorders such as ADHD.

### **Serotonin PET Imaging**

PET scanning with [ $^{11}\text{C}$ ] methyl-L-tryptophan, which is a marker of serotonin (5-hydroxytryptamine [5-HT]) synthesis, is being used to identify overactive serotonin-synthesizing systems to differentiate epileptogenic from nonepileptogenic lesions in tuberous sclerosis prior to neurosurgery (Luat et al. 2007). Synaptic turnover of serotonin secretion is regulated by two processes—reuptake mediated through SERT and negative feedback mediated through serotonin type 1A (5-HT<sub>1A</sub>) autoreceptors. PET tracers can be used to study both of these processes. Antidepressant drugs that bind to and inhibit the serotonin transporter (SERT) have been shown to be associated with symptomatic recovery from depression (Nemeroff and Owens 2009). Radioligands that specifically bind to SERT, such as [ $^{11}\text{C}$ ] 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ( $^{11}\text{C}$ -DASB), have been used to estimate and associate SERT-occupancy rates of selective serotonin reuptake inhibitors (SSRIs) with clinical efficacy (Meyer 2007). Along similar lines, the role of SERT in suicidal behavior has been investigated in studies using SERT-binding PET ligands (Purselle and Nemeroff 2003). Downregulation of 5-HT<sub>1A</sub> receptors has been putatively linked to antidepressant efficacy and to the delay in onset of symptom response after initiation of SSRI treatment (Blier and Ward 2003). Radioligands such as [ $^{11}\text{C}$ ] WAY-100865 have been used to profile changes occurring in 5-HT<sub>1</sub> receptors before, during, and after antidepressant treatment (Fisher et al. 2006). Finally, studies using agents such as  $^{18}\text{F}$ -altanserin have demonstrated that increased binding of downstream postsynaptic serotonin type 2A (5-HT<sub>2A</sub>) receptors in frontal cortex (Brodmann area [BA] 9) was associated with increases in pessimism and self-injurious and suicidal behavior, thereby adding to our understanding of suicidal behavior and depression (Kumar and Mann 2014; Meyer et al. 2008). These methods are likely to lead to reformulation of treatment practices used in the management of depressive disorders and at the same time explain how imbalances in the serotonergic system might disrupt mood-regulating neural circuitry, resulting in depressive disorders (Fisher et al. 2006).

### **Gamma-Aminobutyric Acid SPECT Imaging**

Alterations in the function of  $\gamma$ -aminobutyric acid (GABA) systems in PTSD (Bremner 2007) and panic disorder (Bremner et al. 2000) have been reported on the basis of decreased binding of ( $^{123}\text{I}$ )-iomazenil to benzodiazepine receptors in the BA9 region of patients with these disorders.

### **Amyloid PET Imaging**

Neurodegenerative disorders such as Alzheimer's disease have acquired critical relevance, given the larger proportion of aging population in modern society. Because the pathological changes associated with neurodegeneration (e.g., beta-amyloid deposits, neurofibrillary tangles, decreased metabolic activity) often precede clinical disease by several decades, early identification of these

changes is of paramount importance. PET tracers for amyloid imaging can be roughly classified into  $^{18}\text{F}$ - and  $^{11}\text{C}$ -based tracers.  $^{18}\text{F}$ -based ligands include [ $^{18}\text{F}$ ] FDDNP ([Small et al. 2006](#)), and at least three commercially developed, U.S. Food and Drug Administration-approved amyloid-labeling PET tracers are available for clinical use: florbetapir ([ $^{18}\text{F}$ ] AV-45 [Amyvid], Eli Lilly), flutemetamol (Vizamyl, GE Healthcare), and florbetaben ([ $^{18}\text{F}$ ] BAY94-9172 [Neuraceq], Piramal Imaging).  $^{11}\text{C}$ -based tracers include [ $^{11}\text{C}$ ] PIB (Pittsburgh Compound-B) ([Klunk et al. 2004](#)) and [ $^{11}\text{C}$ ] SB (stilbene) derivatives ([Ono et al. 2003](#)). [ $^{11}\text{C}$ ] PIB in particular has garnered the lion's share of research studies and continues to inform the development of other amyloid-labeling agents. For further information on this rapidly evolving field, readers are referred to the authoritative review of [Vlassenko et al. \(2012\)](#). More recent data pointing to tau accumulation as an earlier marker of neurodegeneration have led to increased interest in the development of new tracers to map tau rather than amyloid deposition ([Dani et al. 2016](#)). PET-based amyloid and tau-imaging tracers have the potential to help identify patients with mild cognitive impairment (MCI) who are at increased risk of converting to dementia ([Mathis et al. 2005](#)). However, it needs to be mentioned in passing that therapies based on combating amyloid deposition have not yielded much success in reversing the course of Alzheimer's disease.

## Microglial PET Imaging

Neuroinflammatory activation has been implicated as a pathogenic factor in patients with a wide range of psychiatric disorders ([Haroon et al. 2012](#)). The precise nature and meaning of these neuroinflammatory changes across various disorders have not yet been clearly delineated. At least some of these neuroinflammatory changes might be mediated through the activation of resident immune cells—namely, the microglial cells, which when activated express a characteristic 18-kDA translocator protein (TSPO). Several PET ligands that label the TSPO binding site have been synthesized and made available for research. The first TSPO ligand to become available was [ $^{11}\text{C}$ ] PK11195 ([Myers et al. 1991](#)), which showed increased microglial activation in several neurological and psychiatric disorders. Initial enthusiasm for this ligand was tempered by the discovery of its high level of nonspecific binding to nonmicroglial tissue (including platelets, plasma proteins, and monocytes) and of the high quantities of TSPO in healthy blood-brain barrier regions, thus reducing the specificity of the signals. Two other compounds reported to have greater specificity in microglial TSPO labeling—including one  $^{11}\text{C}$ -based compound ([ $^{11}\text{C}$ ] PBR28 [[Brown et al. 2007](#)]) and one  $^{18}\text{F}$ -based compound ([ $^{18}\text{F}$ ] FEPPA [[Rusjan et al. 2011](#)])—have been proposed.

The field continues to struggle with many methodological issues. A recent study showed that [ $^{18}\text{F}$ ] FEPPA binding was significantly elevated in prefrontal cortex, insula, and anterior cingulate cortex (ACC) brain regions in depressed

subjects compared with healthy controls ([Setiawan et al. 2015](#)). This finding is important for improving treatment because it implies that therapeutics that reduce microglial activation should be promising for major depressive disorder. On the other hand, two studies of schizophrenic patients have been reported, with the first, using [ $^{18}\text{F}$ ]-FEPPA, reporting negative findings ([Kenk et al. 2015](#)) and the second (not yet published), using [ $^{11}\text{C}$ ]-PBR28, reporting positive findings clouded by the confounding effects of disease pathology and age ([Turkheimer et al. 2015](#)). A recent review ([Turkheimer et al. 2015](#)) summarized three main problems affecting quantification of PET TSPO ligands in the brain—namely, 1) genomic variation (a nucleotide polymorphism in the TSPO gene (rs6971) leads to population-level variation in binding affinity for TSPO tracers); 2) the very high affinity of some of the novel ligands disproportionately increases the TSPO signal at blood-brain barrier regions compared with the signal at the tissue; and 3) the difficulties in obtaining accurate estimates of plasma concentrations of the tracer to be used as a reference value. For a more detailed explanation of the challenges involved in obtaining meaningful data, readers are referred to the excellent review by [Turkheimer et al. \(2015\)](#).

---

## Magnetic Resonance Imaging

---

The basis of MRI technology rests on the magnetic properties of the ions that constitute the underlying tissues. In most biological tissues, these magnetic properties are based on the hydrogen atom, which, as a component of water, is found ubiquitously in organic tissues (water constitutes roughly 80% of brain weight). The nucleus of a hydrogen atom, a single proton, has an intrinsic magnetic property known as moment, or spin, along its axis. The protons in tissue are normally oriented in random directions, but if a powerful external magnetic field is applied, the protons will tend to align in the north/south direction, the more powerful field. Spins can orient either in the direction of the applied field (*parallel*) or in the direction opposite to it (*anti-parallel*), but on average the parallel orientation tends to dominate. This situation results in a net magnetic moment induced by the external field in the tissue; in other words, the tissue becomes slightly magnetized. The intensity of the induced magnetization depends on the proton distribution (i.e., on the local molecular characteristics of the tissue). The strength of the magnetic field used in MR scanners is quantified in terms of *tesla*; currently available clinical scanners range in strength from 1.5 tesla to 3.0 tesla, and the range is even higher for research scanners (up to 7.0 tesla). The magnetic fields generated by these scanners are very strong, consequently leading to intense magnetization and heat generation in any metallic objects placed in or near the scanners. This often leads to safety procedures involving screening for any metallic objects such as metallic clips or implants.

MRI technique primarily involves perturbing the molecular protons aligned parallel to the magnetic field generated by the scanner magnet. This instrumental perturbation (stimulation) is performed by applying short radiofrequency (RF) pulses that, when appropriately tuned to a precise frequency, are able to transiently tip the orientation of the spins away from the applied magnetic field. However, the tendency of the spins is to return to their original orientation coherent with the applied magnetic field, given that the latter state is characterized by a lower energy (in a baseline resting state) known as “relaxation” state. Given that the relaxation of the protons results in a change from a high-energy to a low-energy state, the extra energy is generated as an RF wave, which can be detected by the same RF hardware device that emits the excitation pulses. In MR terminology, this device, referred to as the “transmit-receive” RF coil, has the form of a small cylindrical cage that surrounds the subject’s head in the scanner. The emitted RF wave—or, more precisely, the temporal signature of its decay as the excited spins relax—constitutes the actual MR signal and depends on the molecular characteristics of the local tissue, as well on the particular sequence of excitation pulses employed. The details of the physics that specify how the RF pulse sequences can be engineered to acquire images of the brain with different physiological meanings are beyond the scope of this discussion, and the interested reader is directed elsewhere ([Buxton 2002](#)).

The spin relaxation measured with MRI can be decomposed into longitudinal and transverse components, which are only partially related. Measurement of the relaxation time of the longitudinal component, called *T1*, provides images in which the contrast between different types of tissue (notably, gray matter, white matter, and cerebrospinal fluid) is maximized. Such *T1-weighted images* are capable of defining the anatomy of the living brain with great precision and are therefore used as an anatomical reference for most of the neuroimaging studies. An image of the entire brain with a resolution, or voxel size, of  $1\text{ mm}^3$  (*voxel* stands for “volume pixel,” the unitary element used in MR imaging of the three-dimensional space into which the cortex is divided) can be acquired on a 1.5-tesla clinical scanner in less than 6 minutes.

Measurement of the relaxation time of the transverse component (*T2*), which can be divided into the *T2* and the *T2\** characteristic times, provides images that are influenced by the local inhomogeneity of the magnetic field, which is induced by blood-perfusion patterns or lesions including infarcts or tumors. Hence, *T2-weighted* imaging is also used to identify lesions in the brain not picked up by the *T1* scans. In particular, *T2\*-weighted* images are characterized by a contrast that highlights changes in vascular dynamics that accompany neural activity and are thus employed in functional mapping studies. The advent of a very fast technique for the acquisition of *T2\*-weighted* images, called *echoplanar imaging* (EPI), allows collection of an entire brain volume in 3–4 seconds and has been instrumental in the rapid development of fMRI. The ultrarapid acquisition of MR signals during EPI tends to diminish the *T2\** signal, which becomes negligible

when averaged over several smaller voxels. This diminished signal limits the resolution of standard EPI images, which typically expand to a voxel size of 3–4 cu mm (which is larger than the 1 cu mm voxel size of conventional MRI images), thereby constraining the use of EPI in advanced MR imaging. Thus, EPI images will not be able to provide the submillimetric precision required to visualize columnar organization of the visual cortex (Menon and Goodyear 1999). Table 7-2 lists common applications of MR-based technologies in psychopharmacology research. These techniques will be described in greater detail in the following section.

**TABLE 7-2. Applications of magnetic resonance imaging (MRI) in psychopharmacology research**

Type of imaging	Technique	Method of analysis	Purpose
Structural MRI (sMRI)— T1 based	Voxel-based morphometry (VBM)	Automated	Measure volumes of brain regions in brain disorders and ischemic lesions (hyperintensities)
sMRI—T2 based	Region of interest (ROI) analysis	Manual/automated	Measure volumes of brain regions in brain disorders and ischemic lesions (hyperintensities)
Functional MRI (fMRI)	BOLD technique (described in text)	Computerized algorithm	Measure area of activation in response to cognitive/affective challenge
Functional connectivity analysis	Resting-state activity, independent component analysis (ICA), structural equation modeling	Computerized algorithms, statistical models	Reveal connectivity between different components of neural network during various mental states

*Note.* BOLD=blood oxygenation level-dependent; EEG=electroencephalography; MEG=magnetoencephalography.

<b>Type of imaging</b>	<b>Technique</b>	<b>Method of analysis</b>	<b>Purpose</b>
Diffusion-based MRI	Diffusion-weighted, perfusion-weighted, diffusion tensor imaging (DTI)	Computerized algorithms	Assess tissue integrity by imaging water diffusion in restricted and free space; used in diagnosis of stroke and neurodegeneration
Perfusion-weighted imaging with arterial spin labeling	Blood flow-based imaging using magnetic resonance labeling approaches	Computerized algorithms	Measure neural tissue response to activation or pharmacological challenge paradigms
Magnetic resonance spectroscopy	Detection of concentrations of specific metabolites in cerebral regions	Automated and voxel based (manual)	Detect neuronal and glial metabolic abnormalities in localized (single) or distributed (multiple) brain regions or voxels

#### **Innovative in vivo magnetic resonance approaches**

Machine learning	Identification of minor but consistent patterns of changes in structural and/or functional imaging data	Advanced machine-learning algorithms	Identify consistent patterns of brain changes across disease states; often used for subtyping
------------------	---	--------------------------------------	---

---

*Note.* BOLD=blood oxygenation level-dependent; EEG=electroencephalography; MEG=magnetoencephalography.



Type of imaging	Technique	Method of analysis	Purpose
Multimodality imaging	Combination of data from multiple modalities to obtain meaningful conclusions	EEG/MEG + fMRI + tractography	Reveal structural and functional connection changes in mental disorders
Connectomics	Application of graph theory to connectivity analysis	Computerized approaches	Identify nodal and connectivity changes in brain architecture in different contexts
Hyperscanning	Online linkage of two fMRI scanners in different locations	Web based	Reveal cerebral activation changes during social interactions (social neuroscience technique)

*Note.* BOLD=blood oxygenation level-dependent; EEG=electroencephalography; MEG=magnetoencephalography.

## Functional Magnetic Resonance Imaging

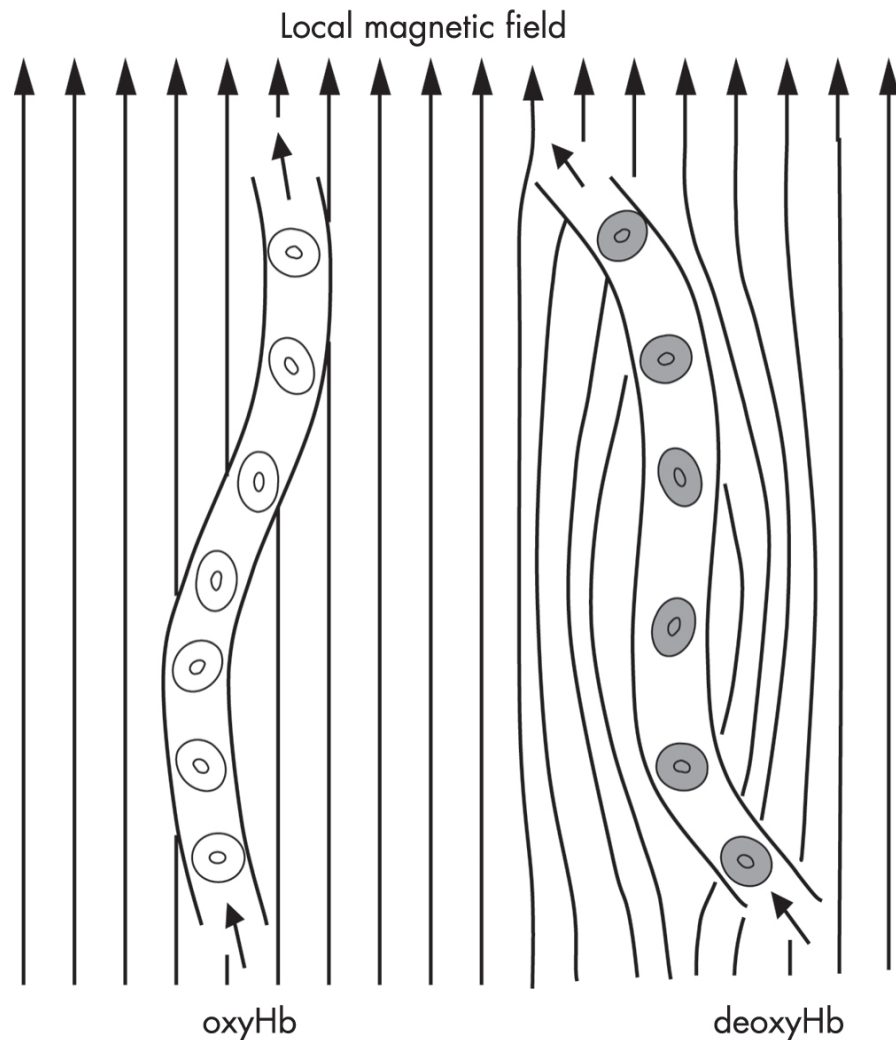
*fMRI* refers to a variant of MRI that sensitively records local changes in regional blood flow resulting from neural activity. The increase in regional blood flow, as engendered by neural activation, results in oxygen consumption that exceeds the oxygen available in the tissues. The higher oxygen consumption causes an apparent *decrease* in deoxyhemoglobin in the activated brain region, leading to a change in the RF perturbation qualities of the local tissue. In the 1930s, Linus Pauling observed that the amount of oxygen carried by hemoglobin is inversely proportional to the degree to which it perturbs a magnetic field. This property of differential magnetization was finally demonstrated in vivo in the late 1980s, and fMRI was born (Ogawa et al. 1992; Thulborn et al. 1982). Many reviewers have considered the relative merits and demerits of fMRI versus PET imaging techniques. A brief summary of the various MR imaging techniques in current research on neuropsychiatric disorders is provided in Table 7-2.

### The BOLD Signal in fMRI

Functional MRI exploits the fact that deoxyhemoglobin has paramagnetic properties and oxyhemoglobin does not. Deoxyhemoglobin disturbs the local



magnetic environment, causing the surrounding protons to dephase even faster than they would otherwise ([Figure 7-3](#)).



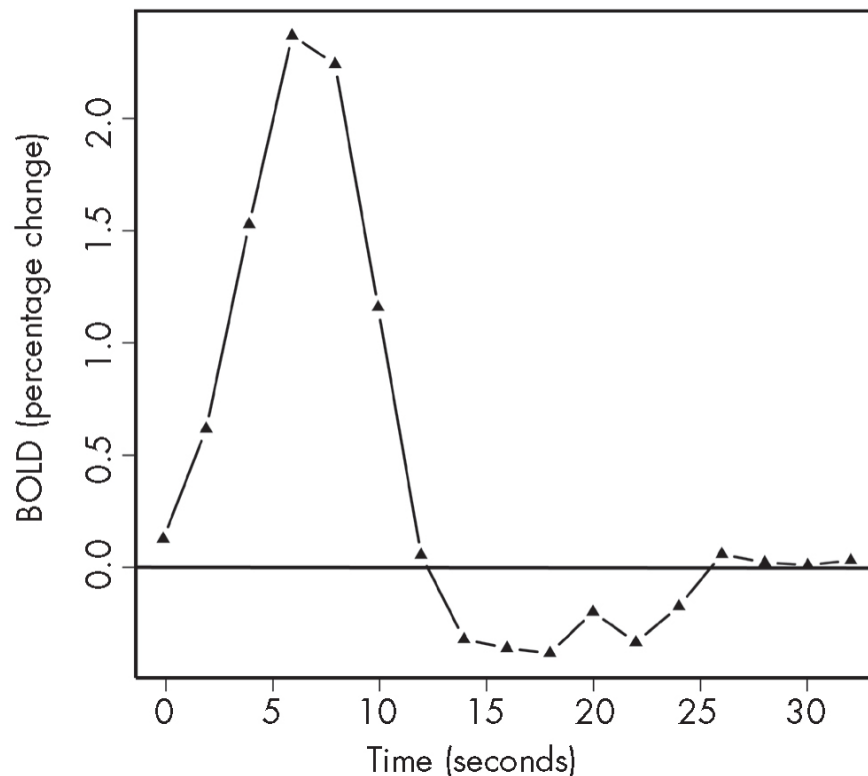
**FIGURE 7-3.** Schematic diagram of the effect of hemoglobin (Hb) on the local magnetic field of brain tissue.

Only deoxyhemoglobin (deoxyHb) has paramagnetic properties and locally distorts the field, leading to faster spin dephasing.

*Source.* Reprinted from Pagnoni G, Berns GS: "Brain Imaging in Psychopharmacology," in *The American Psychiatric Publishing Textbook of Psychopharmacology*, 3rd Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, 2003, pp. 163-172. Copyright 2003, American Psychiatric Publishing, Inc. Used with permission.

Heightened neuronal activity leads to an increase in blood flow, accompanied by a decrease in the amount of deoxyhemoglobin relative to oxyhemoglobin. Because lower deoxyhemoglobin means reduced rapid-spin dephasing, this

increase in blood flow appears as an increase in the MR signal—a phenomenon called the BOLD signal. In response to a regionally specific neuronal activation, the BOLD signal usually increases by about 1% on a standard 1.5-tesla clinical scanner. The intensity of the signal is proportional to the strength of the main magnetic field—for example, the intensity will double in the case of a 3-tesla scanner. The temporal resolution of fMRI is determined both by the hemodynamic response and by the physical constraints of the scanner magnetic fields. The hemodynamic response generally lags behind the neural activity by 3–5 seconds and may last for up to 10–15 seconds (Figure 7-4).



**FIGURE 7-4.** Relative blood oxygenation level-dependent (BOLD) response to 1-second visual stimulation.

These functional magnetic resonance imaging (fMRI) data are from the occipital cortex and were obtained in a healthy volunteer in a 3-tesla scanner. The amplitude of the signal is about 2%, with the peak 5–8 seconds after the stimulus.

*Source.* Reprinted from Pagnoni G, Berns GS: “Brain Imaging in Psychopharmacology,” in *The American Psychiatric Publishing Textbook of Psychopharmacology*, 3rd Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, 2003, pp. 163–172. Copyright 2003, American Psychiatric Publishing, Inc. Used with permission.

The rate at which the scanner can acquire images is influenced by the desired resolution. Generally, the more slices and the finer the resolution within each slice, the longer a whole-brain acquisition takes. Whereas an individual slice can be acquired in as little as 60 milliseconds, whole-brain imaging usually requires about 2–3 seconds. In contrast to the ease with which fMRI measurements can be performed, there are specific limitations with BOLD imaging:

- **Spatial errors.** The BOLD effect originates from venous vessels (capillaries, venules, and veins), so the signal is not exactly collocated either with the locus of neural activity or with the arterial supply. This spatial error may, however, be negligible for brain-mapping studies employing a standard spatial resolution (voxel size  $\sim 50\text{ mm}^3$ ).
- **Bulk head motion and physiological pulsation (heart pulse, respiration) artifacts.** To reduce motion, head movement should be restrained while maintaining a comfortable situation for the subject.
- **Susceptibility artifacts.** The fact that BOLD detects local changes in magnetic susceptibility (due to the variation in deoxyhemoglobin concentration) renders it vulnerable to the large discontinuity that exists at the interfaces between bone/air and bone/liquid. In these regions, the steep variations in tissue density cause a distortion of the local magnetic field, resulting in both a spatial distortion of the image and a drop in the BOLD signal. These spatial distortions make it difficult to detect the small changes associated with deoxyhemoglobin variations. The problematic regions are notably the orbitofrontal cortex and the inferior part of the temporal lobes, which unfortunately are the loci of many interesting neuropsychological processes.

**Functional Imaging: PET-Based Versus fMRI-Based Methods**

At this juncture, it might be helpful to draw a distinction between functional imaging paradigms using PET-based methods and those using fMRI-based methods. Table 7-3 provides a comparison of the advantages and disadvantages of the two imaging techniques.

---

**TABLE 7-3. Advantages and disadvantages of positron emission tomography (PET) versus functional magnetic resonance imaging (fMRI)**

---

**Advantages of PET versus fMRI**

- Quiet (good for acoustic stimulation); fMRI may have noise >90 dB
- Less sensitive to movement artifact
- Allows metabolic and receptor mapping
- Allows imaging of brain regions that are typically difficult to image with fMRI because of the presence of a susceptibility artifact (orbitofrontal cortex,

inferior temporal lobe) that causes both distortion and loss of signal  
Allows the use of standard measurement devices (physiological, behavioral) inside the scanner (i.e., avoids the complication of the need for specially designed MRI-compatible hardware) (In the MRI environment, the presence of a very strong static magnetic field commands the use of diamagnetic components; moreover, every electric device in the scanner room needs to be carefully shielded to prevent interference problems to and from the scanner. Scanning is not used in patients who have pacemakers or ferromagnetic metal parts in their bodies.)

### **Disadvantages of PET versus fMRI**

Injection of a radioactive isotope precludes the use of PET for longitudinal studies in which the same subjects are scanned repeatedly over an extended period of time.

PET provides an integral measure (over time) of brain activity (for activation techniques), with a temporal resolution on the order of minutes because of the lifetime of the isotope. By comparison, fMRI has a temporal resolution on the order of seconds. This prevents the use of sophisticated, event-related designs with PET. Also, the number of images typically collected with PET on a single subject rarely exceeds a dozen, thereby limiting the statistical treatment in the analysis of the data.

Spatial resolution is more limited with PET than with fMRI.

Cyclotron must be located nearby.

PET is more expensive than fMRI (utilization costs per hour: fMRI, ~ \$500; PET, ~ \$2,000).

The acquisition procedure is time-consuming and requires more resources. (One scan typically lasts ~ 3 hours [fMRI typically lasts <1 hour]. In comparison, the MRI experimental setup is easier to perform and can be operated by just one person.)

---

### **Functional Imaging: Neural Activation Studies Versus Resting-State fMRI Studies**

In the decade since publication of the previous edition of this textbook, the technique of functional imaging (PET or BOLD-MRI based) has undergone considerable evolution. Functional MRI studies may be divided into two key types: 1) neural activation studies, which profile increases and/or decreases in regional BOLD response to a specific stimulus, and in which activity changes that deviate from the norm can be assumed to reflect altered tissue functioning due to pathology); and 2) studies that examine interregional connectivity between brain regions during a nonactivated or “resting” state. These two approaches will be described in further detail in the following sections.

## **Neural activation paradigms in psychopharmacological research.**

At the time of writing this chapter, most of the applications of fMRI techniques are still experimental—for example, helping investigators to map areas of functional activation in response to cognitive and affective tasks. However, several of these techniques have begun to provide key clinical information about mechanisms of new treatments and to shed more light on the action of older treatments. Similarly, several novel and innovative uses of imaging methods have been described in the literature.

*Mood and self-referential paradigms.* A core feature of depression involves negative bias and anhedonia, suggesting specific alterations in neural pathways mediating salience, self-reference, and reward. Accordingly, several fMRI studies have reported failed activation of dorsomedial prefrontal cortex (BA10) in depressed patients in response to positive words or pictures ([Lemogne et al. 2009](#); [Mitterschiffthaler et al. 2003](#)). Interestingly, activation of the dorsomedial prefrontal cortex is also seen in tasks requiring self-referential processing in healthy subjects ([Craig et al. 1999](#); [Fossati et al. 2003](#)). A study using an emotional “Go/No-Go” task identified a depression-specific pattern consisting of blunted responses in reward circuits in response to neutral words but exaggerated responses in self-referential areas of the rostral cingulate and medial frontal cortex in response to sad words ([Elliott et al. 2002](#)). Such sensitive tasks can plausibly be used as outcome measures in the evaluation of the efficacy of antidepressant treatments.

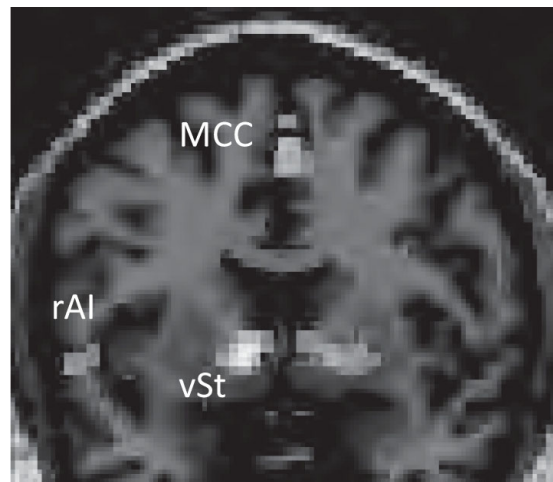
*Facial-expression-processing paradigms.* Another task frequently used in neural activation studies across a range of disorders involves presentation of faces with different emotional expressions, such as angry, sad, fearful, happy, and neutral. Such faces are either overtly presented or hidden behind a mask, depending on the study hypothesis. With overt presentation, subjects typically perform a behavioral task related to classifying some aspect of the faces. Application of such tasks in fMRI studies has produced a large amount of data regarding the neural basis of emotional processing in healthy subjects, demonstrating robust activation of the amygdala in response to emotional faces ([Whalen et al. 1998](#)). Of note, patients with depression, anxiety disorders, or PTSD exhibit increased amygdala responses to the presentation of fearful or angry faces ([Rauch et al. 2000](#); [Shin et al. 2004](#); [Whalen et al. 2002](#)). Facial-expression-processing paradigms have also proved useful in evaluating treatment effects in response to antidepressant drugs ([Sheline et al. 2001](#)), as well as in studying temperamental or genetic contributions to emotional processing ([Hariri et al. 2002](#); [Stein et al. 2007](#)). Similar strategies have identified antidepressant-induced changes with other tasks ([Fu et al. 2007](#)).

*Cognitive “working memory” paradigms.* The “*n*-back” task is a working memory task that captures prefrontal cortical function; it has been used in fMRI

studies to identify altered neural functioning in a variety of disorders, including schizophrenia and depression ([Abdallah et al. 2014](#); [Meyer-Lindenberg and Weinberger 2006](#)). The *n*-back test involves visual presentation of letter stimuli at previously chosen intervals and epochs (e.g., 2-second interval for 30-second epochs) ([Owen et al. 2005](#)). The baseline (control) condition is usually a 0-back condition in which subjects are required to press a button with the right index finger when the stimulus (e.g., the letter “x”) appears. In the experimental condition (1-, 2-, or 3-back), subjects are required to press a button if the presented stimulus is the same as a stimulus presented *n* trials previously (*n*=1, *n*=2, or *n*=3). The task difficulty and the condition are varied in a previously specified order throughout the scan time. Subject performance during scanning in regard to accuracy (number of target stimuli correctly identified) and response time is usually recorded. Increased prefrontal activity is seen in depressed patients relative to control subjects performing this task, an effect amplified by task difficulty ([Harvey et al. 2005](#)). On the other hand, several studies have reported that schizophrenic patients demonstrate deficits in activation of the prefrontal cortex during this task, thought to reflect alterations in dopamine functioning. Normalization of neural activation patterns by antipsychotic drugs is associated with response to treatment. The *n*-back task has also been useful in identifying genetic contributions to schizophrenia risk ([Meyer-Lindenberg and Weinberger 2006](#)). [Bookheimer et al. \(2000\)](#) used a verbal memory paradigm—in which patients memorized unrelated pairs of words during scanning—to study hippocampal activation in patients at risk of developing Alzheimer’s disease. Not only did the carriers of the apolipoprotein E epsilon 4 (*ApoE-ε4*)+ + allele (associated with a higher risk of dementia) show greater hippocampal activation, but this baseline activation pattern predicted longitudinal cognitive decline.

*Reward-processing paradigms.* Reward processing is believed to represent a complex psychological function incorporating a wide range of goal-directed, hedonic behaviors, including motivation, salience, anticipation, experiencing pleasure, and satiety ([Whitton et al. 2015](#)). Most recent data appear to strongly support the presence of aberrant reward-processing activity across multiple psychiatric disorders (transdiagnostic and transnosological biomarker) ranging from major depressive disorder and substance use disorders to bipolar hypomanic episodes and schizophrenia ([Whitton et al. 2015](#)). Reward-processing paradigms are commonly used in studying substance use and craving, and also in studying anhedonia in both depression and schizophrenia ([Whitton et al. 2015](#)). In addiction studies, typically the patient, while lying in a scanner, is presented with multiple contexts associated with drug abuse, and activation of reward-processing circuitry is studied. [Zink et al. \(2006\)](#) used fMRI to study activation of the basal ganglia (a key component of reward circuitry) in healthy volunteers in response to salient stimuli with high motivational relevance. [Figure 7-5](#) illustrates activation of salience and reward-processing

brain regions during a monetary reward task, as visualized with fMRI. The concept of “temporal (or delay) discounting” refers to the extent to which an individual will choose a discounted immediate reward over a delayed reward that is much higher in value. Patients with DSM-IV ([American Psychiatric Association 1994](#)) impulse-control disorders, such as pathological gambling, have been found to show considerable variation in their tendency to use temporal discounting. Studies using fMRI reported that increased activation of paralimbic cortex was observed when subjects chose smaller/earlier rewards, whereas frontoparietal activation was seen when subjects chose larger/later rewards ([Dixon et al. 2006](#); [McClure et al. 2004](#)). Studies of delay discounting might help us develop brain activation-based biomarkers of complex disorders such as DSM-5 ([American Psychiatric Association 2013](#)) substance-related and addictive disorders (including gambling disorder). In a recent study, a combination of [ $^{18}\text{F}$ ] DOPA PET and fMRI was used to demonstrate that decreases in dopamine synthesis resulting from inflammatory activation could lead to decreased activation of the ventral striatal regions in response to potentially rewarding stimuli, which in turn could be correlated with anhedonia ([Capuron et al. 2012](#)).



**FIGURE 7-5.** Activation of the ventral striatum (vSt), midcingulate cortex (MCC), and right anterior insula (rAI) during a monetary reward task, as visualized using functional magnetic resonance imaging.

*See [Plate 17](#) to view this figure in color.*

*Note.* The activation pattern reflects changes in both salience and reward centers in the brain.

*Source.* Image courtesy of Helen Mayberg, M.D.

In conclusion, these examples illustrate the potential of fMRI activation studies in probing brain-behavior relationships in psychiatric disorders, owing to the flexibility of fMRI paradigm design as well as the large variety of standardized tasks and possibility of developing novel tasks.



**Resting-state fMRI studies: neural networks and functional connectivity analysis.** Resting-state neural cells manifest spontaneous activity that triggers a tiny but demonstrable BOLD effect, which (in contrast to other BOLD activations) shows pulsation at much lower frequencies (0.01–0.03 Hz). These low-frequency pulsatile BOLD fluctuations have been shown to be remarkably synchronous among connected structures operating within a neural network designed to execute a specific function ([Biswal et al. 1997](#); [Lowe et al. 2002](#)).

Study of large-scale brain networks that mediate cognitive and affective functions might provide key insights into dysfunctional brain architecture ([Menon 2011](#)). Graph-theory approaches have been used to further refine data obtained using resting-state BOLD MRI data. Brain networks involve collections of brain regions (nodes) and connections (edges), both of which are defined using structural diffusion tensor imaging or resting functional connectivity analysis measured using BOLD fMRI ([Bullmore and Sporns 2009](#)). Damage to nodes or edges from disease processes can lead to aberrant signaling affecting whole networks or subnetworks, often leading to psychiatric syndromes and symptoms. Organizationally, the neural systems involved in regulation of affect and behavior are believed to involve three core intrinsically connected networks:

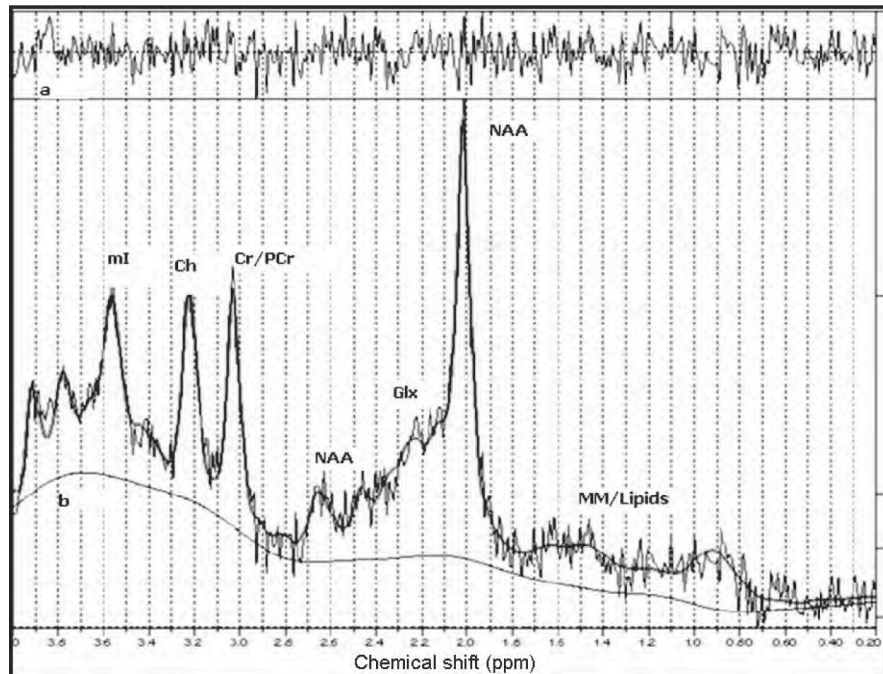
1. **Central Executive Network (CEN):** A frontoparietal network anchored in primary nodal regions involving dorsolateral prefrontal cortex (DLPFC) and posterior parietal regions responsible for actively maintaining and manipulating information in the working memory and making decisions in the context of goal-directed behavior ([Seeley et al. 2007](#)). A large number of studies have documented abnormalities of the CEN in most psychiatric disorders, but most importantly in schizophrenia ([Forbes et al. 2009](#); [Woodward et al. 2011](#)) and depression ([Miller et al. 2015](#)).
2. **Default Mode Network (DMN):** In contrast to the CEN, the DMN preferentially shows greater activity during restful or passive cognitive states ([Buckner and Vincent 2007](#); [Gusnard et al. 2001](#)) and is primarily anchored in the posterior cingulate and the inferior parietal and medial frontal cortices. High activity in these regions during periods of wakeful rest and passive self-reflection have led some to hypothesize that such activity may serve to “consolidate the past, stabilize brain ensembles, and prepare us for the future” ([Buckner and Vincent 2007](#), p. 1066). Abnormalities in the functional connectivity of this network in psychiatric disorders such as schizophrenia ([Bluhm et al. 2007](#)), depression ([Greicius et al. 2007](#)), dementia ([Rombouts et al. 2005](#)), autism ([Cherkassky et al. 2006](#)), and multiple sclerosis ([Lowe et al. 2002](#)) have been reported.
3. **Salience Network (SN):** The SN is anchored primarily in the dorsal ACC and fronto-insular cortex and is believed to be involved in detecting and integrating relevant interoceptive, autonomic, and emotional information



([Seeley et al. 2007](#)). Dysfunction of this network has been consistently associated with anxiety, pain syndromes, and addiction ([Klumpp et al. 2013](#); [Menon 2011](#); [Paulus and Stein 2006](#)).

## Magnetic Resonance Spectroscopy

MRS technology is based on the fact that MR acquisition involves receiving echoed RF waves of multiple cellular chemical constituents. The individual chemical and metabolite constituents could be measured by suppressing the resonance frequency of water molecules. A detailed exposition of the various types of MRS techniques is beyond the scope of this chapter, and the reader is referred to excellent reviews on the topic ([Mason and Krystal 2006](#); C.M. [Moore et al. 1999](#)). Among the markers currently being researched are *N*-acetylaspartate (NAA), glutamate/glutamine, myo-inositol, choline, glutathione, creatine, GABA, phosphomonoester, and phosphodiester ([Lyoo and Renshaw 2002](#)). An example of an MRS spectrum from a healthy control subject is provided in [Figure 7-6](#). Using proton MRS ( $[^1\text{H}]$ -MRS), [Frye et al. \(2007\)](#) were able not only to demonstrate elevated glutamate/glutamine in anterior cingulate/medial prefrontal areas of patients with bipolar depression but also to document reduction of glutamine among patients who showed clinical response to treatment with lamotrigine. Glutamate elevation during MRS is believed to be one of the most consistent findings in bipolar disorder among children and adults ([Gigante et al. 2012](#); [Yüksel and Öngür 2010](#)). Using another sample of adult patients, these same authors reported that ACC glutamine levels were elevated rapidly following administration of the anticonvulsant topiramate (C.M. [Moore et al. 2006](#)). A study using MRS technology reported that cortical GABA concentrations increased following a course of electroconvulsive therapy (ECT) and used this information to hypothesize that this increase in GABA might be associated with clinical recovery ([Sanacora et al. 2003](#)).



**FIGURE 7-6.** Proton magnetic resonance spectroscopy ( $[^1\text{H}]$ -MRS) spectrum from right dorsolateral prefrontal cortex voxel of a healthy individual.

MM=macromolecules; NAA=N-acetylaspartate; Glx=glutamate/glutamine; Cr/PCr=creatine/phosphocreatine; Ch=choline; mI=myo-inositol.

Source. Reprinted from Haroon E, Watari K, Thomas MA, et al.: "Prefrontal Myo-Inositol Concentration and Visuospatial Functioning Among Diabetic Depressed Patients." *Psychiatry Research: Neuroimaging* 171:10-19, 2009. Copyright 2009, Elsevier Ltd. Used with permission.

At present, MRS remains the only in vivo method of measuring glutamate among humans, albeit not without problems. Profiling brain response to inflammation is of great importance to better understand the biological basis of mental disorders. Brain and behavioral responses to inflammation might be mediated by the effect of cytokines and other inflammatory signaling molecules on the interactions between neurons and the astrocytic cells (i.e., neuron-glia coupling) (Haroon et al. 2012; Miller et al. 2013). MRS-based technologies can be used to profile inflammation-induced changes in neuron-glia coupling. Haroon et al. (2014, 2015) demonstrated that induction of high-grade inflammation (following administration of interferon-alpha for the treatment of hepatitis C in nondepressed individuals) was associated with significant increases in glutamate concentrations in the dorsal ACC and left basal ganglia. The increased glutamate concentrations were in turn associated with depression, anhedonia, and reduced psychomotor activity, and these effects were greater in older individuals. In comparison, patients with chronic major

depressive disorder (MDD) associated with high inflammation demonstrated changes mostly in the basal ganglia regions characterized by increases in both glutamate and the astroglial marker myo-inositol ([Haroon et al. 2016](#)). Thus, MRS could be used to further study both the acute and the chronic impact of inflammation on mood-regulating and reward pathways.

## Structural Magnetic Resonance Imaging

As illustrated in [Table 7-2](#), MR technology has provided important information on structural abnormalities in various psychiatric disorders. Use of MR imaging-based methods in research on psychiatric disorders and their treatment is addressed in the chapters on individual disorders (see [Chapters 46-54](#) in this volume). Only a general introduction will be provided here. MR-based volumetric methods involve estimating volumes of cerebral structures using MR images. They may be divided into two types: automated (voxel-based morphometry [VBM]) and manual (region of interest [ROI]) methods. A detailed review of these methods is provided elsewhere ([Pearlson and Calhoun 2007](#)). Using volumetric studies of hippocampus in depression, [Sheline et al. \(2001\)](#) described a subtype of depression associated with hippocampal volume loss, memory impairment, and hippocampal loss of 5-HT<sub>2A</sub> receptors. The alteration of cerebral structure by medications has been reported as well. Using structural MRI methods, G.J. [Moore et al. \(2000\)](#) reported that lithium administration led to a 3% increase in the volume of gray matter within a period of about 4 weeks. Psychiatric disorders are clinically heterogeneous entities, and such structural MRI-based studies have helped us to characterize more specific pathological subtypes of depression. T2-weighted MRI studies have also been used to identify and rate subcortical hyperintensities, the increase of which is believed to result in late-life cerebrovascular disease and late-life depression ([Alexopoulos et al. 1997](#); [Kumar et al. 2002](#); [Parsey and Krishnan 1997](#)).

## Diffusion-Weighted and Diffusion Tensor Imaging

Diffusion-based imaging techniques, including diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI), obtain and use images of the microscopic diffusion properties of water as an indirect measure to estimate the microstructure integrity of all brain tissues, including white matter tracts ([Le Bihan 2003](#)). In free-form water, molecules have isotropic properties (i.e., they diffuse in multiple and often infinite directions). The extent of free diffusivity in all directions is known as *radial diffusivity*. Under restricted conditions in the white matter fiber tracts, the directional diffusion of water is highly restricted to a few vectors due to spatial limitations induced by the tightly packed nerve fibers, resulting in a phenomenon known as *anisotropic diffusion*, and the extent of this restricted or anisotropic diffusion is known as *fractional anisotropy*.

([Kubicki et al. 2007](#)). DTI-based studies have advanced the hypothesis that psychiatric disorders are characterized by altered connectivity (“disconnection syndromes”). Studies employing DTI methods have helped us understand how cerebral organization and connectivity might be altered in psychiatric disorders such as autism ([Alexander et al. 2007](#)), late-life depression (W.D. [Taylor et al. 2007](#)), and schizophrenia ([Nestor et al. 2007](#)). It should be borne in mind that the direction-dependent diffusion of water in white matter tracts corresponds to the predominant directional orientation of the fiber bundles (principal diffusion direction), and by using complex statistical modeling, it is possible to estimate these directions and to trace the fibers’ journey through the brain structure using a technique called probabilistic tractography ([Johansen-Berg et al. 2008](#)). Using this technique, it has also been possible to predict antidepressant treatment responses among patients with late-life depression ([Mettenburg et al. 2012](#)).

## Perfusion-Weighted MR Imaging and Arterial Spin Labeling

Traditionally, the assessment of activity in a tissue volume of interest was made using PET techniques involving exposure to radioactive tracers. Perfusion MRI techniques—which take advantage of the fact that the magnetization properties of arterial blood water are different from those of the underlying tissues—have been used to study increased resting blood flow (indexed by increased flow of arterial blood water). A subtype of perfusion MRI that uses magnetic labeling of increasing flow of arterial water proximal to the tissue volume of interest is known as arterial spin labeling (ASL) and has been used to study brain activity in disease states ([Detre et al. 2009, 2012](#)). Multiple studies have examined the effect of serotonin metabolism changes in depression. For example, it has been demonstrated that depressed patients who have the short allelic variant of the serotonin transporter (s/s group) show significantly increased resting CBF in the amygdala and decreased CBF in the ventromedial prefrontal cortex compared with patients who have the long allelic variant of the serotonin transporter (l/l group) ([Rao et al. 2007](#)). MDD patients subjected to acute tryptophan depletion showed increased resting-state habenular blood flow, and the increased resting-state amygdala blood flow (following acute tryptophan depletion) was associated with a more negative emotional bias score across both MDD and control patients ([Roiser et al. 2009](#)).

## Machine Learning

A major critique of modern neuroimaging studies is that they although they demonstrate statistically significant differences between study and control

groups, they are of limited clinical utility owing to low levels of sensitivity and specificity ([Orrù et al. 2012](#)). This is because conventional statistical analysis techniques aim to identify statistically significant group differences that depend on sample size and power. Machine learning enables the investigator to make sense of otherwise unstructured data by minimizing “noise” and differentiating noise from core data elements that explain most of the variance. For example, machine learning can be used to process imaging information from all brain voxels simultaneously (i.e., whole-brain model) to identify differences between the study and control groups. Thus, machine learning techniques enable us to identify minor but consistent alterations in widely distributed brain networks that can later be combined to profile brain-behavior relationships in neuropsychiatric disorders ([Borgwardt and Fusar-Poli 2012](#); [Davatzikos et al. 2005](#); [Orrù et al. 2012](#)).

## Multimodal Imaging Approaches

Another approach to overcoming the limitations of current neuroimaging study designs has been to use multimodal imaging techniques combined with advanced statistical analyses. For instance, a combined analysis of fMRI, structural MRI, and EEG data employing canonical correlation methods could be used to differentiate patients with schizophrenia from control subjects with a level of accuracy exceeding 90% certainty ([Sui et al. 2014](#)).

---

## Electroencephalography and Magnetoencephalography

---

The brain is an organ with a high level of intrinsic electrical activity. EEG and MEG are technologies that enable the recording of this electrical activity of the brain using scalp electrodes. These techniques are believed to represent brain activity in real time, and with a higher temporal resolution (~ msec) than PET or fMRI. The electrical activity recorded is generated by the postsynaptic potentials of the neurons and hence represents a direct indication of neural activity. The EEG detects the electrical potential of the field, while MEG detects the magnetic component. EEG uses relatively simple equipment, basically a multielectrode helmet, an amplifying and filtering device, and a computer ([Ebner et al. 1999](#)). A minimum of 32 scalp electrodes are needed to localize the sources of the recorded potential EEG, but high-density arrays of 128 or 256 electrodes are employed increasingly in research. MEG, by contrast, employs cutting-edge technology ([Ioannides 2006](#)), because the detection of a magnetic field intensity as weak as the one produced by the brain (~20,000 billion times weaker than the intensity of the Earth’s magnetic field) requires the use of superconducting

coil units based on superconducting quantum interference device (SQUID) technology. These units need to be specially cooled to a temperature near absolute zero. To avoid the intrusion of electromagnetic interference from the environment, the recording takes place in a room that has been appropriately shielded. MEG commonly employs arrays of 100–300 detectors.

Given the high temporal resolution of MEG and EEG, these techniques are used to study simultaneous (time-locked) neural discharges occurring in distant or contiguous groups of neurons, often referred to as “synchronous neural activity” (Tononi and Edelman 1998; Varela et al. 2001). These synchronous neural discharges are seen in both pathological situations (such as seizure discharges) and normal physiological situations (such as during development of function neural circuits). The high temporal resolution also enables measurement of neural response to sensory (somatosensory) or cognitive stimuli delivered from outside, and this process, known as the study of *evoked* or *event-related potentials*, has enabled considerable progress in understanding the pathophysiology of several neurological and psychiatric disorders. The temporal sequence of the neural responses following delivery of the stimulus (known as “time series”) is measured sequentially and averaged to generate a waveform. By combining all waveforms from all detectors, one can develop a surface map of the beginning, middle, and end of the neural response to a given stimulus.

In spite of such advances, there are some barriers to using EEG or MEG in routine clinical contexts. First, these techniques provide limited spatial resolution, given that the recorded electrical signals are averaged over extended regions of the brain. Attempts have been made to overcome this limitation through technical and mathematical means, such as the use of “dense array” (128–256 electrodes) coils to obtain multiple electrical potentials, which can then be combined using complex mathematical models to yield anatomically relevant data. Second, EEG and MEG are essentially surface techniques; because the intensity of the electromagnetic field decreases rapidly with distance, detection of neural signals is restricted to the sources closest to the detectors—that is, the neocortex. The activity of subcortical regions is very difficult to detect.

Despite these limitations, studies using EEG and related technology of evoked potentials have made significant contributions to our understanding of the pathophysiology of neurological and psychiatric disorders. Examples of such studies include the following:

1. Abnormalities in power spectral analysis of the resting-state EEG and study of evoked potentials in response to auditory stimuli have been consistently associated with core cognitive and neurochemical deficits in patients with schizophrenia and might lead to more effective subtyping of the disorder and delivery of more targeted and personalized care (Ford and Mathalon 2005; Turetsky et al. 1998).



2. Studies using dense-array EEG suggest that moderate depression may sensitize limbic networks to respond more strongly to aversive events than to positive events ([Tucker et al. 2003](#)).
3. EEG has been combined with other functional imaging techniques to yield highly specific temporal and spatial information, which could then be used to study deficits in neural systems and reward anticipation across multiple diagnostic entities ([Gorka et al. 2015](#)).
4. Some authors have recommended the use of EEG technologies in conjunction with fMRI to study analgesia and pain management ([Wise and Tracey 2006](#)).
5. Combined PET and EEG technologies using a source localization technique have identified disruption of frontocingulate connectivity among patients with depression ([Pizzagalli et al. 2003](#)). Studies such as these provide critical information that can complement and enhance our understanding of functional imaging approaches.
6. A series of papers have reported consistent evidence showing that quantitative EEG (qEEG) changes are predictive not only of antidepressant response but also of placebo response and might also help identify specific subtypes who will benefit from neuroplasticity-promoting treatments such as transcranial magnetic stimulation ([Leuchter et al. 2015](#)).
7. EEG-derived brain rhythm patterns have been proposed as putative biomarkers for objectively evaluating neuromodulation success and for guiding deep brain stimulation or other target-based neuromodulation strategies for patients with treatment-resistant depression ([Broadway et al. 2012](#)).

---

## Novel Insights From Brain Imaging in Applied Clinical Psychopharmacology

---

### Identifying Individuals at Risk of Developing Psychopathology

#### MAO-PET Labeling Studies

[Sacher et al. \(2012\)](#) used  $^{11}\text{C}$ -harmine PET scanning technology to measure the effect of changes in monoamine oxidase A (MAO-A) binding in brain regions implicated in affective and neurodegenerative disease. They showed that elevated activity of MAO in the ACC and prefrontal cortical area not only was associated with increases in depressive symptoms but also predicted the development of postpartum depression. This study demonstrates how receptor-labeling PET-ligand studies can provide novel therapeutic targets for new drug development and also inform the pathophysiology of depressive conditions. More

importantly, early identification of high-risk individuals might usher in an era of prophylactic medication therapy.

## **Machine-Learning Approach to Profiling Risk of Bipolar Disorder**

Neuroimaging findings from illness-based cohorts are often contaminated by chronicity effects of illness duration, medication exposure, and medical comorbidities ([Hajek et al. 2015](#)). A highly relevant approach in this regard might be to study patterns of neuroimaging change among genetically high-risk individuals, such as biological relatives of probands with a highly heritable disorder such as bipolar disorder, and to compare these high-risk individuals with a population of healthy control subjects. These data can then be analyzed by specialized pattern-recognition software such as support vector machines ([Orrù et al. 2012](#)) to identify patterns that differentiate high-risk individuals from healthy controls. Machine learning has recently been used to identify individuals at high genetic risk for bipolar disorder based on brain structure by comparing offspring of parents with bipolar disorder with an age- and sex-matched control group. Much to the surprise of the investigators, the brain changes, which significantly contributed to the between-group discrimination, included white matter of inferior/middle regions of frontal and temporal gyri and precuneus and not any of the gray matter regions included in the study ([Hajek et al. 2015](#)).

## **Neurochemical Targeting in Antipsychotic Treatment**

### **Mechanisms of Dopamine System Hyperresponsiveness in Schizophrenia**

It has long been known that patients diagnosed with schizophrenia have an exaggerated dopamine response to amphetamine challenge. [Laruelle et al. \(1995\)](#) conducted a landmark study in which they used SPECT to profile intrasynaptic dopamine release in human striatum following dextroamphetamine sulfate (D-amphetamine) challenge testing. Using the D<sub>2</sub> receptor-labeling radiotracer [<sup>123</sup>I]-iodobenzamide ([<sup>123</sup>I]IBZM), they demonstrated a decrease in D<sub>2</sub> receptor availability resulting from exaggerated release of dopamine (which occupied the D<sub>2</sub> receptors in response to amphetamine challenge) in the schizophrenic brains compared with healthy brains ([Laruelle et al. 1995](#)). This study was one of the very first to demonstrate the power of modern neuroimaging to shed light on neurochemical processes that mediate drug action.



## Discrimination of Biological Changes Mediating Effects and Side Effects of Antipsychotic Medication

Antipsychotic pharmacotherapy is heavily based on the premise that a correction of the exaggerated dopaminergic response might overstimulate D<sub>2</sub> receptors. However, excessive and near-total blockade of the D<sub>2</sub> receptors can lead to unwanted extrapyramidal side effects (EPS) and motor symptoms. Using a series of innovative PET ligand-based imaging paradigms, Kapur and colleagues ([Ginovart and Kapur 2012](#); [Kapur and Seeman 2001](#)) explored the question of whether the thresholds for clinical response and for EPS could be separated in terms of differential D<sub>2</sub> occupancy, measured via the PET-based D<sub>2</sub> binding ligand <sup>11</sup>C-raclopride following administration of haloperidol. They found that D<sub>2</sub> occupancy at a threshold of 65% significantly predicted clinical response, whereas D<sub>2</sub> occupancy above 78% produced EPS, and D<sub>2</sub> occupancy above 72% produced significant prolactin elevation. Thus, even with a relatively typical antipsychotic such as haloperidol, it is possible, although not clinically feasible, to obtain an antipsychotic effect without causing EPS just by optimizing D<sub>2</sub> occupancy. The authors later extended this observation to show that whereas even atypical antipsychotic agents with a low propensity to cause EPS, such as quetiapine and clozapine, achieved D<sub>2</sub> binding rates of 60% within 2 hours following administration (which might explain their antipsychotic efficacy), D<sub>2</sub> binding rates declined to less than 20% after 12 hours in the case of quetiapine and to 26% after 24 hours in the case of clozapine (which might underlie these agents' relative lack of EPS). The atypical antipsychotics risperidone and olanzapine achieve robust antipsychotic activity only at dosages producing D<sub>2</sub> receptor occupancy of 65% or greater, which is similar to the action of haloperidol ([Ginovart and Kapur 2012](#); [Kapur and Seeman 2001](#)).

## Profiling to Guide Treatment Selection

Identifying patients who will be ideal candidates for the manifold treatment options for major depressive disorder has been an ongoing challenge ([Alhajji and Nemeroff 2015](#)). Neuroimaging profiles have been proposed as biomarkers that could subtype and identify patients for specific therapies. Accordingly, insula hypometabolism (as indexed by <sup>18</sup>FDG uptake) was shown to be associated with achievement of remission with cognitive-behavioral therapy and poor response to escitalopram, while insula hypermetabolism was associated with achievement of remission with escitalopram and poor response to cognitive-behavioral therapy ([McGrath et al. 2013](#)).

## Subtyping of Clinical Syndromes

Not every patient with schizophrenia responds to D<sub>2</sub>-blocking antipsychotic medications. Using [<sup>18</sup>F] DOPA PET to label presynaptic dopamine synthesis, [Demjaha et al. \(2012\)](#) demonstrated that patients who responded to antipsychotic treatment showed significantly higher [<sup>18</sup>F] DOPA uptake in the striatum compared with patients who did not respond to D<sub>2</sub>-blocking agents. This important study points to the possibility that neuroimaging techniques might be used to profile antipsychotic-responsive versus nonresponsive schizophrenic patient subgroups.

## Elucidating Mechanisms of Action of Novel and Older Treatments

### Neuroimaging Studies of the Mechanism of Ketamine's Antidepressant Effects

Ketamine is a novel antidepressant with both a novel mechanism of action and a rapid antidepressant effect seen within hours of administration (as opposed to a time lapse of weeks). The precise mechanisms underlying its rapid antidepressant effects are being explored using novel neuroimaging techniques. Studies have consistently shown a decrease in pretreatment resting ACC activity and decreased engagement of pregenual ACC in response to cognitive challenge induced by a working-memory paradigm ([Salvadore et al. 2009, 2010](#)). In addition, treatment-resistant depression was associated with decreased neural responses in the right caudate to faces showing positive emotional expression—a change that was reversed following antidepressant response to ketamine ([Murrough et al. 2015](#)). Rapid antidepressant response to ketamine was also associated with decreases in amygdalar activity ([Salvadore et al. 2010](#)). Synaptic potentiation has been proposed as a mechanism underlying chronic antidepressant treatment response, and it is clear that repeated administration of ketamine induces synaptic proteins and enhances synaptic plasticity. A temporal dissociation between acute changes in cortical excitability (measured using MEG) and clinical antidepressant response led to the conclusion that ketamine's antidepressant effects might be mediated by non-*N*-methyl-D-aspartate (NMDA)-induced synaptic plasticity mechanisms ([Cornwell et al. 2012](#)). MRS measurements of glutamate response to ketamine administration among depressed and nondepressed human subjects have shown varied results, with some studies showing no changes ([Forbes et al. 2009](#); [Stone et al. 2012](#); [M.J. Taylor et al. 2012](#); [Valentine et al. 2011](#)) and others showing increases in glutamate concentrations ([Milak et al. 2016](#); [Rowland et al. 2005](#); [Salvadore et al. 2012](#)). Nevertheless, MRS measurements obtained within a short time window of 26 minutes following ketamine administration demonstrated greater increases in glutamate than were seen in scans obtained after longer wait times ([Milak et al. 2016](#)).

## Acute and Delayed Effects of Neuromodulation Using Deep Brain Stimulation

Neuromodulation treatments remain the last few options available for treatment-resistant depression and include commercially available approaches such as ECT, transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS) as well as experimentally available modalities such as transcranial direct current stimulation (tDCS), magnetic seizure therapy, cortical brain stimulation, and DBS. A detailed description of network changes during neuromodulation treatments is beyond the scope of this chapter, and readers are referred to authoritative reviews on the topic published elsewhere ([Smart et al. 2015](#)). Multimodality imaging techniques have been used to guide and inform target selection for neuromodulation treatments based on DBS. Preoperatively acquired diffusion imaging for connectivity-based cortical mapping in combination with postoperative computed tomography could improve neurosurgical targeting and has been used to delineate adaptive changes in white matter tracts and modulation of neural activity in response to the immediate and delayed effects of DBS. Using these cortical mapping techniques, [Johansen-Berg et al. \(2008\)](#) demonstrated that the acute antidepressant effects of DBS were mediated by its effect on a network involving the subgenual ACC region (BA 25), with strongest connections to nucleus accumbens, amygdala, hypothalamus, and orbitofrontal cortex. [Choi et al. \(2015\)](#) used structural connectivity analysis to show that the best intraoperative response to DBS consisted of both interoceptive and exteroceptive changes involving contacts connected to the bilateral ventromedial frontal cortex (via forceps minor and left uncinate fasciculus) and the cingulate cortex (via left cingulum bundle). Later studies at 6 months and 2 years showed that response to DBS not only engaged the above regions but also recruited additional regions ([Crowell et al. 2015](#)). Specifically, all DBS responders showed engagement by subgenual ACC of the same bilateral pathways from their activation volumes in subgenual ACC to 1) medial frontal cortex via forceps minor and uncinate fasciculus, 2) rostral and dorsal cingulate cortex via the cingulum bundle, and 3) subcortical nuclei ([Riva-Posse et al. 2014](#)). Similar strategies are also guiding refined target selection for noninvasive neuromodulation techniques such as repetitive TMS ([Fox et al. 2014](#)).

## Improved Understanding of Mechanism of Action of Older Medications

While multiple newer and faster-acting treatments have become available to treat depression, older agents such as SSRIs continue to be widely useful. Negative cognitive bias is a vulnerability marker for depression, and its neural footprints have been mapped with fMRI indices such as exaggerated amygdalar response to fearful faces. Catherine Harmer and colleagues used a double-blind, placebo-controlled pharmacological fMRI paradigm to demonstrate that a single

dose of intravenous citalopram resulted in significantly greater reductions in amygdalar responses to fearful facial expressions compared with placebo (Murphy et al. 2009). In a subsequent study, the same group demonstrated that oral citalopram given at 10 mg/day for 7 days resulted in similar reductions in exaggerated amygdalar response to negative emotional stimuli, which predicted clinical improvement in depressed mood (Godlewska et al. 2012).

---

## Conclusion

---

Contemporary brain-imaging methods provide a variety of strategies to probe structural, functional, and chemical abnormalities in specific neural circuits relevant to psychiatric illness. Such studies are having a considerable impact on our conceptualization of these disorders, with potential impacts on diagnosis (Mayberg 2003a), clinical management (monitoring occupancy or PIB changes with treatment [Klunk et al. 2004]), and novel treatment development (Mayberg 2009). Brain-imaging studies in psychopharmacology can be categorized both by the scanning technology employed (e.g., MRI, PET, EEG) and by the type of measurement obtained (e.g., activation, resting state, behavioral, biochemical, receptor mapping). Receptor-mapping studies have clearly added to our ability to understand mechanisms of action of psychopharmacological agents and their side-effect profiles. Activation studies, which indirectly measure neuronal activity vis-à-vis changes in CBF, have become widely used with fMRI technology, providing new insights into behaviorally specific subcircuits. Structural MRI studies have also begun to yield considerable data, enabling a better understanding of how the disease processes are regionally localized, where to target for functional imaging, and where to obtain specimens for postmortem histopathological analysis. Multimodal imaging through a combination of fMRI, PET, structural MRI, MRS, and electromagnetic measurement (EEG, MEG) offers the promise of identifying both neuronal and chemical changes related to brain function.

---

## References

---

- Abdallah CG, Jiang L, De Feyter HM, et al: Glutamate metabolism in major depressive disorder. *Am J Psychiatry* 171(12): 1320–1327, 2014 25073688
- Alexander AL, Lee JE, Lazar M, et al: Diffusion tensor imaging of the corpus callosum in Autism. *Neuroimage* 34(1):61–73, 2007 17023185
- Alexopoulos GS, Meyers BS, Young RC, et al: ‘Vascular depression’ hypothesis. *Arch Gen Psychiatry* 54(10):915–922, 1997 9337771
- Alhajji L, Nemeroff CB: Personalized medicine and mood disorders. *Psychiatr Clin North Am* 38(3):395–403, 2015 26300030

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Berns GS: Functional neuroimaging. *Life Sci* 65(24):2531-2540, 1999 10619361
- Biswal BB, Van Kylen J, Hyde JS: Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR Biomed* 10(4-5):165-170, 1997 9430343
- Blier P, Ward NM: Is there a role for 5-HT<sub>1A</sub> agonists in the treatment of depression? *Biol Psychiatry* 53(3):193-203, 2003 12559651
- Bluhm RL, Miller J, Lanius RA, et al: Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. *Schizophr Bull* 33(4):1004-1012, 2007 17556752
- Bookheimer SY, Strojwas MH, Cohen MS, et al: Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med* 343(7):450-456, 2000 10944562
- Borgwardt S, Fusar-Poli P: Third-generation neuroimaging in early schizophrenia: translating research evidence into clinical utility. *Br J Psychiatry* 200(4):270-272, 2012 22474231
- Bremner JD: Functional neuroimaging in post-traumatic stress disorder. *Expert Rev Neurother* 7(4):393-405, 2007 17425494
- Bremner JD, Innis RB, White T, et al: SPECT [I-123]iomazenil measurement of the benzodiazepine receptor in panic disorder. *Biol Psychiatry* 47(2):96-106, 2000 10664825
- Broadway JM, Holtzheimer PE, Hilimire MR, et al: Frontal theta coherence predicts 6-month antidepressant response to subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. *Neuropsychopharmacology* 37(7):1764-1772, 2012 22414813
- Brown AK, Fujita M, Fujimura Y, et al: Radiation dosimetry and biodistribution in monkey and man of <sup>11</sup>C-PBR28: a PET radioligand to image inflammation. *J Nucl Med* 48(12):2072-2079, 2007 18006619
- Buckner RL, Vincent JL: Unrest at rest: default activity and spontaneous network correlations. *Neuroimage* 37(4):1091-1096, discussion 1097-1099, 2007 17368915
- Bullmore E, Sporns O: Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10(3):186-198, 2009 19190637
- Buxton RB: Introduction to Functional Magnetic Resonance Imaging. Principles and Techniques. Cambridge, UK, Cambridge University Press, 2002
- Capuron L, Pagnoni G, Drake DF, et al: Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alpha administration. *Arch Gen Psychiatry* 69(10):1044-1053, 2012 23026954
- Carbon M, Eidelberg D: Modulation of regional brain function by deep brain stimulation: studies with positron emission tomography. *Curr Opin Neurol* 15(4):451-455, 2002 12151842

- Cherkassky VL, Kana RK, Keller TA, Just MA: Functional connectivity in a baseline resting-state network in autism. *Neuroreport* 17(16):1687-1690, 2006 17047454
- Choi KS, Riva-Posse P, Gross RE, Mayberg HS: Mapping the “depression switch” during intraoperative testing of subcallosal cingulate deep brain stimulation. *JAMA Neurol* 72(11):1252-1260, 2015 26408865
- Cornwell BR, Salvatore G, Furey M, et al: Synaptic potentiation is critical for rapid antidepressant response to ketamine in treatment-resistant major depression. *Biol Psychiatry* 72(7):555-561, 2012 22521148
- Craik FIM, Moroz TM, Moscovitch M, et al: In search of the self: a positron emission tomography study. *Psychological Science* 10(1):26-34, 1999 doi: 10.1111/1467-9280.00102
- Cropley VL, Fujita M, Innis RB, Nathan PJ: Molecular imaging of the dopaminergic system and its association with human cognitive function. *Biol Psychiatry* 59(10):898-907, 2006 16682268
- Crowell AL, Garlow SJ, Riva-Posse P, Mayberg HS: Characterizing the therapeutic response to deep brain stimulation for treatment-resistant depression: a single center long-term perspective. *Front Integr Neurosci* 9:41, 2015 26124710
- Dani M, Brooks DJ, Edison P: Tau imaging in neurodegenerative diseases. *Eur J Nucl Med Mol Imaging* 43(6):1139-1150, 2016 26572762
- Davatzikos C, Ruparel K, Fan Y, et al: Classifying spatial patterns of brain activity with machine learning methods: application to lie detection. *Neuroimage* 28(3):663-668, 2005 16169252
- Demjaha A, Murray RM, McGuire PK, et al: Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry* 169(11):1203-1210, 2012 23034655
- Detre JA, Wang J, Wang Z, Rao H: Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. *Curr Opin Neurol* 22(4):348-355, 2009 19491678
- Detre JA, Rao H, Wang DJ, et al: Applications of arterial spin labeled MRI in the brain. *J Magn Reson Imaging* 35(5):1026-1037, 2012 22246782
- Dixon MR, Jacobs EA, Sanders S: Contextual control of delay discounting by pathological gamblers. *J Appl Behav Anal* 39(4):413-422, 2006 17236338
- Ebner A, Sciarretta G, Epstein CM, Nuwer M; The International Federation of Clinical Neurophysiology: EEG instrumentation. *Electroencephalogr Clin Neurophysiol Suppl* 52:7-10, 1999 10590971
- Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ: The neural basis of mood-congruent processing biases in depression. *Arch Gen Psychiatry* 59(7):597-604, 2002 12090812
- Erritzoe D, Talbot P, Frankle WG, Abi-Dargham A: Positron emission tomography and single photon emission CT molecular imaging in schizophrenia. *Neuroimaging Clin N Am* 13(4):817-832, 2003 15024964
- Evans KC, Dougherty DD, Pollack MH, Rauch SL: Using neuroimaging to predict treatment response in mood and anxiety disorders. *Ann Clin Psychiatry* 18(1):33-42, 2006 16517451
- Fisher PM, Meltzer CC, Ziolkowski SK, et al: Capacity for 5-HT<sub>1A</sub>-mediated autoregulation predicts amygdala reactivity. *Nat Neurosci* 9(11):1362-1363, 2006 17013380

- Forbes NF, Carrick LA, McIntosh AM, Lawrie SM: Working memory in schizophrenia: a meta-analysis. *Psychol Med* 39(6):889-905, 2009 18945379
- Ford JM, Mathalon DH: Corollary discharge dysfunction in schizophrenia: can it explain auditory hallucinations? *Int J Psychophysiol* 58(2-3):179-189, 2005 16137779
- Fossati P, Hevenor SJ, Graham SJ, et al: In search of the emotional self: an fMRI study using positive and negative emotional words. *Am J Psychiatry* 160(11):1938-1945, 2003 14594739
- Fox MD, Buckner RL, Liu H, et al: Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. *Proc Natl Acad Sci U S A* 111(41):E4367-E4375, 2014 25267639
- Frye MA, Watzl J, Banakar S, et al: Increased anterior cingulate/medial prefrontal cortical glutamate and creatine in bipolar depression. *Neuropsychopharmacology* 32(12):2490-2499, 2007 17429412
- Fu CH, Williams SC, Brammer MJ, et al: Neural responses to happy facial expressions in major depression following antidepressant treatment. *Am J Psychiatry* 164(4):599-607, 2007 17403973
- Fujimoto T, Takeuch K, Matsumoto T, et al: Abnormal glucose metabolism in the anterior cingulate cortex in patients with schizophrenia. *Psychiatry Res* 154(1):49-58, 2007 17188463
- Gigante AD, Bond DJ, Lafer B, et al: Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: a meta-analysis. *Bipolar Disord* 14(5):478-487, 2012 22834460
- Ginovart N, Kapur S: Role of dopamine D(2) receptors for antipsychotic activity. *Handb Exp Pharmacol* (212):27-52, 2012 23129327
- Godlewska BR, Norbury R, Selvaraj S, et al: Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychol Med* 42(12):2609-2617, 2012 22716999
- Gorka SM, Phan KL, Shankman SA: Convergence of EEG and fMRI measures of reward anticipation. *Biol Psychol* 112:12-19, 2015 26394333
- Greicius MD, Flores BH, Menon V, et al: Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol Psychiatry* 62(5):429-437, 2007 17210143
- Gunn RN, Slifstein M, Searle GE, Price JC: Quantitative imaging of protein targets in the human brain with PET. *Phys Med Biol* 60(22):R363-R411, 2015 26513176
- Gusnard DA, Raichle ME, Raichle ME: Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2(10):685-694, 2001 11584306
- Hajek T, Cooke C, Kopecek M, et al: Using structural MRI to identify individuals at genetic risk for bipolar disorders: a 2-cohort, machine learning study. *J Psychiatry Neurosci* 40(5):316-324, 2015 25853284
- Hariri AR, Mattay VS, Tessitore A, et al: Serotonin transporter genetic variation and the response of the human amygdala. *Science* 297(5580):400-403, 2002 12130784
- Haroon E, Pagnoni G, Heim CM, et al: Brain imaging in psychopharmacology, in *The American Psychiatric Publishing Textbook of Psychopharmacology*, 4th

- Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Publishing, 2009, pp 221-242
- Haroon E, Raison CL, Miller AH: Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology* 37(1):137-162, 2012 21918508
- Haroon E, Woolwine BJ, Chen X, et al: IFN-alpha-induced cortical and subcortical glutamate changes assessed by magnetic resonance spectroscopy. *Neuropsychopharmacology* 39(7):1777-1785, 2014 24481242
- Haroon E, Felger JC, Woolwine BJ, et al: Age-related increases in basal ganglia glutamate are associated with TNF, reduced motivation and decreased psychomotor speed during IFN-alpha treatment: preliminary findings. *Brain Behav Immun* 46:17-22, 2015 25500218
- Haroon E, Fleischer CC, Felger JC, et al: Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. *Mol Psychiatry* 21(10):1351-1357, 2016 26754953
- Harvey PO, Fossati P, Pochon JB, et al: Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage* 26(3):860-869, 2005 15955496
- Herscovitch P, Markham J, Raichle ME: Brain blood flow measured with intravenous H<sub>2</sub>(15)O, I: theory and error analysis. *J Nucl Med* 24(9):782-789, 1983 6604139
- Ioannides AA: Magnetoencephalography as a research tool in neuroscience: state of the art. *Neuroscientist* 12(6):524-544, 2006 17079518
- Johansen-Berg H, Gutman DA, Behrens TE, et al: Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb Cortex* 18(6):1374-1383, 2008 17928332
- Kapur S, Remington G: Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry* 50(11): 873-883, 2001 11743942
- Kapur S, Seeman P: Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? A new hypothesis. *Am J Psychiatry* 158(3): 360-369, 2001 11229973
- Kenk M, Selvanathan T, Rao N, et al: Imaging neuroinflammation in gray and white matter in schizophrenia: an in-vivo PET study with [18F]-FEPPA. *Schizophr Bull* 41(1):85-93, 2015 25385788
- Kennedy C, Des Rosiers MH, Sakurada O, et al: Metabolic mapping of the primary visual system of the monkey by means of the autoradiographic [14C]deoxyglucose technique. *Proc Natl Acad Sci U S A* 73(11):4230-4234, 1976 825861
- Kilts CD, Gross RE, Ely TD, Drexler KP: The neural correlates of cue-induced craving in cocaine-dependent women. *Am J Psychiatry* 161(2):233-241, 2004 14754771
- Klumpp H, Fitzgerald DA, Phan KL: Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 45:83-91, 2013 23665375



- Klunk WE, Engler H, Nordberg A, et al: Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* 55(3):306-319, 2004 14991808
- Kubicki M, McCarley R, Westin CF, et al: A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res* 41(1-2):15-30, 2007 16023676
- Kumar A, Mintz J, Bilker W, Gottlieb G: Autonomous neurobiological pathways to late-life major depressive disorder: clinical and pathophysiological implications. *Neuropsychopharmacology* 26(2):229-236, 2002 11790518
- Kumar JS, Mann JJ: PET tracers for serotonin receptors and their applications. *Cent Nerv Syst Agents Med Chem* 14(2):96-112, 2014 25360773
- Lange C, Kracht L, Herholz K, et al: Reduced glucose metabolism in temporoparietal cortices of women with borderline personality disorder. *Psychiatry Res* 139(2): 115-126, 2005 15978784
- Laruelle M, Abi-Dargham A, van Dyck CH, et al: SPECT imaging of striatal dopamine release after amphetamine challenge. *J Nucl Med* 36(7):1182-1190, 1995 7790942
- Le Bihan D: Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci* 4(6):469-480, 2003 12778119
- Lemogne C, le Bastard G, Mayberg H, et al: In search of the depressive self: extended medial prefrontal network during self-referential processing in major depression. *Soc Cogn Affect Neurosci* 4(3):305-312, 2009 19307251
- Leuchter AF, Hunter AM, Krantz DE, Cook IA: Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments. *Ann N Y Acad Sci* 1344:78-91, 2015 25809789
- Lowe MJ, Phillips MD, Lurito JT, et al: Multiple sclerosis: low-frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity initial results. *Radiology* 224(1):184-192, 2002 12091681
- Luat AF, Makki M, Chugani HT: Neuroimaging in tuberous sclerosis complex. *Curr Opin Neurol* 20(2):142-150, 2007 17351483
- Lyoo IK, Renshaw PF: Magnetic resonance spectroscopy: current and future applications in psychiatric research. *Biol Psychiatry* 51(3):195-207, 2002 11839362
- Magistretti PJ: Neuron-glia metabolic coupling and plasticity. *J Exp Biol* 209(Pt 12):2304-2311, 2006 16731806
- Magistretti PJ, Pellerin L: Astrocytes Couple Synaptic Activity to Glucose Utilization in the Brain. *News Physiol Sci* 14:177-182, 1999a 11390847
- Magistretti PJ, Pellerin L: Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Philos Trans R Soc Lond B Biol Sci* 354(1387):1155-1163, 1999b 10466143
- Mason GF, Krystal JH: MR spectroscopy: its potential role for drug development for the treatment of psychiatric diseases. *NMR Biomed* 19(6):690-701, 2006 16986118
- Mathis CA, Klunk WE, Price JC, DeKosky ST: Imaging technology for neurodegenerative diseases: progress toward detection of specific pathologies. *Arch Neurol* 62(2):196-200, 2005 15710847
- Mayberg HS: Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull* 65:193-207, 2003a 12697626

- Mayberg HS: Positron emission tomography imaging in depression: a neural systems perspective. *Neuroimaging Clin N Am* 13(4):805-815, 2003b 15024963
- Mayberg HS: Targeted electrode-based modulation of neural circuits for depression. *J Clin Invest* 119(4):717-725, 2009 19339763
- McClure SM, Laibson DI, Loewenstein G, Cohen JD: Separate neural systems value immediate and delayed monetary rewards. *Science* 306(5695):503-507, 2004 15486304
- McGrath CL, Kelley ME, Holtzheimer PE, et al: Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry* 70(8):821-829, 2013 23760393
- Menon V: Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci* 15(10):483-506, 2011 21908230
- Menon RS, Goodyear BG: Submillimeter functional localization in human striate cortex using BOLD contrast at 4 tesla: implications for the vascular point-spread function. *Magn Reson Med* 41(2):230-235, 1999 10080267
- Mettenburg JM, Benzinger TL, Shimony JS, et al: Diminished performance on neuropsychological testing in late life depression is correlated with microstructural white matter abnormalities. *Neuroimage* 60(4):2182-2190, 2012 22487548
- Meyer JH: Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. *J Psychiatry Neurosci* 32(2):86-102, 2007 17353938
- Meyer JH, Wilson AA, Rusjan P, et al: Serotonin<sub>2A</sub> receptor binding potential in people with aggressive and violent behaviour. *J Psychiatry Neurosci* 33(6):499-508, 2008 18982172
- Meyer-Lindenberg A, Weinberger DR: Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci* 7(10):818-827, 2006 16988657
- Milak MS, Proper CJ, Mulhern ST, et al: A pilot in vivo proton magnetic resonance spectroscopy study of amino acid neurotransmitter response to ketamine treatment of major depressive disorder. *Mol Psychiatry* 21(3):320-327, 2016 26283639
- Miller AH, Haroon E, Raison CL, Felger JC: Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. *Depress Anxiety* 30(4):297-306, 2013 23468190
- Miller CH, Hamilton JP, Sacchet MD, Gotlib IH: Meta-analysis of functional neuroimaging of major depressive disorder in youth. *JAMA Psychiatry* 72(10):1045-1053, 2015 26332700
- Mintun MA, Raichle ME, Kilbourn MR, et al: A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann Neurol* 15(3):217-227, 1984 6609679
- Mitterschiffthaler MT, Kumari V, Malhi GS, et al: Neural response to pleasant stimuli in anhedonia: an fMRI study. *Neuroreport* 14(2):177-182, 2003 12598724
- Moore CM, Frederick BB, Renshaw PF: Brain biochemistry using magnetic resonance spectroscopy: relevance to psychiatric illness in the elderly. *J Geriatr Psychiatry Neurol* 12(3):107-117, 1999 10593699

- Moore CM, Wardrop M, deB Frederick B, Renshaw PF: Topiramate raises anterior cingulate cortex glutamine levels in healthy men; a 4.0 T magnetic resonance spectroscopy study. *Psychopharmacology (Berl)* 188(2):236-243, 2006 16944105
- Moore GJ, Bebchuk JM, Wilds IB, et al: Lithium-induced increase in human brain grey matter. *Lancet* 356(9237):1241-1242, 2000 11072948
- Murphy SE, Norbury R, O'Sullivan U, et al: Effect of a single dose of citalopram on amygdala response to emotional faces. *Br J Psychiatry* 194(6):535-540, 2009 19478294
- Murrough JW, Collins KA, Fields J, et al: Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder. *Transl Psychiatry* 5:e509, 2015 25689570
- Myers R, Manjil LG, Cullen BM, et al: Macrophage and astrocyte populations in relation to [3H]PK 11195 binding in rat cerebral cortex following a local ischaemic lesion. *J Cereb Blood Flow Metab* 11(2): 314-322, 1991 1997503
- National Institute of Biomedical Imaging and Bioengineering: Nuclear medicine (fact sheet), July 2013. Bethesda, MD, NIBIB, Office of Science Policy and Communications. Available at: <http://www.nibib.nih.gov/sites/default/files/Nuclear%20Medicine%20Fact%20Sheet.pdf>. Accessed February 19, 2016.
- Nemeroff CB, Owens MJ: The role of serotonin in the pathophysiology of depression: as important as ever. *Clin Chem* 55(8):1578-1579, 2009 19498050
- Nestor PG, Kubicki M, Spencer KM, et al: Attentional networks and cingulum bundle in chronic schizophrenia. *Schizophr Res* 90(1-3):308-315, 2007 17150337
- Neumeister A, Nugent AC, Waldeck T, et al: Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. *Arch Gen Psychiatry* 61(8):765-773, 2004 15289275
- Ogawa S, Tank DW, Menon R, et al: Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci U S A* 89(13):5951-5955, 1992 1631079
- Ono M, Wilson A, Nobrega J, et al: 11C-labeled stilbene derivatives as Abeta-aggregate-specific PET imaging agents for Alzheimer's disease. *Nucl Med Biol* 30(6):565-571, 2003 12900282
- Orrù G, Pettersson-Yeo W, Marquand AF, et al: Using Support Vector Machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review. *Neurosci Biobehav Rev* 36(4):1140-1152, 2012 22305994
- Owen AM, McMillan KM, Laird AR, Bullmore E: N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 25(1):46-59, 2005 15846822
- Parsey RV, Krishnan KR: A new MRI ratio method for in-vivo estimation of signal hypointensity in aging and Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 21(8):1257-1267, 1997 9460090
- Paulus MP, Stein MB: An insular view of anxiety. *Biol Psychiatry* 60(4):383-387, 2006 16780813
- Pearlson GD, Calhoun V: Structural and functional magnetic resonance imaging in psychiatric disorders. *Can J Psychiatry* 52(3):158-166, 2007 17479523

- Pizzagalli DA, Oakes TR, Davidson RJ: Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. *Psychophysiology* 40(6):939-949, 2003 14986847
- Post RM, Speer AM, Hough CJ, Xing G: Neurobiology of bipolar illness: implications for future study and therapeutics. *Ann Clin Psychiatry* 15(2):85-94, 2003 12938866
- Purselle DC, Nemeroff CB: Serotonin transporter: a potential substrate in the biology of suicide. *Neuropsychopharmacology* 28(4):613-619, 2003 12655305
- Rao H, Gillihan SJ, Wang J, et al: Genetic variation in serotonin transporter alters resting brain function in healthy individuals. *Biol Psychiatry* 62(6):600-606, 2007 17481593
- Rauch SL, Whalen PJ, Shin LM, et al: Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry* 47(9):769-776, 2000 10812035
- Ravina B, Eidelberg D, Ahlskog JE, et al: The role of radiotracer imaging in Parkinson disease. *Neurology* 64(2):208-215, 2005 15668415
- Reivich M, Kuhl D, Wolf A, et al: The [18F] fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 44(1):127-137, 1979 363301
- Riva-Posse P, Choi KS, Holtzheimer PE, et al: Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 76(12):963-969, 2014 24832866
- Roffman JL, Marci CD, Glick DM, et al: Neuroimaging and the functional neuroanatomy of psychotherapy. *Psychol Med* 35(10):1385-1398, 2005 16164763
- Roiser JP, Levy J, Fromm SJ, et al: The effects of tryptophan depletion on neural responses to emotional words in remitted depression. *Biol Psychiatry* 66(5):441-450, 2009 19539268
- Rombouts SA, Barkhof F, Goekoop R, et al: Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Hum Brain Mapp* 26(4):231-239, 2005 15954139
- Rowland LM, Bustillo JR, Mullins PG, et al: Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. *Am J Psychiatry* 162(2):394-396, 2005 15677610
- Rusjan PM, Wilson AA, Bloomfield PM, et al: Quantitation of translocator protein binding in human brain with the novel radioligand [18F]-FEPPA and positron emission tomography. *J Cereb Blood Flow Metab* 31(8):1807-1816, 2011 21522163
- Sacher J, Rabiner EA, Clark M, et al: Dynamic, adaptive changes in MAO-A binding after alterations in substrate availability: an in vivo [(11)C]-harmine positron emission tomography study. *J Cereb Blood Flow Metab* 32(3):443-446, 2012 22186668
- Salvadore G, Cornwell BR, Colon-Rosario V, et al: Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker

- that predicts rapid antidepressant response to ketamine. *Biol Psychiatry* 65(4):289-295, 2009 18822408
- Salvadore G, Cornwell BR, Sambataro F, et al: Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacology* 35(7):1415-1422, 2010 20393460
- Salvadore G, van der Veen JW, Zhang Y, et al: An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression. *Int J Neuropsychopharmacol* 15(8):1063-1072, 2012 22040773
- Sanacora G, Mason GF, Rothman DL, et al: Increased cortical GABA concentrations in depressed patients receiving ECT. *Am J Psychiatry* 160(3):577-579, 2003 12611844
- Schweitzer JB, Lee DO, Hanford RB, et al: Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity. *Biol Psychiatry* 56(8):597-606, 2004 15476690
- Seeley WW, Menon V, Schatzberg AF, et al: Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27(9):2349-2356, 2007 17329432
- Setiawan E, Wilson AA, Mizrahi R, et al: Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry* 72(3):268-275, 2015 25629589
- Sheline YI, Barch DM, Donnelly JM, et al: Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* 50(9):651-658, 2001 11704071
- Shin LM, Orr SP, Carson MA, et al: Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry* 61(2):168-176, 2004 14757593
- Silverman DH, Cummings JL, Small GW, et al: Added clinical benefit of incorporating 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography into the clinical evaluation of patients with cognitive impairment. *Mol Imaging Biol* 4(4):283-293, 2002 14537119
- Small GW: Neuroimaging and genetic assessment for early diagnosis of Alzheimer's disease. *J Clin Psychiatry* 57 (suppl 14):9-13, 1996 9024331
- Small GW, Kepe V, Ercoli LM, et al: PET of brain amyloid and tau in mild cognitive impairment. *N Engl J Med* 355(25):2652-2663, 2006 17182990
- Smart OL, Tiruvadi VR, Mayberg HS: Multimodal approaches to define network oscillations in depression. *Biol Psychiatry* 77(12):1061-1070, 2015 25681871
- Stein MB, Simmons AN, Feinstein JS, Paulus MP: Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *Am J Psychiatry* 164(2):318-327, 2007 17267796
- Stone JM, Dietrich C, Edden R, et al: Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. *Mol Psychiatry* 17(7):664-665, 2012 22212598
- Sui J, Castro E, He H, et al: Combination of FMRI-SMRI-EEG data improves discrimination of schizophrenia patients by ensemble feature selection. *Conf*

- Proc IEEE Eng Med Biol Soc 2014:3889-3892, 2014 25570841
- Talbot PS, Laruelle M: The role of in vivo molecular imaging with PET and SPECT in the elucidation of psychiatric drug action and new drug development. *Eur Neuropsychopharmacol* 12(6):503-511, 2002 12468013
- Taylor MJ, Tiangga ER, Mhuirheartaigh RN, Cowen PJ: Lack of effect of ketamine on cortical glutamate and glutamine in healthy volunteers: a proton magnetic resonance spectroscopy study. *J Psychopharmacol* 26(5):733-737, 2012 21616979
- Taylor WD, Bae JN, MacFall JR, et al: Widespread effects of hyperintense lesions on cerebral white matter structure. *AJR Am J Roentgenol* 188(6):1695-1704, 2007 17515396
- Thulborn KR, Waterton JC, Matthews PM, Radda GK: Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochim Biophys Acta* 714(2):265-270, 1982 6275909
- Tononi G, Edelman GM: Consciousness and complexity. *Science* 282(5395):1846-1851, 1998 9836628
- Tucker DM, Luu P, Frishkoff G, et al: Frontolimbic response to negative feedback in clinical depression. *J Abnorm Psychol* 112(4):667-678, 2003 14674878
- Turetsky BI, Colbath EA, Gur RE: P300 subcomponent abnormalities in schizophrenia, I: physiological evidence for gender and subtype specific differences in regional pathology. *Biol Psychiatry* 43(2): 84-96, 1998 9474441
- Turkheimer FE, Rizzo G, Bloomfield PS, et al: The methodology of TSPO imaging with positron emission tomography. *Biochem Soc Trans* 43(4):586-592, 2015 26551697
- Valentine GW, Mason GF, Gomez R, et al: The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. *Psychiatry Res* 191(2):122-127, 2011 21232924
- Varela F, Lachaux JP, Rodriguez E, Martinerie J: The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2(4):229-239, 2001 11283746
- Vlassenko AG, Benzinger TL, Morris JC: PET amyloid-beta imaging in preclinical Alzheimer's disease. *Biochim Biophys Acta* 1822(3):370-379, 2012 22108203
- Whalen PJ, Rauch SL, Etcoff NL, et al: Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 18(1): 411-418, 1998 9412517
- Whalen PJ, Shin LM, Somerville LH, et al: Functional neuroimaging studies of the amygdala in depression. *Semin Clin Neuropsychiatry* 7(4):234-242, 2002 12382206
- Whitton AE, Treadway MT, Pizzagalli DA: Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry* 28(1):7-12, 2015 25415499
- Wise RG, Tracey I: The role of fMRI in drug discovery. *J Magn Reson Imaging* 23(6):862-876, 2006 16649197
- Woodward ND, Rogers B, Heckers S: Functional resting-state networks are differentially affected in schizophrenia. *Schizophr Res* 130(1-3):86-93, 2011 21458238

Yüksel C, Öngür D: Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biol Psychiatry* 68(9):785–794, 2010 20728076

Zink CF, Pagnoni G, Chappelow J, et al: Human striatal activation reflects degree of stimulus saliency. *Neuroimage* 29(3):977–983, 2006 16153860

---

The authors wish to acknowledge the significant contribution made by Christine Heim, Ph.D., Guiseppe Pagnoni, Ph.D., and Greg Berns, M.D., Ph.D., in the preparation of the chapter in the previous edition of this Textbook.

Portions of this chapter are reprinted from Berns GS: “Functional Neuroimaging.” *Life Sciences* 65(24):2531–2540, 1999. Copyright 1999, Elsevier Science. Used with permission.

## **PART II**

# Classes of Psychiatric Treatments



# **Antidepressants and Anxiolytics**

## CHAPTER 8

# Monoamine Oxidase Inhibitors

K. Ranga Rama Krishnan, M.D.

---

### History and Discovery

---

Monoamine oxidase inhibitors (MAOIs) were first identified as effective antidepressants in the late 1950s. An early report suggested that iproniazid, an antitubercular agent, had mood-elevating properties in patients who had been treated for tuberculosis ([Bloch et al. 1954](#)). Following these observations, two studies confirmed that iproniazid did indeed have antidepressant properties ([Crane 1957](#); [Kline 1958](#)). [Zeller \(1963\)](#) showed that iproniazid caused potent inhibition of monoamine oxidase (MAO) enzymes both in vivo and in vitro in the brain. He also reported that the medication reversed some of the actions of reserpine. Because reserpine produced significant depression as a side effect, it was suggested that iproniazid might have mood-elevating properties.

The use of iproniazid soon fell into disfavor because of its significant hepatotoxicity. Other MAOIs, both hydrazine derivatives (e.g., isocarboxazid, phenylhydrazine) and nonhydrazine derivatives (e.g., tranylcypromine), were introduced. These MAOIs were not specific for any subtype of MAO enzyme, and they were irreversible inhibitors of MAO (see next section, “Monoamine Oxidase”). Their use has been rather limited because hypertensive crisis by the MAOIs may occur in some patients from potentiation of the pressor effects of amines (such as tyramine) in food ([Blackwell et al. 1967](#)).

In more recent years, there has been a resurgence of interest in the development of new MAOIs—that is, in development of MAOIs that are more selective for specific subtypes of MAO enzyme and that are reversible in nature. Reversible monoamine oxidase A (MAO-A) inhibitors, such as moclobemide, have been introduced in Europe but are not available in the United States. Newer MAOIs, such as selegiline, a monoamine oxidase B (MAO-B) inhibitor, have been introduced. [Table 8-1](#) classifies the MAOIs by structure, selectivity, and reversibility.

TABLE 8-1. Classification of monoamine oxidase inhibitor (MAOI) drugs by structure, selectivity, and reversibility			
Drug	Hydrazine	Selective	Reversible

Drug	Hydrazine	Selective	Reversible
Phenelzine	Yes	No	No
Isocarboxazid	Yes	No	No
Tranylcypromine	No	No	No
Selegiline	No	Yes <sup>a,b</sup>	No
Clorgyline <sup>c</sup>	No	Yes <sup>d</sup>	No
Moclobemide <sup>e</sup>	No	Yes <sup>d</sup>	Yes
Brofaromine <sup>c</sup>	No	Yes <sup>d</sup>	Yes

<sup>a</sup>Selective for monoamine oxidase B (MAO-B) at lower doses.

<sup>b</sup>Becomes nonselective at higher doses.

<sup>c</sup>Never marketed in the United States.

<sup>d</sup>Selective for monoamine oxidase A (MAO-A).

<sup>e</sup>Not commercially available in the United States.

---

## Monoamine Oxidase

---

### A and B Isoenzymes

MAO is widely distributed in mammals. Two isoenzymes, MAO-A and MAO-B, are of special interest ([Cesura](#) and

[Pletscher 1992](#)). Both are present in the central nervous system (CNS) and in some peripheral organs. For example, MAO-A is present in the liver, heart, and pancreas, and MAO-B is present in the liver, posterior pituitary, renal tubules, and endocrine pancreas ([Saura et al. 1992](#)). Both MAO-A and MAO-B are present in discrete cell populations within the CNS. MAO-A is present in both dopamine (DA) and norepinephrine (NE) neurons, whereas MAO-B is present to a greater extent in serotonin (5-HT)-containing neurons. Both are also present in nonaminergic neurons in various subcortical regions of the brain. Glial cells also express MAO-A and MAO-B ([Cesura and Pletscher 1992](#)).

The physiological functions of these two isoenzymes have not been fully elucidated. The main substrates for MAO-A are epinephrine, NE, and 5-HT. The main substrates for MAO-B are phenylethylamine, phenylethanolamine, tyramine, and benzylamine. DA and tryptamine are metabolized by both isoenzymes. The localization of the MAO subtypes does not fully correspond to the neurons containing the substrates. The reason for this discrepancy is unknown. The occurrence of the MAO-B form in 5-HT neurons may actually protect these neurons from amines (other than 5-HT) that could be toxic to them ([Cesura and Pletscher 1992](#)).

The primary structures of MAO-A and MAO-B have been fully described. MAO-A has 527 amino acids, and MAO-B has 520 amino acids. About 70% of the amino acid sequence of the two forms is homologous. The genes for both isoenzymes are located on the short arm of the human X chromosome. MAO-A and MAO-B are linked and have been located in the XP11.23-P11 and XP22.1 regions, respectively. The genes span about 70 kilobases (kb) and consist of about 15 exons and 14 introns. MAO-A has two messenger RNA (mRNA) transcripts of 2.1 and 5.0 kb in length. MAO-B has a 3-kb

mRNA single transcript ([Cesura and Pletscher 1992](#)). A rare inherited disorder, Norrie's disease, is characterized by deletion of both genes; patients with this disorder have very severe mental retardation and blindness. Another rare inherited disorder is Brunner syndrome, caused by a mutation in the MAO-A gene. It is characterized by impulsive aggressiveness and mild mental retardation ([Brunner et al. 1993](#)).

The subunit composition of MAO is unknown. The enzyme is primarily found in the outer mitochondrial membrane; flavin adenine dinucleotide is a cofactor for both MAO-A and MAO-B.

Because the cofactor domain is the same for both of the MAO isoenzymes, the structural differences responsible for substrate specificity are believed to lie in regions of the protein that bind to the hydrophobic moiety of the substrate. Although DA is considered to be a mixed substrate for both MAO-A and MAO-B, the breakdown of DA in the striatal regions of the brain is preferentially by MAO-B. In other regions, MAO-A may be more important. There may be regional differences as to which isoenzyme is responsible for the metabolism of other biogenic amines that are substrates for both forms of MAO ([Cesura and Pletscher 1992](#)).

## Enzyme Kinetics

The enzyme kinetics of MAO-A have not been well studied. The enzyme kinetics for MAO-B, for which more information is available, depend on the nature of the substrate. Some substrates (e.g., tyramine) go through ping-pong mechanisms characterized by oxidation of the amine to the imine form, which is subsequently released from the reduced enzyme before reoxidation occurs. Other substrates (e.g.,

benzylamine) involve formation of a tertiary complex with the enzyme and oxygen ([Husain et al. 1982](#); [Pearce and Roth 1985](#); [Ramsay and Singer 1991](#)).

## Positron Emission Tomographic Studies of MAO-A in Psychiatric Disorders

[<sup>11</sup>C]Harmane is a selective reversible positron emission tomography (PET) radiotracer with high brain uptake that binds with high affinity to MAO-A. A study using this tracer reported highly significant elevations in brain MAO-A binding during episodes of major depressive disorder that persisted even after selective serotonin reuptake inhibitor (SSRI) treatment ([Meyer et al. 2009](#)). Interestingly, subjects with higher MAO-A levels had a higher rate of major depressive episode recurrence ([Meyer et al. 2009](#)).

---

## Mechanism of Action

---

The target function of MAOIs is regulation of the monoamine content within the nervous system. Because MAO is bound to the outer surface of the plasma membrane of the mitochondria, in neurons MAO is unable to deaminate amines that are present inside stored vesicles and can metabolize only amines that are present in the cytoplasm. As a result, MAO maintains a low cytoplasmic concentration of amines within the cells. Inhibition of neuronal MAO produces an increase in the amine content in the cytoplasm. Initially, it was believed that the therapeutic action of MAOIs was a

result of this amine accumulation (Finberg and Youdim 1984; Murphy et al. 1984, 1987). More recently, it has been suggested that secondary adaptive mechanisms may be important for the antidepressant action of these agents.

After several weeks of treatment, MAOIs produce effects such as a reduction in the number of  $\beta$ -adrenoceptors,  $\alpha_1$ - and  $\alpha_2$ -adrenoreceptors, and serotonin type 1 (5-HT<sub>1</sub>) and serotonin type 2 (5-HT<sub>2</sub>) receptors. These changes are similar to those produced by the chronic use of tricyclic antidepressants (TCAs) and other antidepressant treatment (DaPrada et al. 1984, 1989).

MAOIs can be subdivided on the basis of not only the particular type of enzyme inhibition but also the type of inhibition they produce (reversible or irreversible). The reversible MAOIs are basically chemically inert substrate analogs. MAOIs are recognized as substrates by the enzyme and are converted into intermediates by the normal mechanism. These converted compounds react to the inactive site of the enzyme and form a stable bound enzyme. This effect occurs gradually, and there is usually a correlation between the plasma concentration of the reversible inhibitors and pharmacological action.

---

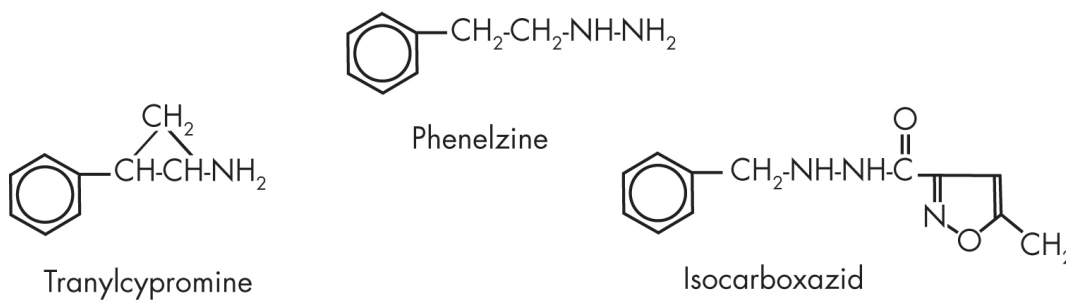
## Pharmacological Profile

---

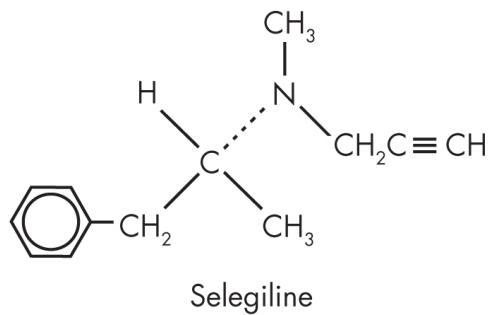
The classic MAOIs inhibit both forms of the enzyme and are divided into two main subtypes: hydrazine and nonhydrazine derivatives (Figure 8-1). The hydrazine derivatives, two of which are currently available (phenelzine and isocarboxazid), are related to iproniazid. One nonhydrazine derivative, tranylcypromine, is commercially available.



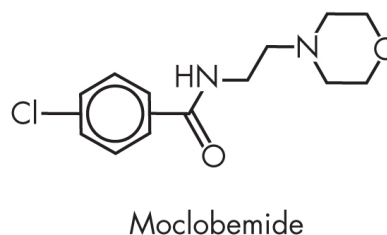
### Irreversible nonselective (classic) MAOIs



### Irreversible selective MAOI



### Reversible MAO-A inhibitor



**FIGURE 8-1.** Chemical structures of monoamine oxidase inhibitors (MAOIs).

Among the selective MAOIs, clorgyline (which was never marketed in the United States) is an example of an irreversible inhibitor of MAO-A, whereas selegiline is an irreversible inhibitor of MAO-B. Moclobemide is the only reversible inhibitor of MAO-A on the market (available in the United Kingdom and Australia, but not in the United States).

Three classic MAOIs (i.e., phenelzine, isocarboxazid, and tranylcpromine) are of clinical interest. Clinicians must recognize that these drugs not only inhibit MAO but also exert other actions that may be clinically relevant. Thus, these compounds can block MAO uptake—tranylcpromine more than isocarboxazid or phenelzine. In addition, because

tranylcypromine is structurally similar to amphetamine, it is believed to exert stimulant-like actions in the brain. Many issues are common to all three of these MAOIs.

---

## Irreversible MAOIs

---

### Indications and Efficacy

As discussed in the following subsections, irreversible MAOIs have been found to be effective in treating a variety of psychiatric disorders ([Table 8-2](#)).

---

**TABLE 8-2. Indications for use of irreversible monoamine oxidase inhibitors (MAOIs)**

---

Definitely effective	Other possible uses
Atypical depression	Obsessive-compulsive disorder
Major depressive disorder	Narcolepsy
Dysthymia	Headache
Melancholia	Chronic pain syndrome
Panic disorder	Generalized anxiety disorder
Posttraumatic stress disorder	Premenstrual dysphoria
Bulimia nervosa	
Atypical facial pain	

---

<sup>a</sup>Selegiline is the only MAOI that is useful in the treatment of Parkinson’s disease.

## **Definitely effective**

## **Other possible uses**

Anergic depression

Treatment-resistant  
depression

Parkinson's disease<sup>a</sup>

<sup>a</sup>Selegiline is the only MAOI that is useful in the treatment of Parkinson's disease.

## **Major Depressive Disorder and Atypical Depression**

Many studies have examined the efficacy of the irreversible MAOIs in the treatment of different types of depression. MAOIs have been effective in the treatment of major depressive disorder and atypical depression (defined as depression with anxiety or chronic pain, reversed vegetative symptoms, and rejection sensitivity [[Quitkin et al. 1990](#)]) ([Davidson et al. 1987a](#); [Himmelhoch et al. 1982, 1991](#); [Johnstone 1975](#); [Johnstone and Marsh 1973](#); [McGrath et al. 1986](#); [Paykel et al. 1982](#); [Quitkin et al. 1979, 1990, 1991](#); [Rowan et al. 1981](#); [Thase et al. 1992](#); [Vallejo et al. 1987](#); [White et al. 1984](#); [Zisook et al. 1985](#)). Although early studies of relatively low-dosage regimens suggested that the efficacy of MAOIs was lower than that of TCAs, more recent studies have documented that their efficacy is comparable.

[Quitkin et al. \(1979, 1991\)](#) reviewed both phenelzine and tranylcypromine studies in patients with either atypical depression or melancholic depression. The authors reported that phenelzine appeared to be effective for the treatment of atypical depression.

Relatively few studies have investigated MAOIs in patients with endogenous depression (i.e., depression without known precipitating factors). From the limited number of patient

studies, it is difficult to conclude that phenelzine is effective in the treatment of these patients. In addition, very few well-controlled studies have compared tranylcypromine with placebo. Three of the four studies that compared tranylcypromine with placebo showed that tranylcypromine was more effective ([Himmelhoch et al. 1982](#); [Moises and Beckmann 1981](#); [White et al. 1984](#)). In one study, a nonsignificant trend was found favoring tranylcypromine ([Nolen 1989](#)). Studies have also documented the efficacy of tranylcypromine in treating anergic depression and, at high doses, treatment-resistant depression ([Himmelhoch et al. 1982, 1991](#); [Thase et al. 1992](#); [White et al. 1984](#)). In the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, patients who had failed to respond to at least three treatment options were randomly assigned to tranylcypromine or a combination of venlafaxine and mirtazapine. Remission rates were modest for both the tranylcypromine group and the extended-release venlafaxine plus mirtazapine group, and the rates were not statistically different between groups ([McGrath et al. 2006](#)).

The heterogeneity of acetylation rate may account for some of the variance in response to phenelzine ([Johnstone 1975](#); [Johnstone and Marsh 1973](#); [Paykel et al. 1982](#); [Rowan et al. 1981](#)). One-half of the patients in a given population are often slow acetylators. An initial study by [Johnstone and Marsh \(1973\)](#) suggested that slow acetylators improve more with phenelzine than do fast acetylators. Other groups have been unable to confirm the relation between acetylation, acetylator type, and response to MAOIs.

Early studies suggested that irreversible MAOIs are particularly effective in patients who have atypical depression. The concept of atypical depression remains controversial and has not been completely validated. In

general, patients with atypical depression have an earlier age at onset than do patients with melancholic depression, and the prevalence of dysthymia, alcohol abuse, sociopathy, and atypical depression is increased in the relatives of patients with atypical depression. The best differentiating criterion appears to be that phenelzine and other irreversible MAOIs are more effective than TCAs in treating these patients ([Cesura and Pletscher 1992](#); [Quitkin et al. 1990](#); [Zisook et al. 1985](#)). A meta-review noted evidence that MAOIs are superior to TCAs, but not SSRIs, in treating atypical depression ([Cipriani et al. 2007](#)).

Some studies have also suggested that MAOIs are effective in treating major depressive disorder and melancholic depression ([Davidson et al. 1987a](#); [McGrath et al. 1986](#); [Vallejo et al. 1987](#)). In a Cochrane review, [Lima and Moncrieff \(2000\)](#) noted that MAOIs were comparable in efficacy to other classes of antidepressants in treating dysthymia.

## **Panic Disorder**

Both single- and double-blind studies have demonstrated the efficacy of phenelzine and iproniazid in treating panic disorder ([Lydiard et al. 1989](#); [Quitkin et al. 1990](#); [Tyrer et al. 1973](#)). About 50%–60% of patients with panic disorder respond to irreversible MAOIs. In the early stages of treatment, patients may have a worsening of symptoms. This is reduced in clinical practice by combining the MAOI with a benzodiazepine for the initial phase of the study. It has been suggested that in addition to having an antipanic effect, phenelzine has an antiphobic action ([Kelly et al. 1971](#)). The time course of effect and the dose used are similar to those for major depressive disorder.

## **Social Phobia**

[Liebowitz et al. \(1992\)](#) reported that phenelzine is effective in treating social phobia. In an open-label study, [Versiani et al. \(1988\)](#) suggested that tranylcypromine is effective. [Versiani et al. \(1992\)](#) also demonstrated the efficacy of the reversible MAOI moclobemide in a double-blind study. About 50% of patients respond to MAOIs, and the onset of response is gradual (usually about 2–3 weeks) ([Liebowitz et al. 1992](#)).

A Cochrane review of pharmacotherapy for social phobia noted that whereas classic irreversible MAOIs were comparable in efficacy to SSRIs, reversible MAOIs were less efficacious ([Stein et al. 2004](#)).

## **Obsessive-Compulsive Disorder**

Although initial case reports suggested that irreversible MAOIs may be effective in treating obsessive-compulsive disorder ([Jenike 1981](#)), no double-blind studies conducted have indicated efficacy ([Jenike et al. 1997](#)).

## **Posttraumatic Stress Disorder**

The classic MAOI phenelzine has been proven effective for the treatment of posttraumatic stress disorder (PTSD) in single-blind trials ([Davidson et al. 1987b](#)) and a double-blind crossover trial ([Kosten et al. 1991](#)).

## **Generalized Anxiety Disorder**

MAOIs are not usually used to treat generalized anxiety disorder because the risk-benefit ratio favors the use of SSRIs, azapirones, or benzodiazepines. When they are used, MAOIs are used primarily for treating treatment-resistant generalized anxiety disorder.

## **Bulimia Nervosa**

Both phenelzine and isocarboxazid have been shown to be effective in treating some symptoms of bulimia nervosa ([Kennedy et al. 1988](#); [McElroy et al. 1989](#); [Walsh et al. 1985, 1987](#)).

## **Premenstrual Dysphoria**

Preliminary studies and clinical experience suggest that MAOIs may be effective in the treatment of premenstrual dysphoria ([Glick et al. 1991](#)).

## **Chronic Pain**

MAOIs are believed to be effective in the treatment of atypical facial pain and other chronic pain syndromes. However, only limited data on these conditions are available.

## **Neurological Diseases**

The classic MAOIs have not been found to be effective for treating neurological disorders such as Parkinson's disease and Alzheimer's dementia. However, the MAO-B inhibitor selegiline has been shown to be effective in slowing the progression of Parkinson's disease ([Cesura and Pletscher 1992](#)), although the mechanism underlying this effect is unknown.

# **Side Effects and Toxicology**

The side effects of irreversible MAOIs are generally not more severe or frequent than those of other antidepressants ([Zisook 1984](#)). The most frequent side effects include dizziness, headache, dry mouth, insomnia, constipation, blurred vision, nausea, peripheral edema, forgetfulness, fainting spells, trauma, urinary hesitancy, weakness, and myoclonic jerks. Loss of weight and appetite may occur with

isocarboxazid use ([Davidson and Turnbull 1982](#)). Hepatotoxicity is rare with the currently available irreversible MAOIs, unlike with iproniazid. However, liver enzymes, such as aspartate transaminase and alanine transaminase, are elevated in 3%–5% of patients. Liver function tests must be done when patients have symptoms such as malaise, jaundice, and excessive fatigue.

Some side effects of irreversible MAOIs first emerge during maintenance treatment ([Evans et al. 1982](#)). These side effects include weight gain (which occurs in almost one-half of patients), edema, muscle cramps, carbohydrate craving, sexual dysfunction (usually anorgasmia), pyridoxine deficiency ([Goodheart et al. 1991](#)), hypoglycemia, hypomania, urinary retention, and disorientation. Peripheral neuropathy ([Goodheart et al. 1991](#)) and speech blockage ([Goldstein and Goldberg 1986](#)) are rare side effects of irreversible MAOIs. Weight gain is more of a problem with hydrazine compounds, such as phenelzine, than with tranylcypromine. Therefore, weight gain that is caused by hydrazine derivatives is an indication to switch to tranylcypromine. Edema is also more common with phenelzine than with tranylcypromine.

The management of some of these side effects can be difficult. Orthostatic hypotension is common with irreversible MAOIs. Addition of salt and salt-retaining steroids such as fludrocortisone (9- $\alpha$ -fluorohydrocortisone) is sometimes effective in treating orthostatic hypotension. Elastic support stockings are also helpful. Small amounts of coffee or tea taken during the day also keep the blood pressure elevated. The dose of fluorohydrocortisone should be adjusted carefully, because in elderly patients it could provoke cardiac failure resulting from fluid retention.



Sexual dysfunction that occurs with irreversible MAOIs is also difficult to treat. Common problems include anorgasmia, decreased libido, impotence, and delayed ejaculation ([Harrison et al. 1985](#); [Jacobson 1987](#)). Cyproheptadine is sometimes effective in treating sexual dysfunction such as anorgasmia. Bethanechol may also be effective in some patients.

Insomnia occasionally occurs as an intermediate or late side effect of irreversible MAOIs. Changing the time of administration does not seem to help much, although dosage reduction may be helpful. Adding trazodone at bedtime is effective, but this should be done with caution. Myoclonic jerks, peripheral neuropathy, and paresthesias, when present, are also difficult to treat. When a patient has paresthesia, the clinician should evaluate for peripheral neuropathy and pyridoxine deficiency. In general, patients taking irreversible MAOIs should also receive concomitant pyridoxine therapy. When myoclonic jerks occur, patients can be treated with cyproheptadine.

Irreversible MAOIs also have the potential to suppress anginal pain; therefore, coronary artery disease could be overlooked or underestimated.

Patients with hyperthyroidism are more sensitive to irreversible MAOIs because of their overall sensitivity to pressor amines. Irreversible MAOIs can also worsen hypoglycemia in patients taking hypoglycemic agents such as insulin.

## Dietary Interactions

After the introduction of irreversible MAOIs, several reports of severe headaches in patients who were taking these compounds were published ("[Cheese and Tranylcypromine](#)")

1970; Cronin 1965; Hedberg et al. 1966; Simpson and Gratz 1992). These headaches were caused by a drug-food interaction. The risk of such an interaction is highest for tranylcypromine and lower for phenelzine, provided that the dose of the latter remains low. However, the clinician must keep in mind that this interaction can occur even at low doses with any of the classic MAOIs. The interaction of irreversible MAOIs with food has been attributed to increased tyramine levels. Tyramine, which has a pressor action, is present in a number of foodstuffs. It is normally broken down by the MAO enzymes and has both direct and indirect sympathomimetic actions. It has been suggested that the potentiation of tyramine by an MAOI may be secondary to increased release of NE rather than to the MAOI. Adrenaline would increase the indirect sympathetic activity of tyramine. The spontaneous occurrence of hypertensive crises in a few patients lends support to this hypothesis (O'Brien et al. 1992; Zajecka and Fawcett 1991).

The tyramine effect of food is potentiated by MAOIs 10- to 20-fold. A mild tyramine interaction occurs with about 6 mg of tyramine; 10 mg can produce a moderate episode, and 25 mg can produce a severe episode that is characterized by hypertension, occipital headache, palpitations, nausea, vomiting, apprehension, occasional chills, sweating, and restlessness. On examination, neck stiffness, pallor, mild pyrexia, dilated pupils, and motor agitation may be seen. The reaction usually develops within 20-60 minutes after ingestion of food. Occasionally, the reaction can be very severe and may lead to alteration of consciousness, hyperpyrexia, cerebral hemorrhage, and death. Death is exceedingly rare (Cooper 1989).

The classic treatment of the hypertensive reaction is phentolamine (5 mg) administered intravenously (Youdim et

al. 1987; Zisook 1984). Nifedipine, a calcium channel blocker, has been shown to be effective (Stumpf 1988). Nifedipine has an onset of action of about 5 minutes, and it lasts approximately 3–5 hours; in fact, some clinicians have suggested that patients should carry nifedipine with them for immediate use in the event of a hypertensive crisis.

Because of the drug interaction of the classic MAOIs with food, clinicians usually make several dietary recommendations (Table 8-3). These recommendations are quite varied.

---

**TABLE 8-3. Food restrictions for monoamine oxidase inhibitors (MAOIs)**

---

<b>To be avoided</b>	<b>To be used in moderation</b>
Cheese (except cream cheese and cottage cheese)	Coffee
Overripe (aged) fruit (e.g., overripe bananas or avocados)	Chocolate
Fava beans	Colas
Sausage, salami	Tea
Beef and chicken livers	Soy sauce
Monosodium glutamate	Beer, other wines
Sauerkraut	
Pickled fish	
Brewer's yeast	
Fermented products	
Sherry, liqueurs	
Red wine	

---

MAOI diets recommend restriction of cheese (except cream cheese and cottage cheese), red wine, sherry, liqueurs, pickled fish, overripe (aged) fruit, brewer's yeast, fava beans, beef and chicken liver, and fermented products. Some diets recommend restriction of all alcoholic beverages, coffee, chocolate, colas, tea, yogurt, soy sauce, avocados, and bananas. Notably, many of the restricted foods—for example, avocados and bananas—rarely cause hypertensive crisis. For example, an interaction may occur only if overripe fruit is eaten or, in the case of bananas, if the skin is eaten (which is an uncommon practice in the United States). Similarly, unless a person ingests large amounts of caffeine, the interaction is usually not clinically significant. Although there is greater risk of noncompliance with highly restrictive diets, the clinician, when discussing restrictions and cautions with the patient, should emphasize the need to adhere to dietary restrictions and the potential risks that arise by breaking the diet ([Gardner et al. 1996](#)).

In evaluating patients who may have had a drug-food reaction, the clinician should evaluate the hypertensive reaction and differentiate it from histamine headache, which also can occur with an MAOI. Histamine headaches are usually accompanied by hypotension, colic, loose stools, salivation, and lacrimation ([Cooper 1967](#)). The clinician should provide both oral and printed instructions about food and drug interactions to patients who are taking classic MAOIs.

## Drug-Drug Interactions

Drug-drug interactions are also extremely important concerns in patients taking irreversible MAOIs. The extensive inhibition of MAO enzymes by MAOIs raises the

potential for a number of interactions with other drugs (Table 8-4). Of particular importance, many over-the-counter medications can interact with MAOIs. These medications include cough syrups containing sympathomimetic agents, which in the presence of an MAOI can precipitate a hypertensive crisis.

**TABLE 8-4. Drug interactions with monoamine oxidase inhibitors (MAOIs)**

<b>Drug</b>	<b>Interaction</b>	<b>Comment</b>
Other MAOIs (e.g., furazolidone, pargyline, procarbazine)	Potential of side effects; convulsions possible	Allow at least 1 week before changing to another MAOI
Tricyclic antidepressants (TCAs) (e.g., maprotiline, bupropion)	Possibility of severe side effects, such as hypertension and convulsions; serotonin syndrome	Allow at least 2 weeks before changing to an MAOI; combinations have been used occasionally for refractory depression
Carbamazepine	Low possibility of interaction; similar to TCAs	Same as for TCAs

<b>Drug</b>	<b>Interaction</b>	<b>Comment</b>
Cyclobenzaprine	Low possibility of interaction; similar to TCAs	Same as for TCAs
Selective serotonin reuptake inhibitors (SSRIs)	Serotonin syndrome	Avoid combinations; allow at least 2 weeks before changing to an MAOI and 5 weeks if switching from fluoxetine to an MAOI
Stimulants (e.g., methylphenidate, dextroamphetamine)	Potential for increased blood pressure (hypertension)	Avoid combination
Buspirone	Potential for increased blood pressure (hypertension)	Avoid use; if used, monitor blood pressure

<b>Drug</b>	<b>Interaction</b>	<b>Comment</b>
Meperidine	Possibility of severe, potentially fatal interaction (see text); serotonin syndrome	Avoid combination
Dextromethorphan	Reports of brief psychosis	Avoid high doses
Direct sympathomimetics (e.g., L-dopa)	Increased blood pressure	Avoid use if possible; if they need to be used, use with caution
Indirect sympathomimetics	Hypertensive crisis possible	Avoid use
Oral hypoglycemics (e.g., insulin)	Worsening of hypoglycemia possible	Monitor blood sugar levels and adjust medications
Fenfluramine	Serotonin syndrome possible	Avoid use
L-Tryptophan	Serotonin syndrome possible	Avoid use

Another area of caution is the use of MAOIs in patients who need surgery. Potential interactions include those with narcotic drugs, especially meperidine. Meperidine

administered with MAOIs can produce a syndrome characterized by coma, hyperpyrexia, and hypertension. This syndrome has been reported primarily with phenelzine; however, it has also been reported with tranylcypromine ([Mendelson 1979](#); [Stack et al. 1988](#)). [Stack et al. \(1988\)](#) noted that this syndrome is most likely to occur with meperidine and that it may be related to that drug's serotonergic properties (similar to serotonin syndrome). Similar reactions have not been reported to any significant extent with other narcotic analgesics such as morphine and codeine. In fact, many patients probably receive these medications without problems. Only a small fraction of patients may have this interaction, and it could reflect a serotonin toxicity effect. In general, current opinion favors the use of morphine when intra- or postoperative narcotics are needed in patients taking MAOIs.

The issue of whether directly acting sympathomimetic amines interact with MAOIs is more controversial. Intravenous administration of sympathomimetic amines to patients receiving MAOIs does not provoke hypertension. When a bolus infusion of any of various catecholamines is given to healthy volunteer subjects who have been taking phenelzine or tranylcypromine for 1 week, a potentiation of the pressor effect of phenylephrine occurs, but no clinically significant potentiation of cardiovascular effects of NE, epinephrine, or isoproterenol occurs ([Wells 1989](#)).

In general, direct sympathomimetic amine-MAOI interactions do not appear to produce significant cardiovascular problems. However, there is a low incidence of hypertensive episodes in the presence of indirect sympathomimetics. Ideally, these compounds should not be used in patients who are receiving MAOIs. A direct-acting compound is preferable to an indirect-acting compound.



Caution should be exercised when using MAOIs in patients with pheochromocytoma or with cardiovascular, cerebrovascular, or hepatic disease. Because phenelzine tablets contain gluten, they should not be given to patients with celiac disease.

Each patient should be given a card indicating that he or she is taking an MAOI and instructed to carry the card at all times. A medical bracelet indicating that the wearer takes an MAOI is also a good idea.

---

## Specific Monoamine Oxidase Inhibitors

---

### Phenelzine

Phenelzine, a hydrazine derivative, is a potent irreversible MAOI and is the best studied of the MAOIs.

#### Pharmacokinetics

Phenelzine is a substrate as well as an inhibitor of MAO. Major identified metabolites of phenelzine include phenylacetic acid and *p*-hydroxyphenylacetic acid. Phenelzine undergoes acetylation, and therefore drug levels are lower in fast acetylators than in slow acetylators. However, because phenelzine is an irreversible inhibitor, plasma concentrations are not relevant. The antidepressant effect, the degree of inhibition of MAO, and the amount of free phenelzine excreted in the urine are all significantly greater in slow acetylators than in fast acetylators ([Baker et al. 1999](#)).

## **Indications**

Phenelzine is useful in the treatment of major depressive disorder, atypical depression, panic disorder, social phobia, and atypical facial pain (see section “Indications and Efficacy” earlier in this chapter).

## **Side Effects**

The primary side effects of phenelzine are similar to those of other MAOIs. Hepatitis secondary to phenelzine may occur in rare cases (<1 in 30,000). The most difficult side effect, often leading to discontinuation, is postural hypotension.

## **Contraindications**

The contraindications to phenelzine include known sensitivity to the drug, pheochromocytoma, congestive heart failure, and history of liver disease. (In addition, see sections “Dietary Interactions” and “Drug-Drug Interactions” earlier in this chapter.)

# **Isocarboxazid**

Isocarboxazid is an irreversible MAOI of the hydrazine type.

## **Pharmacokinetics**

Isocarboxazid is rapidly absorbed from the gastrointestinal tract and is metabolized in the liver. It is primarily excreted as hippuric acid. Its half-life is of little interest because it is an irreversible MAOI. Chemically, isocarboxazid is 5-methyl-3-isoxazolecarboxylic acid 2-benzylhydrazide. Isocarboxazid is a colorless crystalline substance with very little taste.

## **Indications**

Isocarboxazid is the least studied of the MAOIs. It is indicated for the treatment of depression.

### **Side Effects**

The side effects of isocarboxazid are similar to those of phenelzine, described earlier in this section. Postural hypotension is the most common problem.

### **Contraindications**

The contraindications to isocarboxazid are similar to those of phenelzine, described earlier in this section.

## **Tranylcypromine**

Tranylcypromine, a nonhydrazine irreversible MAOI, increases the concentration of NE, epinephrine, and 5-HT in the CNS. Tranylcypromine has a mild stimulant effect.

### **Pharmacokinetics**

Limited data exist on the pharmacokinetics of tranylcypromine. The drug is excreted within 24 hours. The dynamic effect lasts for up to 5 days after withdrawal. There is considerable debate about whether tranylcypromine is metabolized to amphetamine; most studies in the literature indicate that this does not occur.

### **Indications**

Tranylcypromine is indicated for the treatment of major depressive disorder without melancholia.

### **Side Effects**

The side effects of tranylcypromine are similar to those of other MAOIs. In addition, problems with physical dependence on tranylcypromine have been reported. Thus, withdrawal symptoms, such as anxiety, restlessness, depression, and headache, may occur. Syndrome of inappropriate antidiuretic hormone (SIADH) has been reported with tranylcypromine. Rare cases of toxic hepatitis have also been reported. Tranylcypromine can lead to increased agitation, insomnia, and restlessness, compared with phenelzine.

## Contraindications

The contraindications to tranylcypromine are the same as those for phenelzine, described earlier in this section. In addition, in view of the greater potential for hypertensive episodes, tranylcypromine should be used with particular caution in patients with cerebrovascular or cardiovascular disease.

## Moclobemide

Moclobemide, a reversible inhibitor of MAO-A enzyme ([Amrein et al. 1989](#)), has a higher potency in vivo than in vitro. Therefore, it has been suggested that moclobemide is a prodrug and that it is metabolized to a form with higher affinity for MAO-A than the parent compound. After single- or repeated-dose administration of moclobemide, the recovery of MAO-A activity is much quicker than that seen with other MAOIs. One of the metabolites of moclobemide does inhibit MAO-B; however, this action is minimally significant in humans. When administered to rats, moclobemide increases the concentration of 5-HT, NE, epinephrine, and DA in rat brain ([Haefely et al. 1992](#)). These effects are short lasting,

and they parallel the time course of MAO-A inhibition. In addition, unlike with irreversible inhibitors, repeated administration does not increase the inhibition.

Moclobemide only partially potentiates the blood pressor effect of oral tyramine ([DaPrada et al. 1989](#)). This is because it is a reversible inhibitor with a low affinity for the MAO isoenzymes and is easily displaced by the pressor amines ingested in food. On the basis of these studies, moclobemide is thought to be safer than irreversible MAOIs.

## Pharmacokinetics

After oral administration of moclobemide, peak plasma concentrations are reached within 1 hour. The drug is about 50% bound to plasma proteins and is extensively metabolized; only 1% of the compound is excreted (unchanged) in the urine. The half-life of the compound is approximately 12 hours. Moclobemide is extensively metabolized; 95% of the administered dose is excreted in the urine. The metabolites are pharmacologically inactive. The presence of food reduces the rate (but not the extent) of moclobemide absorption.

## Indications

Moclobemide has been studied in all types of depressive disorders ([Gabelic and Kuhn 1990](#); [Larsen et al. 1991](#); [Rossel and Moll 1990](#)). Controlled trials have found that it is superior to placebo. In addition, moclobemide has been found to be as effective as imipramine, desipramine, clomipramine, and amitriptyline in the treatment of depression. The dosage required is 300–600 mg/day.

Unlike the classic MAOIs, moclobemide has been found to be effective in treating both endogenous and nonendogenous depression. In addition, in combination with antipsychotics,

the drug seems to be effective in treating psychotic depression ([Amrein et al. 1989](#)). Moclobemide has also been effective in treating bipolar endogenous depression.

[Versiani et al. \(1992\)](#) compared phenelzine, moclobemide, and placebo and reported that both phenelzine and moclobemide were superior to placebo in treating patients with social phobia. Given the efficacy of classic MAOIs in the treatment of other psychiatric disorders, such as bulimia, panic disorder, and PTSD, it is likely that patients with such disorders would also respond to a reversible MAOI. Additional trials of moclobemide are required to confirm its utility in other psychiatric disorders.

## Side Effects

Nausea was the only side effect noted to be greater in patients taking moclobemide than in patients taking placebo. Thus, the profile of moclobemide seems to be ideal in that it causes few or no major side effects. Case reports have shown no toxicity after overdoses of up to 20 g ([Amrein et al. 1989](#)).

## Dietary Interactions

Intravenous tyramine pressor tests indicate that a single dose of moclobemide increases tyramine sensitivity ([Cusson et al. 1991](#)). However, this increase is marginal, compared with the increase associated with other MAOIs. Under most conditions, there appears to be limited drug-food interaction. However, to minimize even mild tyramine pressor effects, the recommended action is to administer moclobemide after a meal rather than before it. In a study in which tyramine was administered in doses up to 100 mg, inpatients pretreated with moclobemide had no significant changes in blood pressure. The drug also has minimal effect on cognitive performance and no effect on body weight or

hematological parameters ([Wesnes et al. 1989](#); [Youdim et al. 1987](#)).

## Drug-Drug Interactions

Several studies have examined potential drug-drug interactions with moclobemide ([Amrein et al. 1992](#)). No drug interaction with lithium has been reported. No interactions with benzodiazepines or antipsychotics have been reported ([Amrein et al. 1992](#)). Parallel data suggest that moclobemide can potentiate the effects of meperidine; therefore, the narcotic-MAOI interaction may occur. Combination with other antidepressants (including SSRIs) is best avoided in view of potential serotonin toxicity. Until proven otherwise, it would be prudent to avoid the combination of moclobemide with opiates like meperidine. A pharmacokinetic interaction has been observed with cimetidine that requires the reduction of the moclobemide dose because cimetidine reduces the clearance of moclobemide.

## Selegiline Hydrochloride

Selegiline hydrochloride is an irreversible MAO-B inhibitor ([Cesura and Pletscher 1992](#)). Its primary use is in the treatment of Parkinson's disease, as an adjunct to L-dopa and carbidopa. The average dosage for Parkinson's disease is 5–10 mg/day. The exact mechanism of action of MAO-B in Parkinson's disease is unknown ([Gerlach et al. 1996](#); [Hagan et al. 1997](#); [Lyytinen et al. 1997](#)).

## Pharmacokinetics

Selegiline is metabolized to levoamphetamine, methamphetamine, and *N*-desmethylselegiline. Selegiline hydrochloride undergoes significant first-pass metabolism

following oral administration. Transdermal delivery avoids the first-pass effect and provides greater levels of unchanged drug and reduced levels of metabolites compared with the oral regimen. The time to reach the peak is less than 1 hour. The elimination half-life of selegiline is about 1.5 hours. There is at least a threefold increase in the area under the curve (AUC) of selegiline with food ([Mahmood 1997](#)).

## **Indications and Efficacy**

The efficacy of selegiline in treating depression has not been well studied. [Quitkin et al. \(1984\)](#) showed that selegiline was superior to placebo administered to patients with depression in a 6-week double-blind study. Dosages of more than 10–20 mg/day were needed. The dosage required for treating depression may be much higher than that required to treat Parkinson's disease. At higher dosages, dietary interactions could occur. Early studies also found that selegiline is of modest benefit in patients with Alzheimer's disease ([Lawlor et al. 1997](#)).

## **Side Effects**

The few side effects that have been noted with selegiline include nausea, dizziness, and light-headedness. When the drug is abruptly discontinued, nausea, hallucinations, and confusion have been reported.

## **Dietary Interactions**

Because MAO-B is not involved in the intestinal tyramine interaction, dietary interaction with selegiline (at low dosages of 5–10 mg/day) would probably be minimal. An interaction between selegiline and narcotics has been reported and should be kept in mind.



## **Drug-Drug Interactions**

Selegiline's potential drug interactions are similar to those of other MAOIs, and there is a risk for serotonin syndrome if selegiline is combined with other drugs (including SSRIs) that can increase serotonin.

## **Selegiline Transdermal System**

The selegiline transdermal system (STS) was developed to overcome limitations of orally administered MAOIs, particularly dietary tyramine restrictions. STS does not overcome drug-drug interactions. It bypasses the gut, thereby reducing drug-food interactions. The pharmacokinetic and pharmacodynamic properties promote the inhibition of MAO-A and MAO-B in the CNS while avoiding significant inhibition of intestinal and liver MAO-A enzymes. Three different strengths of STS patch are currently marketed: 20 mg/20 cm<sup>2</sup>, 30 mg/30 cm<sup>2</sup>, and 40 mg/40 cm<sup>2</sup>. The three patch sizes deliver 24-hour doses of selegiline averaging 6 mg, 9 mg, and 12 mg, respectively. Use of the 6-mg patch does not call for dietary modification. A restricted "MAOI diet" is advised for the higher-dosage 9-mg and 12-mg patches to avoid any risk of hypertensive crisis. Patients are strongly advised to follow these restrictions.

## **Pharmacokinetics**

Following dermal application of the STS patch, 25%–30% of the selegiline content on average is delivered systemically over 24 hours. Consequently, the degree of drug absorption is one-third higher than the average amounts of 6–12 mg/24 hours. In comparison with oral dosing, transdermal dosing

results in substantially higher exposure to selegiline and lower exposure to metabolites.

## Indications and Efficacy

The efficacy of STS as a treatment for major depressive disorder was established in two placebo-controlled studies of 6 and 8 weeks' duration in adult outpatients with major depressive disorder. In both studies, patients were randomly assigned to double-blind treatment with drug patch or placebo. The 6-week trial showed that 6 mg/24 hours was significantly more effective than placebo, as assessed by scores on the 17-item Hamilton Rating Scale for Depression (Ham-D) ([Amsterdam 2003](#)). In an 8-week dosage titration trial, depressed patients receiving the drug patch (starting dosage was 6 mg/24 hours, with possible increases to 9 mg/24 hours or 12 mg/24 hours based on clinical response) showed significant improvement compared with those receiving placebo on the primary outcome measure, the 28-item Ham-D total score ([Feiger et al. 2006](#)). In another trial, 322 patients meeting DSM-IV-TR ([American Psychiatric Association 2000](#)) criteria for major depressive disorder who had responded during an initial 10-week open-label treatment phase were randomly assigned either to continuation at the same dose or to placebo under double-blind conditions for observation of relapse. In this double-blind phase, patients receiving continued STS experienced a significantly longer time to relapse ([Amsterdam and Bodkin 2006](#)). The efficacy was also studied in a double-blind study of depressed adolescents. There was no significant difference between patients receiving STS and those receiving placebo ([DelBello et al. 2014](#)).

## Side Effects

The main side effects with STS are diarrhea, skin irritation, and insomnia.

## **Drug-Drug Interactions**

Potential drug-drug interactions for STS are the same as for other MAOIs.

---

## **Conclusion**

---

Various MAOIs have been shown to be effective in treating a wide variety of psychiatric disorders, including depression, panic disorder, social phobia, and PTSD. The classic MAOIs are currently used only rarely as first-line medication because of potential dietary interactions and other long-term side effects. The reversible inhibitors of MAO-A enzyme, such as moclobemide, which have fewer side effects and no dietary restrictions compared with classic MAOIs, are unlikely to be introduced in the United States. In fact, the risk-benefit ratio for these compounds is highly favorable compared with other antidepressants. The MAO-B inhibitor selegiline is used to reduce the progression of Parkinson's disease. Its utility in treating other degenerative disorders is currently being assessed. STS reduces dietary interactions when used at low doses and is now approved for the treatment of major depressive disorder. New applications and a wider use of these compounds may be found in the near future.

---

## **References**

---

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Arlington, VA, American Psychiatric Association, 2000
- Amrein R, Allen SR, Guentert TW, et al: The pharmacology of reversible monoamine oxidase inhibitors. *Br J Psychiatry Suppl* (6):66-71, 1989 2695128
- Amrein R, Güntert TW, Dingemanse J, et al: Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* 106 (suppl):S24-S31, 1992 1546135
- Amsterdam JD: A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J Clin Psychiatry* 64(2):208-214, 2003 12633131
- Amsterdam JD, Bodkin JA: Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. *J Clin Psychopharmacol* 26(6):579-586, 2006 17110814
- Baker GB, Urichuk LJ, McKenna KF, et al: Metabolism of monoamine oxidase inhibitors. *Cell Mol Neurobiol* 19(3):411-426, 1999 10319194
- Blackwell B, Marley E, Price J, et al: Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. *Br J Psychiatry* 113(497):349-365, 1967 6034391
- Bloch RG, Dooneief AS, Buchberg AS, et al: The clinical effect of isoniazid and iproniazid in the treatment of pulmonary tuberculosis. *Ann Intern Med* 40(5):881-900, 1954 13159064
- Brunner HG, Nelen M, Breakefield XO, et al: Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* 262(5133): 578-580, 1993 8211186

- Cesura AM, Pletscher A: The new generation of monoamine oxidase inhibitors. *Prog Drug Res* 38:171-297, 1992 1609114
- Cheese and tranylcypromine (letter). *BMJ* 3(5718):354, 1970 5451971
- Cipriani A, Geddes JR, Furukawa TA, et al: Metareview on short-term effectiveness and safety of antidepressants for depression: an evidence-based approach to inform clinical practice. *Can J Psychiatry* 52(9):553-562, 2007 17953159
- Cooper AJ: M.A.O. inhibitors and headache (letter). *BMJ* 4(5576):420, 1967 4964185
- Cooper AJ: Tyramine and irreversible monoamine oxidase inhibitors in clinical practice.. *Br J Psychiatry Suppl* (6):38-45, 1989 2695126
- Crane GE: Iproniazid (Marsilid) phosphate, a therapeutic agent for mental disorders and debilitating diseases. *Psychiatr Res Rep Am Psychiatr Assoc* 8:142-152, 1957 13542682
- Cronin D: Monoamine-oxidase inhibitors and cheese (letter). *BMJ* 2(5469):1065, 1965 5826297
- Cusson JR, Goldenberg E, Laroche P: Effect of a novel monoamine-oxidase inhibitor, moclobemide on the sensitivity to intravenous tyramine and norepinephrine in humans. *J Clin Pharmacol* 31(5):462-467, 1991 2050833
- DaPrada M, Kettler R, Burkard W, et al: Moclobemide, an antidepressant with short-lasting MAO-A inhibition: brain catecholamines/tyramine pressor effects in rats, in *Monoamine Oxidase and Disease*. Edited by Tipton K, Dostert P, Strolin Benedetti M. New York, Academic Press, 1984, pp 137-154
- DaPrada M, Kettler R, Keller HH, et al: Neurochemical profile of moclobemide, a short-acting and reversible inhibitor of monoamine oxidase type A. *J Pharmacol Exp Ther* 248(1):400-414, 1989 2783611
- Davidson J, Turnbull C: Loss of appetite and weight associated with the monoamine oxidase inhibitor

- isocarboxazid. J Clin Psychopharmacol 2(4):263-266, 1982 7119133
- Davidson J, Raft D, Pelton S: An outpatient evaluation of phenelzine and imipramine. J Clin Psychiatry 48(4):143-146, 1987a 3549705
- Davidson J, Walker JI, Kilts C: A pilot study of phenelzine in the treatment of post-traumatic stress disorder. Br J Psychiatry 150:252-255, 1987b 3651684
- DelBello MP, Hochadel TJ, Portland KB, et al: A double-blind, placebo-controlled study of selegiline transdermal system in depressed adolescents. J Child Adolesc Psychopharmacol 24(6):311-317, 2014 24955812
- Evans DL, Davidson J, Raft D: Early and late side effects of phenelzine. J Clin Psychopharmacol 2(3):208-210, 1982 7096609
- Feiger AD, Rickels K, Rynn MA, et al: Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. J Clin Psychiatry 67(9):1354-1361, 2006 17017821
- Finberg JPM, Youdim MBH: Reversible monoamine oxidase inhibitors and the cheese effect, in Monoamine Oxidase and Disease: Prospects for Therapy With Reversible Inhibitors. Edited by Tipton KF, Dostert P, Strolin Benedetti M. New York, Academic Press, 1984, pp 479-485
- Gabelic I, Kuhn B: Moclobemide (Ro 11-1163) versus tranylcypromine in the treatment of endogenous depression (abstract). Acta Psychiatr Scand Suppl 360:63, 1990 2248076
- Gardner DM, Shulman KI, Walker SE, Taylor SA: The making of a user friendly MAOI diet. J Clin Psychiatry 57(3):99-104, 1996 8617704
- Gerlach M, Youdim MB, Riederer P: Pharmacology of selegiline. Neurology 47 (6 suppl 3):S137-S145, 1996 8959982

- Glick R, Harrison W, Endicott J, et al: Treatment of premenstrual dysphoric symptoms in depressed women. *J Am Med Womens Assoc* 46(6):182-185, 1991 1744374
- Goldstein DM, Goldberg RL: Monoamine oxidase inhibitor-induced speech blockage. *J Clin Psychiatry* 47(12):604, 1986 3782047
- Goodheart RS, Dunne JW, Edis RH: Phenelzine associated peripheral neuropathy—clinical and electrophysiologic findings. *Aust NZ J Med* 21(3):339-340, 1991 1659356
- Haefely W, Burkard WP, Cesura AM, et al: Biochemistry and pharmacology of moclobemide, a prototype RIMA. *Psychopharmacology (Berl)* 106 (suppl):S6-S14, 1992 1546143
- Hagan JJ, Middlemiss DN, Sharpe PC, et al: Parkinson's disease: prospects for improved drug therapy. *Trends Pharmacol Sci* 18(5):156-163, 1997 9184476
- Harrison WM, Stewart J, Ehrhardt AA, et al: A controlled study of the effects of antidepressants on sexual function. *Psychopharmacol Bull* 21(1):85-88, 1985 3885294
- Hedberg DL, Gordon MW, Glueck BC Jr: Six cases of hypertensive crisis in patients on tranylcypromine after eating chicken livers. *Am J Psychiatry* 122(8):933-937, 1966 5948152
- Himmelhoch JM, Fuchs CZ, Symons BJ: A double-blind study of tranylcypromine treatment of major anergic depression. *J Nerv Ment Dis* 170(10):628-634, 1982 7050302
- Himmelhoch JM, Thase ME, Mallinger AG, et al: Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry* 148(7):910-916, 1991 2053632
- Husain M, Edmondson DE, Singer TP: Kinetic studies on the catalytic mechanism of liver monoamine oxidase. *Biochemistry* 21(3):595-600, 1982 7066309
- Jacobson JN: Anorgasmia caused by an MAOI (letter). *Am J Psychiatry* 144(4):527, 1987 3565632

- Jenike MA: Rapid response of severe obsessive-compulsive disorder to tranylcypromine. *Am J Psychiatry* 138(9):1249-1250, 1981 7270737
- Jenike MA, Baer L, Minichiello WE, et al: Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. *Am J Psychiatry* 154(9):1261-1264, 1997 9286186
- Johnstone EC: Relationship between acetylator status and response to phenelzine. *Mod Probl Pharmacopsychiatry* 10:30-37, 1975 1101047
- Johnstone EC, Marsh W: The relationship between response to phenelzine and acetylator status in depressed patients. *Proc R Soc Med* 66(9):947-949, 1973 4616245
- Kelly D, Mitchell-Heggs N, Sherman D: Anxiety and the effects of sodium lactate assessed clinically and physiologically. *Br J Psychiatry* 119(549):129-141, 1971 5565900
- Kennedy SH, Piran N, Warsh JJ, et al: A trial of isocarboxazid in the treatment of bulimia nervosa. *J Clin Psychopharmacol* 8(6):391-396, 1988 3069879
- Kline NS: Clinical experience with iproniazid (Marsilid). *J Clin Exp Psychopathol* 19 (2 suppl 1):72-78, discussion 78-79, 1958 13549569
- Kosten TR, Frank JB, Dan E, et al: Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. *J Nerv Ment Dis* 179(6):366-370, 1991 2051152
- Larsen JK, Gjerris A, Holm P, et al: Moclobemide in depression: a randomized, multicentre trial against isocarboxazide and clomipramine emphasizing atypical depression. *Acta Psychiatr Scand* 84(6):564-570, 1991 1792931
- Lawlor BA, Aisen PS, Green C, et al: Selegiline in the treatment of behavioural disturbance in Alzheimer's disease. *Int J Geriatr Psychiatry* 12(3):319-322, 1997 9152715



- Liebowitz MR, Schneier F, Campeas R, et al: Phenelzine vs atenolol in social phobia. A placebo-controlled comparison. *Arch Gen Psychiatry* 49(4):290-300, 1992 1558463
- Lima MS, Moncrieff J: Drugs versus placebo for dysthymia. *Cochrane Database Syst Rev* (4):CD001130, 2000 11034701
- Lydiard RB, Laraia MT, Howell EF, et al: Phenelzine treatment of panic disorder: lack of effect on pyridoxal phosphate levels. *J Clin Psychopharmacol* 9(6):428-431, 1989 2687338
- Lyytinen J, Kaakkola S, Ahtila S, et al: Simultaneous MAO-B and COMT inhibition in L-Dopa-treated patients with Parkinson's disease. *Mov Disord* 12(4):497-505, 1997 9251066
- Mahmood I: Clinical pharmacokinetics and pharmacodynamics of selegiline. An update. *Clin Pharmacokinet* 33(2):91-102, 1997 9260033
- McElroy SL, Keck PE Jr, Pope HG Jr, et al: Pharmacological treatment of kleptomania and bulimia nervosa. *J Clin Psychopharmacol* 9(5):358-360, 1989 2677062
- McGrath PJ, Stewart JW, Harrison W, et al: Phenelzine treatment of melancholia. *J Clin Psychiatry* 47(8):420-422, 1986 3525522
- McGrath PJ, Stewart JW, Fava M, et al: Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR\*D report. *Am J Psychiatry* 163(9):1531-1541, quiz 1666, 2006 16946177
- Mendelson G: Narcotics and monoamine oxidase-inhibitors (letter). *Med J Aust* 1(9):400, 1979 470771
- Meyer JH, Wilson AA, Sagrati S, et al: Brain monoamine oxidase A binding in major depressive disorder: relationship to selective serotonin reuptake inhibitor treatment, recovery, and recurrence. *Arch Gen Psychiatry* 66(12):1304-1312, 2009 19996035

- Moises HW, Beckmann H: Antidepressant efficacy of tranylcypromine isomers: a controlled study. *J Neural Transm* 50(2-4):185-192, 1981 7017068
- Nolen WA: Tranylcypromine in depression resistant to cyclic antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry* 13(1-2):155-158, 1989 2664883
- Murphy DL, Garrick NA, Aulakh CS, et al: New contributions from basic science to understanding the effects of monoamine oxidase inhibiting antidepressants. *J Clin Psychiatry* 45(7 pt 2):37-43, 1984 6735994
- Murphy DL, Sunderland T, Garrick NA, et al: Selective amine oxidase inhibitors: basic to clinical studies and back, in *Clinical Pharmacology in Psychiatry*. Edited by Dahl SG, Gram A, Potter W. Berlin, Springer-Verlag, 1987, pp 135-146
- O'Brien S, McKeon P, O'Regan M, et al: Blood pressure effects of tranylcypromine when prescribed singly and in combination with amitriptyline. *J Clin Psychopharmacol* 12(2):104-109, 1992 1573032
- Paykel ES, West PS, Rowan PR, et al: Influence of acetylator phenotype on antidepressant effects of phenelzine. *Br J Psychiatry* 141:243-248, 1982 6753997
- Pearce LB, Roth JA: Human brain monoamine oxidase type B: mechanism of deamination as probed by steady-state methods. *Biochemistry* 24(8):1821-1826, 1985 4016087
- Quitkin F, Rifkin A, Klein DF: Monoamine oxidase inhibitors. A review of antidepressant effectiveness. *Arch Gen Psychiatry* 36(7):749-760, 1979 454092
- Quitkin FM, Liebowitz MR, Stewart JW, et al: L-Deprenyl in atypical depressives. *Arch Gen Psychiatry* 41(8):777-781, 1984 6430257
- Quitkin FM, McGrath PJ, Stewart JW, et al: Atypical depression, panic attacks, and response to imipramine and phenelzine. A replication. *Arch Gen Psychiatry* 47(10):935-941, 1990 2222132

- Quitkin FM, Harrison W, Stewart JW, et al: Response to phenelzine and imipramine in placebo nonresponders with atypical depression: a new application of the crossover design. *Arch Gen Psychiatry* 48(4):319-323, 1991 2009033
- Ramsay RR, Singer TP: The kinetic mechanisms of monoamine oxidases A and B. *Biochem Soc Trans* 19(1):219-223, 1991 2037155
- Rossel L, Moll E: Moclobemide versus tranylcypromine in the treatment of depression. *Acta Psychiatr Scand Suppl* 360:61-62, 1990 2248075
- Rowan PR, Paykel ES, West PS, et al: Effects of phenelzine and acetylator phenotype. *Neuropharmacology* 20(12B):1353-1354, 1981 7322308
- Saura J, Kettler R, DaPrada M, et al: Quantitative enzyme radioautography with 3H-Ro 41-1049 and 3H-Ro 19-6327 in vitro: localization and abundance of MAO-A and MAO-B in rat CNS, peripheral organs, and human brain. *J Neurosci* 12(5):1977-1999, 1992 1578281
- Simpson GM, Gratz SS: Comparison of the pressor effect of tyramine after treatment with phenelzine and moclobemide in healthy male volunteers. *Clin Pharmacol Ther* 52(3):286-291, 1992 1526086
- Stack CG, Rogers P, Linter SPK: Monoamine oxidase inhibitors and anaesthesia. A review. *Br J Anaesth* 60(2):222-227, 1988 3278728
- Stein DJ, Ipser JC, Balkom AJ: Pharmacotherapy for social phobia. *Cochrane Database Syst Rev* (4):CD001206, 2004 15495010
- Stumpf JL: Drug therapy of hypertensive crises. *Clin Pharm* 7(8):582-591, 1988 3048849
- Thase ME, Mallinger AG, McKnight D, et al: Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *Am J Psychiatry* 149(2):195-198, 1992 1734739

- Tyrer P, Candy J, Kelly D: A study of the clinical effects of phenelzine and placebo in the treatment of phobic anxiety. *Psychopharmacology (Berl)* 32(3):237-254, 1973 4586902
- Vallejo J, Gasto C, Catalan R, et al: Double-blind study of imipramine versus phenelzine in melancholias and dysthymic disorders. *Br J Psychiatry* 151:639-642, 1987 3446308
- Versiani M, Mundim FD, Nardi AE, et al: Tranylcypromine in social phobia. *J Clin Psychopharmacol* 8(4):279-283, 1988 3209719
- Versiani M, Nardi AE, Mundim FD, et al: Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. *Br J Psychiatry* 161:353-360, 1992 1393304
- Walsh BT, Stewart JW, Roose SP, et al: A double-blind trial of phenelzine in bulimia. *J Psychiatr Res* 19(2-3):485-489, 1985 3900362
- Walsh BT, Gladis M, Roose SP, et al: A controlled trial of phenelzine in bulimia. *Psychopharmacol Bull* 23(1):49-51, 1987 3299445
- Wells DG: Monoamine oxidase inhibitors revisited. *Can J Anaesth* 36:64-74, 1989 2563341
- Wesnes KA, Simpson PM, Christmas L, et al: Acute cognitive effects of moclobemide and trazodone, alone and in combination with alcohol, in the elderly. *Br J Clin Pharmacol* 27(5):647P-648P, 1989
- White K, Razani J, Cadow B, et al: Tranylcypromine vs nortriptyline vs placebo in depressed outpatients: a controlled trial. *Psychopharmacology (Berl)* 82(3):258-262, 1984 6425910
- Youdim MBH, DaPrada M, Amrein R (eds): The cheese effect and new reversible MAO-A inhibitors. *Proceedings of the Round Table of the International Conference on New Directions in Affective Disorders*, Jerusalem, Israel, April 5-9, 1987

- Zajacka J, Fawcett J: Susceptibility to spontaneous MAOI hypertensive episodes (letter). J Clin Psychiatry 52(12):513-514, 1991 1752854
- Zeller EA: Diamine oxidase, in The Enzymes, 2nd Edition, Vol 8. Edited by Boyer PD, Lardy H, Myrback K. London, Academic Press, 1963, pp 313-335
- Zisook S: Side effects of isocarboxazid. J Clin Psychiatry 45(7 Pt 2):53-58, 1984 6376485
- Zisook S, Braff DL, Click MA: Monoamine oxidase inhibitors in the treatment of atypical depression. J Clin Psychopharmacol 5(3):131-137, 1985 3889078

## CHAPTER 9

# Tricyclic and Tetracyclic Drugs

J. Craig Nelson, M.D.

The tricyclic antidepressant agents hold an important place in the history of treatments for depression. They were the first class of antidepressant compounds to be widely used in depression and remained the first-line treatment for more than 30 years. The observation of their activity led to theories of drug action involving norepinephrine and serotonin. Indeed, this “psychopharmacological bridge” suggested that alterations of these neurotransmitters might cause depression ([Bunney and Davis 1965](#); [Prange 1964](#); [Schildkraut 1965](#)). The tricyclics were extensively studied, and through this study, the field developed several key principles to guide the management of depressive illness. For example, the importance not only of providing an adequate dosage and duration of medication during acute treatment but also of sustaining symptom improvements through the use of continuation treatment became recognized. The adverse events associated with the tricyclics required that psychiatrists become familiar with a variety of syndromes, such as anticholinergic delirium, delayed cardiac conduction, and orthostatic hypotension. The observation that tricyclic plasma concentrations varied widely stimulated interest in the relationship of these drug concentrations to hepatic metabolism and to clinical activity. The field was introduced to the concepts of genetic polymorphisms in the cytochrome P450 (CYP) enzyme system. Finally, our knowledge of how these drugs worked became the basis for the discovery of new drugs such as the selective serotonin reuptake inhibitors (SSRIs).

---

## History and Discovery

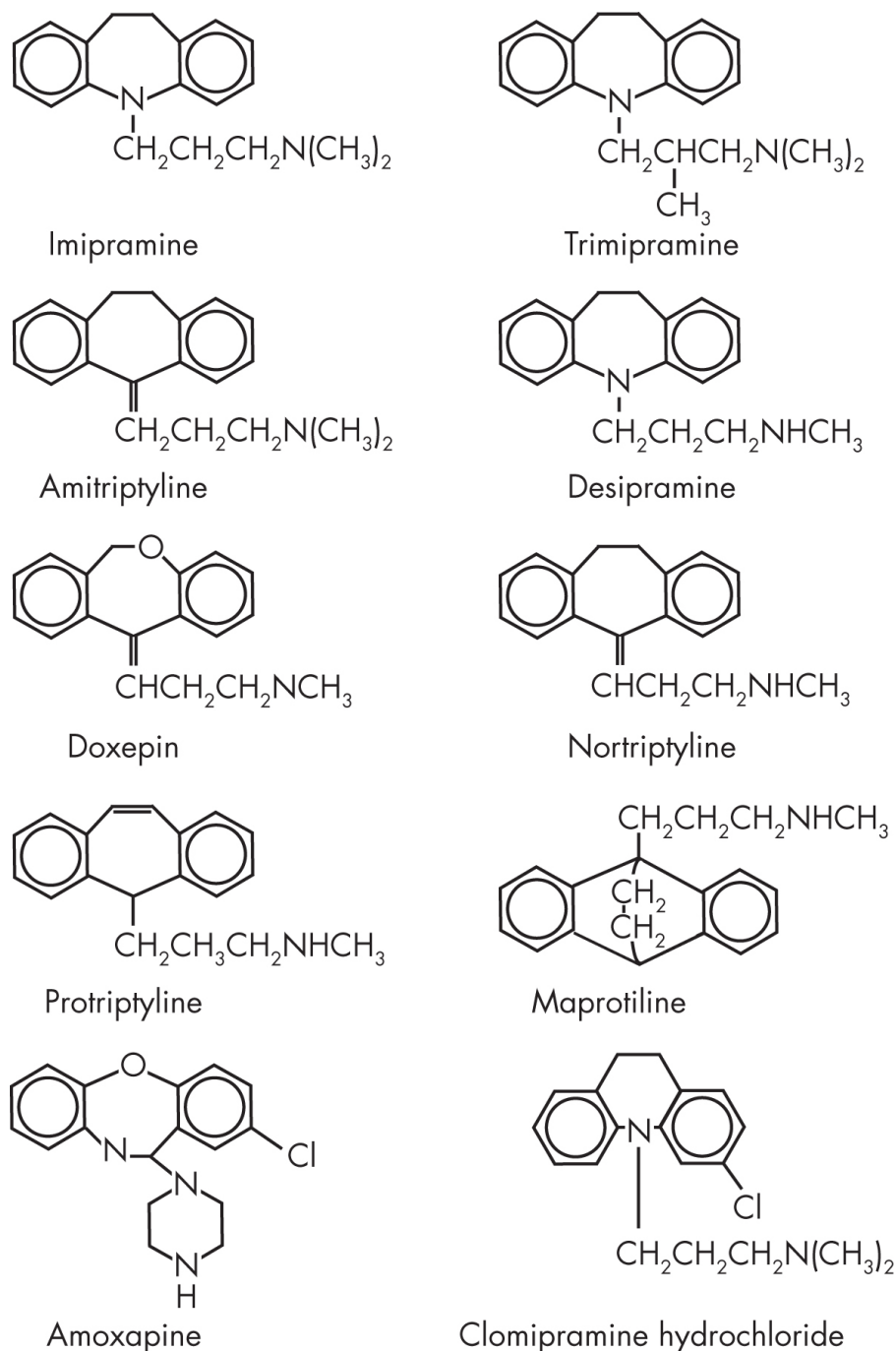
In 1957, Roland Kuhn, a Swiss psychiatrist, investigated the clinical effects of imipramine in human subjects in part to determine whether its sedative properties might be useful ([Kuhn 1958, 1970](#)). He found that although imipramine was not useful in calming agitated patients, the drug *did* appear to ameliorate symptoms in depressed patients.

After imipramine was introduced, several other antidepressant compounds were developed and marketed. These compounds had a basic tricyclic or tetracyclic structure and shared many of the secondary effects for which the tricyclics came to be known.

---

## Structure-Activity Relations

Tricyclic and tetracyclic compounds are categorized on the basis of their chemical structure ([Figure 9-1](#)). The tricyclics have a central three-ring structure, hence the name. The tertiary-amine tricyclics, such as amitriptyline and imipramine, have two methyl groups at the end of the side chain. These compounds can be demethylated to secondary amines, such as desipramine and nortriptyline. The tetracyclic compound maprotiline has a four-ring central structure. Five tertiary amines have been marketed in the United States—amitriptyline, clomipramine, doxepin, imipramine, and trimipramine. The three secondary-amine compounds are desipramine, nortriptyline, and protriptyline. All of these compounds, in addition to amoxapine and maprotiline, have been approved for use in major depressive disorder with the exception of clomipramine, which in the United States is approved for use only in obsessive-compulsive disorder (OCD).



**FIGURE 9-1.** Chemical structures of tricyclic and tetracyclic antidepressants.

The nature of the side chain appears to be important for the tricyclics' function. The tertiary tricyclic agents—amitriptyline, imipramine, and clomipramine—are more potent in blocking the serotonin transporter. The secondary tricyclics are much more potent in blocking the norepinephrine transporter (Table 9-1) (Bolden-Watson and Richelson 1993; Tatsumi et al. 1997).

**TABLE 9-1.** Affinity of tricyclics and tetracyclics for neurotransmitter transporter



**and specific receptors (expressed as equilibrium dissociation constants)**

Drug	Potency uptake blockade			Receptor binding affinity					
	5-HT	NE	DA	$\alpha_1$	$\alpha_2$	H <sub>1</sub>	M <sub>1</sub>	5-HT <sub>1A</sub>	
Amitriptyline	4.3	35	3,250	27	940	1.1	18	450	1
Amoxapine	58.0	16	4,310	50	2,600	25	1,000	220	1
Clomipramine	0.28	38	2,190	38	3,200	31	37	7,000	2
Desipramine	17.6	0.83	3,190	130	7,200	110	198	6,400	3
Doxepin	68.0	29.5	12,100	24	1,100	0.24	80	276	2
Imipramine	1.4	37	8,500	90	3,200	11	90	5,800	1
Maprotiline	5,800.0	11.1	1,000	90	9,400	2	570	12,000	1
Nortriptyline	18.0	4.37	1,140	60	2,500	10	150	294	4
Protriptyline	19.6	1.41	2,100	130	6,600	25	25	3,800	6
Trimipramine	149.0	2,450	3,780	24	680	0.27	58	8,400	3
<b>Reference</b>									
Pentolamine				15					
Yohimbine					1.6				
D- Chlorpheniramine						15			
Atropine							2.4		
Serotonin								0.72	
Ketanserin									2

*Note.* Affinity and potency=equilibrium dissociation constants in molarity.  $\alpha_1$ = $\alpha_1$ -adrene  $\alpha_2$ = $\alpha_2$ -adrenergic; DA=dopamine; 5-HT=serotonin; 5-HT<sub>1A</sub>=serotonin<sub>1A</sub>; 5-HT<sub>2</sub>=serot H<sub>1</sub>=histamine<sub>1</sub>; M<sub>1</sub>=muscarinic<sub>1</sub>; NE=norepinephrine.

*Source.* Potency uptake data adapted from Tatsumi et al. 1997. Receptor affinity data adapted from Richelson and 1984.

The structure of amoxapine differs from the structures of the other tricyclics. With a central three-ring structure and a side chain unlike those of the tricyclics, amoxapine is structurally closer to the antipsychotic loxapine, from which it is derived. Similar to the secondary tricyclics, it is a potent norepinephrine reuptake inhibitor. Unlike all of the other compounds in this group, amoxapine, and particularly its metabolite 7-hydroxyamoxapine, blocks postsynaptic dopamine receptors (Coupet et al. 1979). As a result, it is the only compound in the group that has antipsychotic activity in addition to antidepressant effects.

Maprotiline also differs from the others in this group. Although maprotiline is tetracyclic, its side chain is identical to that in desipramine, nortriptyline, and protriptyline. As would be predicted from this similarity, maprotiline is most potent in blocking the norepinephrine transporter (Randrup and Braestrup 1977).

---

## Pharmacological Profile

---

### Reuptake Blockade

Early in the history of the tricyclic and tetracyclic antidepressants, the ability of these compounds to block the transporter site for norepinephrine was described ([Axelrod et al. 1961](#)) (see [Table 9-1](#)). The tertiary amines have greater affinity for the serotonin transporter, whereas the secondary amines are relatively more potent at the norepinephrine transporter. During the administration of amitriptyline, imipramine, or clomipramine, these tertiary amines are demethylated to secondary amines; thus, both serotonergic and noradrenergic effects occur. In addition, because dopamine is inactivated by norepinephrine transporters in the frontal cortex ([Bymaster et al. 2002](#)), norepinephrine reuptake inhibitors would be expected to increase dopamine concentrations in that region.

### Receptor Sensitivity Changes

The initial reuptake blockade described above is followed by a specific sequence of events ([Blier et al. 1987](#); [Charney et al. 1991](#); [Tremblay and Blier 2006](#)). Because the tertiary tricyclic compounds inhibit the uptake of serotonin, the levels of serotonin rise. As the result of inhibitory feedback from the presynaptic somatodendritic serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) autoreceptor, the firing rate of the presynaptic serotonin neuron falls, and concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, decline rapidly. Over a 10- to 14-day period, the presynaptic autoreceptor is desensitized, and when this occurs, the tonic firing rate returns to its pretreatment rate. With both a normal firing rate and reuptake blockade, serotonin transmission is enhanced. The tricyclic agents also sensitize or upregulate postsynaptic 5-HT<sub>1A</sub> receptors ([de Montigny and Aghajanian 1978](#)). These changes further enhance the effects of serotonin.

The tricyclics also downregulate the 5-HT<sub>2</sub> receptors (; [Peroutka and Snyder 1980](#)). In preclinical experiments, when the 5-HT<sub>2</sub> receptor was blocked by an antagonist, the effects of serotonin were enhanced ([Lakoski and Aghajanian 1985](#); [Marek et al. 2003](#)). Some of the tricyclics—particularly amoxapine and doxepin, and to some extent amitriptyline—have 5-HT<sub>2</sub> antagonist properties relatively comparable to their reuptake potency (see [Table 9-1](#)) ([Tatsumi et al. 1997](#)).

The sequence of events with chronic dosing in the noradrenergic system is more complicated ([Tremblay and Blier 2006](#)). As in the serotonergic system, reuptake inhibition results in a rapid decline in norepinephrine turnover, as reflected by a drop in concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine, and attenuation of the firing rate of the noradrenergic neuron. This effect appears to be mediated by the presynaptic somatodendritic  $\alpha_2$ -adrenergic autoreceptor, which provides inhibitory feedback to the presynaptic neuron. In contrast to the firing rate of serotonergic neurons, the firing rate of noradrenergic neurons remains inhibited with chronic treatment ([Szabo and Blier 2001](#)), suggesting that somatodendritic  $\alpha_2$  receptors do not desensitize. Norepinephrine concentrations do increase at postsynaptic sites such as the hippocampus and frontal cortex. This may indicate desensitization of terminal  $\alpha_2$  autoreceptors.

With chronic treatment, the postsynaptic  $\beta$ -adrenergic receptor is downregulated, or decreased in density (Sulser et al. 1978). Current evidence suggests that  $\beta$ -adrenergic receptor downregulation is likely a compensatory change. Overall, chronic administration of a norepinephrine reuptake inhibitor appears to override the downregulation of the postsynaptic  $\beta$ -receptor, resulting in enhanced noradrenergic transmission. This effect manifests as enhanced formation of the second messenger cyclic adenosine monophosphate (cAMP) (Duman et al. 1997) and is reflected clinically by a persistent increase in heart rate (Roose et al. 1998; Rosenstein and Nelson 1991).

## Secondary Effects

The tricyclic and tetracyclic compounds have a variety of additional actions mediated by other receptors (Cusack et al. 1994; Richelson and Nelson 1984) (see Table 9-1). For example, these compounds block muscarinic receptors, producing anticholinergic effects. Although these anticholinergic effects have generally been thought to mediate the adverse effects of tricyclics and tetracyclics, a double-blind randomized crossover study in 19 subjects with major depressive disorder found that the anticholinergic drug scopolamine had a beneficial effect on depressive and anxious symptoms (Furey and Drevets 2006). Consistent with this finding, donepezil, a cholinergic drug (a cholinesterase inhibitor), when given as an adjunct to an SSRI, increased the risk of depression relapse in older adults (Reynolds et al. 2011). The tricyclics also block histamine<sub>1</sub> (H<sub>1</sub>) receptors and  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, resulting in a variety of other effects (as discussed in the next section). Tricyclics act on voltage-gated sodium channels, which explains their adverse cardiac effects; however, these same actions may contribute to the beneficial effects of tricyclics on pain (Liang et al. 2014; Priest and Kaczorowski 2007). The potency of secondary effects of the tricyclics and tetracyclics varies considerably. Among the tricyclics, amitriptyline is the most anticholinergic and desipramine the least anticholinergic. Doxepin is the most potent H<sub>1</sub> antagonist among the tricyclics, but mirtazapine is even more potent. The consequences of these secondary effects are discussed below.

---

## Pharmacokinetics and Disposition

---

### Absorption

Absorption of the tricyclic and tetracyclic drugs occurs in the small intestine and is rapid and reasonably complete. Peak levels are reached within 2–8 hours following ingestion. Exceptions include protriptyline (peak levels reached between 6 and 12 hours after ingestion) and maprotiline (peak levels not reached until 8 hours or longer). Although peak levels may have implications for side effects, peak levels are relatively unimportant with respect to efficacy because the antidepressant action of these drugs occurs over several weeks.

### Volume of Distribution

The tricyclic and tetracyclic compounds are basic lipophilic amines and are concentrated in a variety of tissues throughout the body. As a result, they have a high volume of distribution. For example, concentrations of these drugs in cardiac tissue exceed concentrations in plasma.

## Plasma Protein Binding

The tricyclic and tetracyclic compounds are extensively bound to plasma proteins (e.g., 90% or greater) because of their lipid solubility. Exceptions are the hydroxy metabolites, which have lower plasma protein binding than the parent compounds.

## First-Pass Metabolism

Following absorption, the tricyclics are taken up in the circulation but pass first through the liver, and metabolism of the drug begins—the so-called first-pass effect. As a result, the amount of the compound that enters the systemic circulation is reduced.

## Hepatic Metabolism

Hepatic metabolism is the principal method of clearance for the tricyclic and tetracyclic compounds. Only a small portion of drug is eliminated by the kidneys. Rates of hepatic metabolism vary widely from person to person, resulting in dramatic differences in steady-state plasma concentrations. Elimination half-lives for most of the tricyclic and tetracyclic compounds average about 24 hours or longer; thus, the drugs can be given once a day (Table 9-2). Amoxapine has a shorter half-life than the other tricyclics and is an exception.

**TABLE 9-2. Dosage, clearance, and apparent therapeutic plasma concentrations of tricyclics and tetracyclics**

Drug	Plasma		Therapeutic	
	Half-life (hours)	Clearance (L/hour)	Dosage range (mg/day)	Plasma level (ng/mL)
<b>Tertiary tricyclics</b>				
Amitriptyline	5-45	20-70	150-300	
Clomipramine	15-60	20-120	150-300	>150 <sup>a</sup>
Doxepin	10-25	40-60	150-300	
Imipramine	5-30	30-100	150-300	>200 <sup>a</sup>
Trimipramine	15-40	40-105		

<sup>a</sup>Total concentration of the parent compound and the desmethyl metabolite.

Source. Adapted from Nelson JC: "Tricyclic and Tetracyclic Drugs," in *Comprehensive Textbook of Psychiatry/VII*, 7th Edition. Edited by Kaplan HI, Sadock BJ. Baltimore, MD, Lippincott Williams & Wilkins, 2000, p. 2494. Copyright 2000, Lippincott Williams & Wilkins. Used with permission.

Drug	Plasma		Therapeutic	
	Half-life (hours)	Clearance (L/hour)	Dosage range (mg/day)	Plasma level (ng/mL)
<b>Secondary tricyclics</b>				
Desipramine	10-30	80-170	75-300	>125
Nortriptyline	20-55	15-80	50-150	50-150
Protriptyline	55-200	5-25	15-60	
<b>Tetracyclics</b>				
Amoxapine	5-10	225-275	150-300	
Maprotiline	25-50	15-35	100-225	

<sup>a</sup>Total concentration of the parent compound and the desmethyl metabolite.

Source. Adapted from Nelson JC: "Tricyclic and Tetracyclic Drugs," in *Comprehensive Textbook of Psychiatry/VII*, 7th Edition. Edited by Kaplan HI, Sadock BJ. Baltimore, MD, Lippincott Williams & Wilkins, 2000, p. 2494. Copyright 2000, Lippincott Williams & Wilkins. Used with permission.

Hepatic metabolism of the tricyclics and tetracyclics occurs along two principal metabolic pathways. *Demethylation of the side chain* converts the tertiary amines to secondary amines. The other pathway in hepatic metabolism is *hydroxylation of the ring structure*, which produces hydroxy metabolites. In some cases, the levels of the metabolite are substantial. The concentration of 10-hydroxynortriptyline usually exceeds that of the parent compound (Bertilsson et al. 1979). Usually 2-hydroxydesipramine is present at levels approximately 40%–50% of those of the parent compound, but these ratios are quite variable and depend on the rate of hydroxylation (Bock et al. 1983; Potter et al. 1979). Hydroxyimipramine and hydroxyamitriptyline are present at very low concentrations and are clinically unimportant. The hydroxy metabolites are then conjugated and excreted. The conjugated metabolites are not active.

Hydroxynortriptyline and hydroxydesipramine both block the norepinephrine transporter (Bertilsson et al. 1979; Potter et al. 1979). Both have antidepressant activity (Nelson et al. 1988b; Nordin et al. 1987). The norepinephrine reuptake potency of hydroxydesipramine is comparable to that of the parent compound. There are two isomers of hydroxynortriptyline, *E*- and *Z*-10-hydroxynortriptyline. *E*-10-hydroxynortriptyline is present at levels four times higher than those of the *Z* isomer and is about 50% as potent as nortriptyline in blocking norepinephrine uptake.

The principal metabolic pathway for amoxapine is hydroxylation, during which 7-hydroxyamoxapine and 8-hydroxyamoxapine are produced (Coupet et al. 1979). These compounds differ: whereas 7-hydroxyamoxapine has high-potency antipsychotic properties but a short half-life, 8-hydroxyamoxapine is metabolized more slowly and appears to contribute to the drug's antidepressant action.

The CYP2D6 pathway appears to be responsible for hydroxylation of desipramine and nortriptyline (Brøsen et al. 1991). In fact, desipramine is considered to be the prototypic substrate for CYP2D6 because it has no other major metabolic pathways. Demethylation of the tertiary-amine compounds involves a number of CYP isoenzymes, including 1A2, 3A4, and 2C19. These hepatic isoenzymes are under the control of specific genes, and gene loci for several of these isoenzymes, including CYP2D6, have been identified. Approximately 5%–10% of Caucasians are homozygous for the recessive autosomal 2D6 trait, resulting in

deficient hydroxylation of desipramine and nortriptyline (Brøsen et al. 1985; Evans et al. 1980). These individuals are termed *poor metabolizers*, whereas those with adequate 2D6 enzyme are referred to as *extensive metabolizers*. Among individuals of Asian descent, approximately 50% carry the CYP2D6\*10 allele, which is associated with intermediate metabolism of 2D6 substrates (Ji et al. 2002). For example, the elimination half-life of nortriptyline is doubled in individuals homozygous for this allele (Yue et al. 1998). Approximately 20% of Asian individuals have a genetic polymorphism resulting in deficient CYP2C19 metabolism.

The variability in plasma concentrations that results from these metabolic differences is substantial. For example, in a sample of 83 Caucasian inpatients who were given a fixed dose (2.5 mg/kg) of desipramine, we observed steady-state plasma concentrations ranging from 20 ng/mL to 934 ng/mL (Nelson 1984).

## P-Glycoprotein and the Blood-Brain Barrier

P-glycoprotein (P-gp) is located at the blood-brain barrier and acts as an efflux pump. Its function is to protect the organism from exogenous compounds. It is hypothesized that by limiting uptake of antidepressants into the central nervous system (CNS), P-gp contributes to medication resistance. Most tricyclics are substrates of P-gp (Akamine et al. 2012; O'Brien et al. 2012). The effectiveness of P-gp is reduced in the presence of P-gp inhibitors (e.g., verapamil and quinidine), and these agents would be expected to raise CNS concentrations of P-gp substrates (Weiss et al. 2003); however, the utility of adjunctive treatment with a P-gp inhibitor to improve outcomes has not been demonstrated.

P-gp is encoded by the *ABCB1* gene. Polymorphisms of the *ABCB1* gene decrease the efficiency of P-gp and should result in higher CNS concentrations of P-gp substrates. The first study to examine the contribution of the *ABCB1* gene to antidepressant effectiveness found that remission of depression was more likely if *ABCB1* polymorphisms were present and the antidepressant was a P-gp substrate, but found no association if the antidepressant was not a P-gp substrate (Uhr et al. 2008). Yet a recent review and meta-analysis of the association of *ABCB1* variants and outcome reported considerable variability in the findings of 16 studies conducted, both in terms of whether any association was found and in terms of which genetic variant was associated with greater response (Breitenstein et al. 2015). Furthermore, the two largest studies included in this meta-analysis (GENDEP [Genome-Based Therapeutic Drugs for Depression] and STAR\*D [Sequenced Treatment Alternatives to Relieve Depression]) found that none of the *ABCB1* variants was associated with response to P-gp substrate antidepressants. The lack of association in the largest studies suggests limited applicability of the *ABCB1* genotype as a predictor of response in depression.

## Steady-State Concentrations

*Steady state* is the point on a fixed dose at which plasma concentrations of the drug reach a plateau. Steady state is achieved after five half-lives. If blood level monitoring is employed, a sample is drawn immediately before the next dose is scheduled to be given, usually in the morning, after the patient's level has reached steady state. Steady-state drug concentrations should remain relatively stable as long as the dosage is constant, the patient is adherent to the medication regimen, and no interactive drugs are added. If only one sample is drawn, the clinician should bear in mind that even if the laboratory error is

low, there will be moderate biological variability ( $\pm 10\%$ – $15\%$ ). Single blood level samples are better viewed as estimates than as precise measures.

When the drug concentration is measured, the total of both the free and bound drug is reported. Drug concentrations in the cerebrospinal fluid are proportional to the free levels. The *free concentration* is dependent on dose and hepatic clearance but is not affected by plasma protein binding ([Greenblatt et al. 1998](#)). Factors that affect plasma proteins—malnutrition, inflammation—may lead to changes in the bound fraction, but the absolute free concentration is unaffected.

## Linear Kinetics

Most of the tricyclics have linear kinetics; that is, concentration increases in proportion to dose within the therapeutic range. There are exceptions. Desipramine, for example, has nonlinear kinetics at the usual dosage range ([Nelson and Jatlow 1987](#)). In cases of overdose, nonlinear changes are more likely to occur, and the clinician cannot assume that usual rates of drug elimination will be maintained.

## Effects of Aging

Changes in the pharmacodynamics and pharmacokinetics of medications occur with aging, yet some are relatively unimportant ([Greenblatt et al. 1998](#)). The ratio of fat to lean body mass increases, and cardiac output and hepatic blood flow decrease. There may be further changes associated with medical illness. But the clinical importance of these changes is usually relatively minor because of the dramatic variability of hepatic metabolism. The activity of the CYP3A4 pathway does slow with age ([von Moltke et al. 1995](#)), and concentrations of the tertiary amines are increased somewhat in older individuals ([Abernethy et al. 1985](#)). Alternatively, most studies of nortriptyline ([Katz et al. 1989](#); [Young et al. 1984](#)) and desipramine ([Abernethy et al. 1985](#); [Nelson et al. 1985, 1995](#)) indicate that ratios of blood level to dosage of these drugs are relatively unaffected by aging, suggesting that the 2D6 isoenzyme is not similarly affected. Renal clearance of the hydroxy metabolites does decrease with age ([Nelson et al. 1988a](#); [Young et al. 1984](#)). As a result, concentrations of hydroxynortriptyline may be substantially elevated in older patients.

In children, the clearance of tricyclic compounds is increased. Half-lives of imipramine are shorter, and ratios of desmethyylimipramine to imipramine are higher, consistent with more rapid metabolism ([Geller 1991](#); [Rapoport and Potter 1981](#)). Alternatively, a study of desipramine in children found that the clearance of both desipramine and hydroxydesipramine was increased, so that hydroxy metabolite–parent compound ratios were not elevated ([Wilens et al. 1992](#)).

## Relationship of Plasma Concentration to Clinical Action

### Plasma Concentration and Response

Marked interindividual variability of tricyclic plasma concentrations was described by [Hammer and Sjöqvist in 1967](#). This finding suggested that drug level monitoring might ensure that therapeutic blood levels are achieved and might help to avoid toxic levels. In carefully selected inpatients with endogenous or melancholic major depression, treatment



with adequate levels of imipramine or desipramine resulted in robust response rates of about 85% (Glassman et al. 1977; Nelson et al. 1982). But similar relationships have proven difficult to demonstrate in depressed outpatients. In outpatients, drug-placebo differences are often small, and the effect of drug treatment is harder to detect. Depressed outpatients may be more heterogeneous and include individuals who are not responsive to any drug treatment. It is logical to conclude that blood level relationships determined in severely depressed inpatients might be used as a guide for treatment of outpatients, but this assumption has not been empirically validated.

A task force of the American Psychiatric Association (1985) that reviewed studies relating tricyclic plasma levels and response concluded that a relationship had been demonstrated for imipramine, desipramine, and nortriptyline (see Table 9-2). Data on the relationship between blood level and response in depression are limited or conflicting for the other tricyclic and tetracyclic compounds.

### Plasma Concentration and Toxicity

Blood level monitoring may help to avoid toxicity. The risk of delirium is substantially increased at amitriptyline plasma concentrations above 450 ng/mL and is moderately increased at concentrations above 300 ng/mL (Livingston et al. 1983; Preskorn and Simpson 1982). But amitriptyline is the most anticholinergic tricyclic and is most likely to produce delirium. The risk of first-degree atrioventricular block is also increased at imipramine plasma concentrations greater than 350 ng/mL (Preskorn and Irwin 1982). The risk of seizures also increases at higher dosages and, presumably, higher blood levels, although a clear plasma level threshold for seizures has not been demonstrated. Following overdose, tricyclic blood levels greater than 1,000 ng/mL can be achieved, and the risks of delirium, stupor, cardiac abnormalities, and seizures are all substantially increased (Preskorn and Irwin 1982; Rudorfer and Young 1980; Spiker et al. 1975). The value of blood level monitoring for avoidance of serious adverse effects has been difficult to demonstrate; given that rates of serious toxicity are low, large samples would be required to demonstrate any increase in risk at higher blood levels.

If blood level monitoring is undertaken, the clinician should bear in mind that many factors—including laboratory variability, blood sampling errors, missed doses, and biological variability—can affect drug concentrations. For this reason, the clinician should not view the concentration reported as a precise measure. Yet because concentrations vary across such a wide range, it may be very helpful to know whether the level is low (e.g., 25–75 ng/mL), moderate (e.g., 100–300 ng/mL), or high (e.g., 300–1,000 ng/mL).

### Prospective Dosing Techniques

The demonstrated relationship between timed drug concentrations after a single tricyclic dose and the steady-state level achieved suggests the possibility of using plasma levels obtained early in treatment to rapidly adjust the dose. A clinical study using desipramine found that treatment could be initiated at full dosage once the dosage needed to reach a therapeutic level was determined from a 24-hour blood level following a test dose (Nelson et al. 1987). However, the practical application of this method was limited. Most laboratories are not prepared to determine drug concentrations accurately at very low levels (as needed following a test dose) and are unable to report results quickly. A more practical and clinically feasible method is to start the drug at a low or moderate fixed dose, obtain a blood sample after 5–7 days on that dose, and then make further adjustments based on that level. There are exceptions. Elderly depressed patients often require



gradual dosing in order to assess tolerance. In patients with panic attacks, lower starting doses are employed to avoid exacerbation of panic attacks.

---

## Mechanism of Action

---

Early studies observed that the tricyclic agents blocked uptake of monoamines at the norepinephrine and serotonin transporters ([Axelrod et al. 1961](#)). This drug effect was quickly put forward as a possible mechanism of action. The observation that reserpine, which depletes presynaptic catecholamines, might induce depression in vulnerable individuals supported this hypothesis ([F.K. Goodwin and Bunney 1971](#)). Confirmation that norepinephrine and serotonin do in fact mediate the action of monoamine reuptake inhibitors was provided by subsequent challenge studies in depressed patients. For example, administration of a tryptophan-free diet rapidly depletes serotonin and causes relapse in depressed patients who have been successfully treated with a serotonin reuptake inhibitor but not a norepinephrine reuptake inhibitor ([Delgado et al. 1990](#)). Alternatively, administration of  $\alpha$ -methyl-*p*-tyrosine (AMPT), which interrupts the synthesis of catecholamines, caused relapse in patients who were being successfully treated with noradrenergic agents but not those receiving serotonergic drugs ([Delgado et al. 1993](#)). These studies provide supporting evidence that serotonin and norepinephrine mediate antidepressant effects, but they do not necessarily imply that alterations in these neurotransmitter systems are central to the etiology of depression.

Subsequent research on the mechanism of action of the tricyclics and other antidepressant drugs has shifted to include consideration of factors affecting postsynaptic signal transduction ([Manji et al. 1995](#)). Such factors include coupling of G proteins to the adrenergic receptor or to adenylyl cyclase and the activity of membrane phospholipases and protein kinases. Other newer targets, including glucocorticoid receptors ([Barden 1996](#)), neurotrophic factors ([Duman et al. 1997](#)), and gene expression ([Lesch and Manji 1992](#); [Nibuya et al. 1996](#); [Schwaninger et al. 1995](#)), have been explored.

---

## Indications and Efficacy

---

### Major Depressive Disorder

The efficacy of the tricyclic and tetracyclic compounds in major depression is well established. The evidence for their effectiveness has been reviewed previously ([Agency for Health Care Policy and Research 1993](#); [Davis and Glassman 1989](#)). Imipramine is the most extensively studied tricyclic antidepressant, in part because new drugs were often compared with it. In 30 of 44 placebo-controlled studies, imipramine was more effective than placebo. If data from these studies are combined, 65% of 1,334 patients *completing* treatment with imipramine were substantially improved, whereas 30% of those on placebo improved. *Intention-to-treat* response rates for placebo-controlled studies of imipramine in outpatients were 51% for imipramine and 30% for placebo ([Agency for Health Care Policy and Research 1993](#)). The other tricyclic and tetracyclic antidepressants appeared comparable to imipramine in efficacy.

The tricyclic compounds are also effective when used for maintenance treatment. [Frank et al. \(1990\)](#) found that imipramine, at full dosage, effectively maintained nearly 80% of

the depressed patients for a 3-year period, compared with 10% of those on placebo. In this study, maintenance psychotherapy had an intermediate effect, with about 30% of the patients remaining well. In practice, clinicians may encounter patients with chronic depression, with residual symptoms, or with comorbid medical and psychiatric disorders. For such patients, the effects of maintenance treatment are less robust.

The U.S. Food and Drug Administration (FDA) has approved all of the tricyclic and tetracyclic compounds discussed in this chapter for the treatment of depression, with the exception of clomipramine. In Europe, clomipramine is also used for depression; in fact, it is regarded by many as the most potent antidepressant.

## Depression With Melancholic Features (Severe Depression)

The efficacy of the tricyclic compounds appears to vary in different subtypes of depression. The early studies of tricyclic compounds were frequently conducted in hospitalized patients with severe or melancholic depression, and in these patients the tricyclics were found to be effective. In fact, the tricyclics may be especially effective in this group. Two studies of imipramine and desipramine found rates of response of about 85% in severely depressed hospitalized patients who did not have a history of treatment-resistant depression, did not have prominent personality disorder, received an adequate plasma concentration of the drug, and completed treatment ([Glassman et al. 1977](#); [Nelson et al. 1982](#)).

When the SSRIs were introduced, it was suggested that they might be less effective than the tricyclic antidepressants in treating severe or melancholic depression. However, in a large meta-analysis of more than 100 comparison studies, [Anderson \(2000\)](#) found that tricyclic antidepressants and SSRIs had comparable efficacy. In a separate meta-analysis of 25 inpatient studies ([Anderson 1998](#)), the advantage of the tricyclics appeared limited to those with dual action, namely amitriptyline and clomipramine. In outpatient populations, the designation of melancholia does not appear to predict an advantage for tricyclic antidepressants versus SSRIs ([Anderson and Tomenson 1994](#); [Montgomery 1989](#)).

## Depression With Anxious Distress

The use of tricyclics in anxious depression—or *depression with anxious distress* in DSM-5 ([American Psychiatric Association 2013](#)) terminology—has been frequently studied. Doxepin, amoxapine, and maprotiline have received FDA approval for use in patients with depression and symptoms of anxiety. Direct comparison studies, however, have found little indication that one tricyclic is better than another for treatment of anxious depression. Compared with depressed patients who are not prominently anxious, depressed patients who are anxious may respond less well to amitriptyline ([Kupfer and Spiker 1981](#)), imipramine ([Roose et al. 1986](#)), and desipramine ([Nelson et al. 1994](#)). Yet these drugs are still more effective than placebo in anxious depressed patients, and it is not established that another drug class is more effective in these patients.

## Depression With Atypical Features

A series of studies examined the efficacy of imipramine in depressed patients with atypical features ([Liebowitz et al. 1984, 1988](#)). Imipramine was more effective than placebo but significantly less effective than the monoamine oxidase inhibitor (MAOI) phenelzine. Other investigators have reported the value of switching from a tricyclic to an MAOI in tricyclic-refractory depressed patients with atypical features ([McGrath et al. 1987](#); [Thase et al. 1992](#)). In fact, the validity and utility of atypical depression were in large part supported by this observed differential response.

## Depression With Psychotic Features

In 1975, [Glassman et al.](#) observed that imipramine was less effective in patients with major depression who had delusions. Subsequently, [Chan et al. \(1987\)](#) reviewed several studies involving more than 1,000 patients and found that antidepressants—usually tricyclics—given alone were effective in approximately two-thirds of depressed patients without psychosis but in only about one-third of those with psychotic features. Several open studies reviewed elsewhere ([Nelson 1987](#)) and one prospective study ([Spiker et al. 1985](#)) found that the tricyclics, when combined with an antipsychotic, are effective in psychotic depression.

[Anton and Burch \(1990\)](#) suggested that because of its antipsychotic effects, amoxapine might be effective for psychotic depression. In a double-blind study, these researchers demonstrated that amoxapine was comparable in efficacy to the combination of perphenazine and amitriptyline in treating psychotic depression ([Anton and Burch 1990](#)).

## Bipolar Depression

Forty years ago, it was suggested that the MAOI antidepressants might be more effective than the tricyclics in treating bipolar depression ([Himmelhoch et al. 1972](#)). Later, [Himmelhoch et al. \(1991\)](#) demonstrated in a double-blind study that tranylcypromine was more effective than imipramine for bipolar depression. Because tricyclics are more likely than other agents to induce mania ([Wehr and Goodwin 1987](#)), they are not recommended for monotherapy of bipolar depression.

## Persistent Depressive Disorder (Dysthymia)

The new DSM-5 diagnostic category *persistent depressive disorder (dysthymia)* includes both chronic major depressive disorder and dysthymia. Imipramine appears to be effective in treating chronic depression and to be relatively comparable to sertraline in efficacy ([Keller et al. 1998](#); [Kocsis et al. 1988](#)). Imipramine and desipramine have both been studied in controlled trials in dysthymia. Imipramine was found to be more effective than placebo for acute treatment ([Thase et al. 1996](#)), and desipramine was more effective than placebo for maintenance treatment ([Miller et al. 2001](#)) of dysthymia.

## Late-Life Depression

[Gerson et al. \(1988\)](#) reviewed studies of tricyclic antidepressants in older patients reported prior to 1986. They found 13 placebo-controlled trials but noted several methodological problems. Although tricyclics were effective, overall response rates in older patients appeared to be lower than rates in nonelderly patients ([Agency for Health](#)

Care Policy and Research 1993). Katz et al. (1990) performed one of the first placebo-controlled trials of nortriptyline in the treatment of patients older than 80 years living in a residential care facility. Nortriptyline was more effective than placebo. The doses employed and levels achieved were similar to those in younger subjects. This study remains the only study to date showing an advantage for an antidepressant over placebo in depressed nursing home patients.

## Depression in Children

In children and adolescents, the tricyclic antidepressants have not demonstrated superiority over placebo (Ryan 1992).

## Panic Disorder

Although none of the tricyclic or tetracyclic drugs is approved for use in panic disorder, imipramine was the first drug described for use in this disorder (Klein 1964). The efficacy of both tertiary and secondary tricyclics has been demonstrated in controlled trials (Jobson et al. 1978; Munjack et al. 1988; Zitrin et al. 1980). In treating this disorder, the drug is initiated at a low dose to avoid exacerbation of panic symptoms.

## Obsessive-Compulsive Disorder

Unlike depression, which responds to a variety of antidepressant agents, OCD appears to require treatment with a serotonergic agent. Clomipramine, the most serotonergic of the tricyclics, is approved by the FDA for use in OCD, and its efficacy in this disorder is well established (Greist et al. 1995). Studies comparing its effectiveness with that of noradrenergic agents such as desipramine found that clomipramine was substantially superior (Leonard et al. 1989). Although the SSRIs are effective in treating OCD, there is a suggestion that clomipramine may be superior (Greist et al. 1995). Whether this suggested superiority is due to the dual mechanism of clomipramine or to other factors is unclear.

## Attention-Deficit/Hyperactivity Disorder

The efficacy of the stimulant drugs in treating attention-deficit/hyperactivity disorder (ADHD) is well established. The tricyclics, especially desipramine, also appear to be of value. In one study, desipramine, given at dosages greater than 4 mg/kg for 3–4 weeks, was effective in two-thirds of the children, whereas placebo was effective in only 10% (Biederman et al. 1989). Desipramine was also found to be more effective than placebo in adults with ADHD (Wilens et al. 1996). One of the advantages of desipramine is its low potential for abuse. Unfortunately, five cases of sudden death were reported in the early 1990s in children being treated with desipramine (Riddle et al. 1991, 1993). All were under the age of 12 years. As a result, desipramine is contraindicated in children younger than 12 years (discussed in greater detail below; see section “Side Effects and Toxicology”). Given that tricyclics as a group share the same adverse cardiac effects, there is reason to be concerned that other tricyclics might also have safety issues in young children (see also Chapter 55, “Treatment of Child and Adolescent Disorders”).

## Pain Syndromes

The tricyclics and the tetracyclic maprotiline have been widely used in various chronic pain syndromes. In a review of the literature, [O'Malley et al. \(1999\)](#) identified 56 controlled studies involving tricyclic antidepressant therapy for various pain syndromes, including headache (21 studies), fibromyalgia (18 studies), functional gastrointestinal syndromes (11 studies), idiopathic pain (8 studies), and tinnitus (2 studies); and [Salerno et al. \(2002\)](#) identified 7 more placebo-controlled trials of tricyclics or maprotiline used for chronic back pain. These agents were quite effective; the mean effect size (0.87) and the drug-placebo difference in response rates (32%) in the pain trials were more robust than those usually observed in placebo-controlled studies in depression. The analgesic effects of these compounds were not simply the result of their antidepressant effects.

The mechanism of these agents' analgesic effects appears to differ from that of their antidepressant effects. The antinociceptive actions of the antidepressants result from actions on descending norepinephrine and serotonin pathways in the spinal cord ([Yoshimura and Furue 2006](#)). In animals, the antinociceptive effects of norepinephrine reuptake inhibitors and combined norepinephrine-serotonin reuptake inhibitors appear to be more potent than those of SSRIs ([Mochizuki 2004](#)). In humans, there is some evidence that the combined-action agents amitriptyline and clomipramine are more effective than the SSRI fluoxetine ([Max et al. 1992](#)) or the norepinephrine-selective agents maprotiline ([Eberhard et al. 1988](#)) and nortriptyline ([Panerai et al. 1990](#)). In humans, antidepressant dosing and timing of effects for pain differ from those for depression. For example, usual dosages of amitriptyline required for pain management ( $\leq 75$  mg/day) are lower than those required to treat depression (15–300 mg/day), and response occurs more quickly, usually within the first 1 or 2 weeks.

## Other Indications

Imipramine has been used for treatment of nocturnal enuresis in children, with FDA approval, and controlled trials indicate efficacy ([Rapoport et al. 1980](#)). The dose of imipramine is usually 25–50 mg at bedtime. Amitriptyline and nortriptyline also appear to be useful for this indication, although they are not FDA approved for use in the disorder. The mechanism of action is unclear but may in part be anticholinergic. Given the serious cardiac risks attached to desipramine's use in children younger than 12 years (discussed in earlier subsection "Attention-Deficit/Hyperactivity Disorder"), concerns have been raised regarding whether tricyclics other than desipramine might also pose safety risks in this population. However, the low doses used in imipramine treatment of pediatric nocturnal enuresis may reduce this risk.

Tricyclic antidepressant drugs have been extensively studied in patients with schizophrenia. However, in the absence of a major depressive episode, these agents appear to be of limited value ([Siris et al. 1978](#)).

The more sedating tricyclics have been used to treat insomnia, and doxepin (as Silenor) is FDA approved for this indication. Because of its antihistaminic effects, doxepin has also been used for pruritis and is FDA indicated (as Zonalon) for short-term management of moderate pruritis in atopic dermatitis and lichen simplex chronicus.

---

## Side Effects and Toxicology

---

Distinguishing side effects during tricyclic treatment from the somatic symptoms of depression can be complicated. During treatment, patients may attribute somatic symptoms to drug side effects even if the symptoms were preexisting. One study found that the strongest predictor of overall somatic symptom severity was the severity of the depression at the time of assessment (Nelson et al. 1984).

Another general factor contributing to side effects is the patient's vulnerability. For example, one of the best predictors of orthostatic hypotension during treatment is the presence of orthostatic hypotension prior to treatment (Glassman et al. 1979). Seizures are most likely in a patient with a history of seizures (Rosenstein et al. 1993). Cardiac conduction problems are most likely to occur in patients with preexisting conduction delay (Roose et al. 1987a).

Antidepressant drugs do have effects on a variety of organs and can produce adverse effects. The in vitro potency or affinity of antidepressant compounds for various receptor sites (see Table 9-1) is one factor determining the likelihood that specific side effects will be produced. A related issue is how the in vitro potency of a secondary effect relates to the potency of the primary action of the drug. If the secondary effect is more potent, it will occur at concentrations below the therapeutic level of the drug. For example, orthostatic hypotension often occurs at plasma concentrations below the usual therapeutic threshold. Alternatively, the proarrhythmic and proconvulsant effects of the tricyclic antidepressants become more pronounced at elevated blood levels or those encountered in overdose.

## Central Nervous System Effects

The principal action of the tricyclic and tetracyclic agents in the CNS is to reduce the symptoms of depression. Nondepressed subjects given imipramine may feel sleepy, quieter, light-headed, clumsy, and tired. These effects are generally unpleasant (DiMascio et al. 1964).

The anticholinergic and antihistaminic effects of the tricyclics and tetracyclics can produce confusion or delirium. The incidence of delirium is dose dependent, with delirium risk increasing at blood levels above 300 ng/mL (Livingston et al. 1983; Preskorn and Simpson 1982). The risk of delirium appears to be higher with the more anticholinergic agents, such as amitriptyline. Patients with concurrent dementia are particularly vulnerable to the development of delirium, and the more anticholinergic tricyclics should be avoided in such patients. Intramuscular or intravenous physostigmine can be used to reverse or reduce the symptoms of delirium, but physostigmine's short duration of action makes its continued use difficult.

Seizures can occur with all of the tricyclic and tetracyclic agents and are dosage and blood level related (Rosenstein et al. 1993). For clomipramine, the risk of seizures is reported to be 0.5% at dosages up to 250 mg/day. At clomipramine dosages above 250 mg/day, the seizure risk increases to 1.67% (clomipramine new drug application data on file with the FDA). The seizure risk for such as imipramine and amitriptyline were not well established at the time of marketing. Two of the largest studies found that seizure risk varied from 0 to 0.6% or 0.7% for various tricyclic compounds and were clearly dose related (Jick et al. 1983; Peck et al. 1983). The risk of seizures is substantially increased following overdose (Spiker et al. 1975). The cumulative data to date suggest that amoxapine, clomipramine, and maprotiline present the highest seizure risk among this group of agents (Johannessen Landmark et al. 2016). The risk of convulsions is increased in patients with predisposing factors such as a history of seizures, the presence of brain



injury, or the use of antipsychotics. The mechanism by which tricyclics produce seizures is not well understood.

A fine, rapid tremor can occur with use of tricyclic agents. Because tremors are dose dependent, tend to occur at higher blood levels, and are not typical depressive symptoms, development of a tremor may be a clinical indicator of an elevated blood level ([Nelson et al. 1984](#)).

Because the 7-hydroxy metabolite of amoxapine has antipsychotic properties, administration of amoxapine carries the potential risk of neuroleptic malignant syndrome and tardive dyskinesia. Although these adverse events are rare, the seriousness of the risk and the availability of alternatives suggest that use of amoxapine should be reserved for patients whose clinical condition warrants treatment with an agent possessing antipsychotic properties.

## Anticholinergic Effects

The tricyclics block muscarinic receptors and can cause a variety of anticholinergic side effects, such as dry mouth, constipation, blurred vision, and urinary hesitancy. These effects can precipitate an ocular crisis in patients with narrow-angle glaucoma. The tricyclic and tetracyclic compounds vary substantially in their muscarinic potency (see [Table 9-1](#)). Amitriptyline is the most potent, and desipramine is the least anticholinergic. Amoxapine and maprotiline also have minimal anticholinergic effects. Anticholinergic effects can contribute to tachycardia, but tachycardia also occurs as a result of stimulation of  $\beta$ -adrenergic receptors in the heart. Thus, tachycardia also occurs in patients receiving desipramine, which is minimally anticholinergic ([Rosenstein and Nelson 1991](#)).

Although anticholinergic effects are annoying, they are usually not serious. They can, however, become severe. An ocular crisis in patients with narrow-angle glaucoma is an acute condition associated with severe pain. Urinary retention can be associated with stretch injuries to the bladder. Constipation can progress to severe obstipation. (Paralytic ileus has been described but is rare.) In these conditions, medication must be discontinued and appropriate supportive measures instituted. Elderly patients are at greatest risk for severe adverse consequences. The incidence of severe anticholinergic adverse reactions is increased by concomitant administration of other anticholinergic agents. Use of a tricyclic with weak anticholinergic properties, such as nortriptyline or desipramine, can help to reduce the likelihood of these problems.

Anticholinergic side effects may benefit from other interventions. Bethanechol (Urecholine) at a dosage of 25 mg three or four times a day may be helpful in patients with urinary hesitancy. The regular use of stool softeners helps to manage constipation. Patients with narrow-angle glaucoma who are receiving pilocarpine eye drops regularly can be treated with a tricyclic, as can those who have had an iridectomy. Tricyclic agents do not affect patients with chronic open-angle glaucoma.

## Antihistaminic Effects

Several of the tricyclic compounds and maprotiline have clinically significant antihistaminic effects. Doxepin, the most potent  $H_1$  receptor antagonist among the tricyclics, is more potent than diphenhydramine but less potent than mirtazapine. Central  $H_1$  receptor blockade can contribute to sedation and delirium and also appears to be related to the increased appetite and associated weight gain that patients may develop

with chronic treatment. Because of their sedating effects, the tricyclic antidepressants, especially amitriptyline, have been used as hypnotics. Given their cardiac effects and lethality in overdose, this practice should be discouraged.

## Cardiovascular Effects

Orthostatic hypotension is one of the most common reasons for discontinuation of tricyclic antidepressant treatment (Glassman et al. 1979). It can occur with all of the tricyclics but appears to be less pronounced with nortriptyline (Roose et al. 1981; Thayssen et al. 1981). The  $\alpha_1$ -adrenergic blockade associated with the tricyclics contributes to orthostatic hypotension; however, it is the postural reflex that is primarily affected. Resting supine blood pressure may be unaffected or can even be elevated (Walsh et al. 1992). Orthostatic hypotension is most likely to occur or is most severe in patients who have preexisting orthostatic hypotension (Glassman et al. 1979). It is also aggravated by concurrent antihypertensive medications, especially volume-depleting diuretic agents. The elderly are more likely to have preexisting hypotension and are also more vulnerable to the consequences of orthostatic hypotension, such as falls and hip fractures.

Orthostatic hypotension often occurs at low medication blood levels. Gradual dosage adjustment may allow accommodation to the subjective experience of light-headedness, but the actual orthostatic blood pressure changes do not accommodate within a reasonable period of time (e.g., 4 weeks) (Roose et al. 1998). As a consequence, patients who experience serious symptomatic orthostatic hypotension may not be treatable with a tricyclic antidepressant. Fludrocortisone (Florinef) has been used to raise blood pressure, but in this author's experience it is not very effective. If patients are receiving antihypertensives, it may be possible and helpful to reduce the dosage of these agents.

Desipramine has been reported to raise supine blood pressure in young women (ages 18–45 years), although it is not clear that this effect is limited to that age group (Walsh et al. 1992). The elevation in blood pressure may be similar to that reported for venlafaxine.

Tachycardia occurs with all of the tricyclics, not just the more anticholinergic agents. Both supine and postural pulse changes can occur, and the standing pulse can be markedly elevated. A study of nortriptyline, dosed to a therapeutic plasma concentration, found a mean pulse increase of 11% (8 beats per minute) (Roose et al. 1998). Patients do not accommodate to the pulse rise, which can persist for months. Tachycardia is more prominent in young patients, who appear to be more sensitive to sympathomimetic effects, and is one of the most common reasons for drug discontinuation in adolescents. A persistent pulse rise, however, increases cardiac work and may be clinically significant in patients with ischemic heart disease.

The effect of tricyclic antidepressants on cardiac conduction has been a subject of great interest. Cardiac arrhythmia is the principal cause of death following tricyclic overdose (Spiker et al. 1975). Apparently, through inhibition of sodium/potassium ( $\text{Na}^+/\text{K}^+$ ) adenosine triphosphatase (ATPase), the tricyclics stabilize electrically excitable membranes and delay conduction, particularly His ventricular conduction. Consequently, the tricyclics have type I antiarrhythmic qualities or quinidine-like effects.

At therapeutic blood levels, the tricyclics can have beneficial effects on ventricular excitability. In patients with preexisting conduction delay, however, the tricyclic antidepressants can cause heart block (Glassman and Bigger 1981; Roose et al. 1987b). A pretreatment QTc interval of 450 milliseconds or greater indicates that conduction is already delayed and that the patient is not a candidate for tricyclic antidepressant treatment. High drug plasma levels (e.g., imipramine plasma concentrations  $>350$  ng/mL)



increase the risk of first-degree atrioventricular heart block ([Preskorn and Irwin 1982](#)). The tricyclic antidepressants do not reduce cardiac contractility or cardiac output ([Roose et al. 1987a](#)).

[Glassman et al. \(1993\)](#), noting that the type I antiarrhythmic drugs routinely given following myocardial infarction actually increase the risk of sudden death, suggested that the tricyclics may pose similar risks. The risk of sudden death is also increased when heart rate variability is reduced, and the tricyclics reduce heart rate variability ([Roose et al. 1998](#)).

As mentioned earlier (see subsection “Attention-Deficit/Hyperactivity Disorder”), five cases of sudden death were reported in children younger than 12 years who were receiving desipramine ([Riddle et al. 1991, 1993](#)). It was suggested that the immature conduction system in some children might render them more vulnerable to the cardiac effects of desipramine. However, no cardiac abnormalities were observed in a study of 71 children with 24-hour cardiac monitoring ([Biederman et al. 1993](#)). These findings suggest that cardiac events in children are not dose dependent and that electrocardiogram monitoring is not likely to identify those at risk.

## Hepatic Effects

Acute hepatitis has been associated with use of imipramine ([Horst et al. 1980](#); [Moskovitz et al. 1982](#); [Weaver et al. 1977](#)) or desipramine ([Powell et al. 1968](#); [Price et al. 1983](#)). Mild increases in liver enzymes (less than three times normal) are not uncommon and usually can be monitored safely over a period of days or weeks. Enzyme changes do not appear to be related to drug concentrations ([Price et al. 1984](#)). Acute hepatitis is relatively uncommon but can occur. The etiology is not well established, but in some cases the condition appears to represent a hypersensitivity reaction. Tricyclic-induced acute hepatitis is characterized by very high enzyme levels (e.g., aspartate aminotransferase [AST] levels >800), which develop within days. The enzyme pattern can be either hepatocellular or cholestatic. Enzyme changes may precede clinical symptoms, especially in the hepatocellular form. If a random blood test indicates mildly elevated liver enzymes, enzyme levels can be followed for a few days. Because of the rapid rise in liver enzyme levels in acute hepatitis, that condition will become evident quickly and will be easily distinguished from mild, persistent enzyme level elevations.

Acute hepatitis is a dangerous and potentially fatal condition. If it develops, the antidepressant must be discontinued and should not be introduced again, because the next reaction may be more severe.

## Other Side Effects

Increased sweating can occur with the tricyclic compounds; occasionally, sweating can be marked. Carbohydrate craving also can occur, and when coupled with antihistaminic effects can lead to significant weight gain. Weight gain appears to be greater with the tertiary compounds than with the secondary agents. Sexual dysfunction has been described with the tricyclics but appears to be less common than with the SSRIs. This side effect appears to be associated with the more serotonergic compounds such as clomipramine. Tricyclic antidepressants can cause allergic skin rashes, which are sometimes associated with photosensitivity reactions. Various blood dyscrasias also have been reported; fortunately, these are very rare.

## Overdose

Because antidepressants are used by depressed patients who are at risk for overdose, the lethality of antidepressant drugs in overdose is of great concern. A tricyclic overdose of 10 times the total daily dosage can be fatal ([Gram 1990](#); [Rudorfer and Robins 1982](#)). Death most commonly results from cardiac arrhythmia. However, seizures, CNS depression, and respiratory depression also can occur. Although the use of tricyclics in depression has declined, amitriptyline remains widely used for other indications, such as pain. The total number of amitriptyline-associated deaths reported to U.S. poison control centers is more than twice the number of deaths associated with all other tricyclics and tetracyclics combined ([Mowry et al. 2014](#)). All of the tricyclic and tetracyclic compounds can be dangerous in overdose; however, two reports found that the ratio of deaths to number of prescriptions written was relatively low for clomipramine compared with that for other tricyclics ([Cassidy and Henry 1987](#); [Farmer and Pinder 1989](#)).

## Teratogenicity

The long history of tricyclic use without observation of birth defects argues for the safety of these agents. Of course, the patient must be informed of the possible risks and benefits of taking the drug and the risks of discontinuing treatment before making a decision. The risk of recurrence is particularly high during or following pregnancy for patients with a prior history of depression.

If tricyclics are continued during pregnancy, dosage adjustment may be required because of metabolic changes ([Altshuler and Hendrick 1996](#)). Drug withdrawal following delivery can occur in the infant and is characterized by tachypnea, cyanosis, irritability, and poor sucking reflex. Drugs in this class should be discontinued 1 week prior to delivery if possible. The tricyclics are excreted in breast milk at concentrations similar to those in plasma, but the actual quantity delivered is very small, so that drug levels in the infant are usually undetectable ([Rudorfer and Potter 1997](#); also see [Chapter 57, "Psychopharmacology During Pregnancy and Lactation"](#)).

---

## Drug-Drug Interactions

---

Both pharmacodynamic and pharmacokinetic drug interactions should be considered.

## Pharmacodynamic Interactions

Serious pharmacodynamic interactions can occur between the tricyclics and the MAOIs. The most dangerous scenario—administration of a large dose of a tricyclic to a patient who is already taking an MAOI—could result in a sudden increase in catecholamines and a potentially fatal hypertensive reaction. Tricyclics and MAOIs have been used together to treat patients with refractory depression ([Goldberg and Thornton 1978](#); [Schuckit et al. 1971](#)). When used in combination, treatment is begun with lower dosages, and either the two compounds are started together or the tricyclic is started first.

The most common pharmacodynamic interaction involving tricyclics occurs when they are added to other sedating agents, resulting in increased sedation. By blocking the norepinephrine transporters, the tricyclics block the uptake and thus interfere with the

actions of guanethidine and tyramine. Desipramine and the other tricyclics reduce the effect of clonidine.

Quinidine is an example of a drug with a potential for dynamic and kinetic interaction with tricyclics. Because the tricyclics have quinidine-like effects, the effects of tricyclics and quinidine on cardiac conduction are potentially additive. In addition, quinidine is a potent CYP2D6 isoenzyme inhibitor that can raise tricyclic levels, further adding to the problem.

## Pharmacokinetic Interactions

A number of drugs can block the metabolic pathways of the tricyclics, resulting in higher and potentially toxic blood levels of drug. Desipramine has been of particular interest because it is metabolized via the CYP2D6 isoenzyme and there are no major alternative pathways. Inhibition of CYP2D6 can result in very high desipramine plasma levels, and toxicity can occur ([Preskorn et al. 1990](#)). Quinidine, mentioned above, is a very potent CYP2D6 inhibitor. Fluoxetine and paroxetine, duloxetine, bupropion, and some antipsychotics also inhibit CYP2D6. Fluoxetine and paroxetine at usual dosages raise desipramine levels, on average, three- to fourfold in individuals who are extensive metabolizers ([Preskorn et al. 1994](#)). CYP2D6 inhibitors would be expected to block nortriptyline metabolism, but the magnitude of this interaction has not been well studied.

Because the tertiary tricyclics are metabolized by several pathways (CYP1A2, 3A4, 2C19), a selective inhibitor of one pathway would be unlikely to have a significant effect on their plasma levels. Although numerous drug interactions have been described, many are of doubtful clinical significance (for comprehensive reviews, see [Nemeroff et al. 1996](#); [Pollock 1997](#)).

Enzyme induction can also occur, which may render the tricyclic acted upon ineffective. Unlike enzyme inhibition, which occurs quickly, enzyme induction requires synthesis of new enzyme, and the full effect may take 2-3 weeks to develop. Barbiturates and carbamazepine are potent inducers of CYP3A4; induction by phenytoin appears to be less pronounced. Although CYP2D6 is a noninducible isoenzyme, phenobarbital reduces the availability of desipramine substantially. Apparently when CYP3A4 is induced, it becomes an important metabolic pathway for desipramine and the other tricyclics. In this author's experience, it can be difficult to attain an effective blood level of desipramine in the presence of a barbiturate.

Nicotine induces the CYP1A2 pathway and may lower concentrations of the tertiary tricyclics, but the secondary tricyclics (e.g., desipramine, nortriptyline) are less affected.

Acute ingestion of alcohol can reduce first-pass metabolism, resulting in higher tricyclic levels. Because tricyclic overdose is often associated with alcohol ingestion, this is an important consideration. Alternatively, chronic use of alcohol appears to induce hepatic isoenzymes and may lower tricyclic levels ([Shoaf and Linnoila 1991](#)).

The tricyclics themselves appear to be weak enzyme inhibitors, and few clinically significant interactions have been described. The tertiary tricyclics compete with warfarin for some metabolic enzymes (e.g., CYP1A2) and may raise warfarin levels.

---

## Conclusion

---

The tricyclic drugs were the mainstay of treatment for depression for three decades. Although the second-generation antidepressants appear to be better tolerated, no new

agent has been shown to be more effective than the tricyclics, and if anything, there has been concern that the new agents may be less effective. The tricyclics were “dirty” drugs; that is, they had multiple actions. Although their side effects have been emphasized, these multiple actions may contribute to their efficacy. Not only does amitriptyline block uptake of 5-HT, but its metabolite blocks uptake of norepinephrine, and in addition, amitriptyline is a 5-HT<sub>2</sub> antagonist. Furthermore, the anticholinergic effects of amitriptyline may contribute to antidepressant activity. The principal drawback of this class of agents is the risk of serious cardiac adverse effects. Tricyclics can aggravate arrhythmia in patients with preexisting conduction delay. They also may increase the risk of sudden death in children and in patients with ischemic heart disease. Moreover, a week’s supply of medication taken in overdose can be fatal. Because of these adverse effects, it is unlikely that there will be a resurgence of interest in the tricyclics. Nevertheless, the efficacy of these agents across a range of disorders, including pain, illustrates the potential advantages of antidepressant drugs that have multiple actions.

---

## References

---

- Abernethy DR, Greenblatt DJ, Shader RI: Imipramine and desipramine disposition in the elderly. *J Pharmacol Exp Ther* 232(1):183-188, 1985 3965690
- Agency for Health Care Policy and Research: Clinical Practice Guideline: Depression in Primary Care: Treatment of Major Depression, Vol 2. Rockville, MD, U.S. Government Printing Office, 1993
- Akamine Y, Yasui-Furukori N, Ieiri I, Uno T: Psychotropic drug-drug interactions involving P-glycoprotein. *CNS Drugs* 26(11):959-973, 2012 23023659
- Altshuler LL, Hendrick VC: Pregnancy and psychotropic medication: changes in blood levels. *J Clin Psychopharmacol* 16(1):78-80, 1996 8834425
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Arlington, VA, American Psychiatric Association, 2013
- American Psychiatric Association Task Force on the Use of Laboratory Tests in Psychiatry: Tricyclic antidepressants—blood level measurements and clinical outcome: an APA Task Force report. *Am J Psychiatry* 142(2):155-162, 1985 3881999
- Anderson IM: SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 7 (suppl 1):11-17, 1998 9597346
- Anderson IM: Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord* 58(1):19-36, 2000 10760555
- Anderson I, Tomenson B: A meta-analysis of the efficacy of selective serotonin reuptake inhibitors compared to tricyclic antidepressants in depression (abstract). *Neuropsychopharmacology* 10 (suppl):106, 1994
- Anton RF Jr, Burch EA Jr: Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. *Am J Psychiatry* 147(9):1203-1208, 1990 2201223
- Axelrod J, Whitby LG, Hertting G: Effect of psychotropic drugs on the uptake of H<sup>3</sup>-norepinephrine by tissues. *Science* 133(3450):383-384, 1961 13685337
- Barden N: Modulation of glucocorticoid receptor gene expression by antidepressant drugs. *Pharmacopsychiatry* 29(1):12-22, 1996 8852529
- Bertilsson L, Mellström B, Sjöqvist F: Pronounced inhibition of noradrenaline uptake by 10-hydroxymetabolites of nortriptyline. *Life Sci* 25(15):1285-1292, 1979 513959
- Biederman J, Baldessarini RJ, Wright V, et al: A double-blind placebo controlled study of desipramine in the treatment of ADD, I: efficacy. *J Am Acad Child Adolesc Psychiatry*

- 28(5):777-784, 1989 2676967
- Biederman J, Baldessarini RJ, Goldblatt A, et al: A naturalistic study of 24-hour electrocardiographic recordings and echocardiographic findings in children and adolescents treated with desipramine. *J Am Acad Child Adolesc Psychiatry* 32(4):805-813, 1993 8340302
- Blier P, de Montigny C, Chaput Y: Modifications of the serotonin system by antidepressant treatments: implications for the therapeutic response in major depression. *J Clin Psychopharmacol* 7 (6 suppl):24S-35S, 1987 3323264
- Bock JL, Nelson JC, Gray S, Jatlow PI: Desipramine hydroxylation: variability and effect of antipsychotic drugs. *Clin Pharmacol Ther* 33(3):322-328, 1983 6130865
- Bolden-Watson C, Richelson E: Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci* 52(12):1023-1029, 1993 8445992
- Breitenstein B, Brückl TM, Ising M, et al: ABCB1 gene variants and antidepressant treatment outcome: a meta-analysis. *Am J Med Genet B Neuropsychiatr Genet* 168B(4):274-283, 2015 25847751
- Brøsen K, Otton SV, Gram LF: Sparteine oxidation polymorphism in Denmark. *Acta Pharmacol Toxicol (Copenh)* 57(5):357-360, 1985 4090995
- Brøsen K, Zeugin T, Meyer UA: Role of P450 IID6, the target of the sparteine-debrisoquin oxidation polymorphism, in the metabolism of imipramine. *Clin Pharmacol Ther* 49(6):609-617, 1991 2060250
- Bunney WE Jr, Davis JM: Norepinephrine in depressive reactions. A review. *Arch Gen Psychiatry* 13(6):483-494, 1965 5320621
- Bymaster FP, Katner JS, Nelson DL, et al: Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 27(5):699-711, 2002 12431845
- Cassidy S, Henry J: Fatal toxicity of antidepressant drugs in overdose. *Br Med J (Clin Res Ed)* 295(6605):1021-1024, 1987 3690249
- Chan CH, Janicak PG, Davis JM, et al: Response of psychotic and nonpsychotic depressed patients to tricyclic antidepressants. *J Clin Psychiatry* 48(5):197-200, 1987 3571174
- Charney DS, Delgado PL, Price LH, et al: The receptor sensitivity hypothesis of antidepressant action: a review of antidepressant effects on serotonin function, in *The Role of Serotonin in Psychiatric Disorders*. Edited by Brown SL, van Praag HM. New York, Brunner/Mazel, 1991, pp 29-56
- Coupet J, Rauh CE, Szues-Myers VA, Yünger LM: 2-Chloro-11-(1-piperazinyl)dibenz[b, f][1, 4]oxazepine (amoxapine), an antidepressant with antipsychotic properties—a possible role for 7-hydroxyamoxapine. *Biochem Pharmacol* 28(16):2514-2515, 1979 41531
- Cusack B, Nelson A, Richelson E: Binding of antidepressants to human brain receptors: focus on newer generation compounds. *Psychopharmacology (Berl)* 114(4):559-565, 1994 7855217
- Davis JM, Glassman AH: Antidepressant drugs, in *Comprehensive Textbook of Psychiatry*. Edited by Kaplan HI, Sadock BJ. Baltimore, MD, Williams & Wilkins, 1989, pp 1627-1655
- Delgado PL, Charney DS, Price LH, et al: Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch Gen Psychiatry* 47(5):411-418, 1990 2184795
- Delgado PL, Miller HL, Salomon RM, et al: Monoamines and the mechanism of antidepressant action: effects of catecholamine depletion on mood of patients treated with antidepressants. *Psychopharmacol Bull* 29(3):389-396, 1993 8121966
- de Montigny C, Aghajanian GK: Tricyclic antidepressants: long-term treatment increases responsivity of rat forebrain neurons to serotonin. *Science* 202(4374):1303-1306, 1978 725608

- DiMascio A, Heninger G, Klerman GL: Psychopharmacology of imipramine and desipramine: a comparative study of their effects in normal males. *Psychopharmacology (Berl)* 5:361-371, 1964 14151549
- Duman RS, Heninger GR, Nestler EJ: A molecular and cellular theory of depression. *Arch Gen Psychiatry* 54(7):597-606, 1997 9236543
- Eberhard G, von Knorring L, Nilsson HL, et al: A double-blind randomized study of clomipramine versus maprotiline in patients with idiopathic pain syndromes. *Neuropsychobiology* 19(1):25-34, 1988 3054623
- Evans DAP, Mahgoub A, Sloan TP, et al: A family and population study of the genetic polymorphism of debrisoquine oxidation in a white British population. *J Med Genet* 17(2):102-105, 1980 7381862
- Farmer RD, Pinder RM: Why do fatal overdose rates vary between antidepressants? *Acta Psychiatr Scand Suppl* 354:25-35, 1989 2589101
- Frank E, Kupfer DJ, Perel JM, et al: Three-year outcomes for maintenance therapies in recurrent depression. *Arch Gen Psychiatry* 47(12):1093-1099, 1990 2244793
- Furey ML, Drevets WC: Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 63(10): 1121-1129, 2006 17015814
- Geller B: Psychopharmacology of children and adolescents: pharmacokinetics and relationships of plasma/serum levels to response. *Psychopharmacol Bull* 27(4):401-409, 1991 1813890
- Gerson SC, Plotkin DA, Jarvik LF: Antidepressant drug studies, 1964 to 1986: empirical evidence for aging patients. *J Clin Psychopharmacol* 8(5):311-322, 1988 3053796
- Glassman AH, Bigger JT Jr: Cardiovascular effects of therapeutic doses of tricyclic antidepressants. A review. *Arch Gen Psychiatry* 38(7):815-820, 1981 7247643
- Glassman AH, Kantor SJ, Shostak M: Depression, delusions, and drug response. *Am J Psychiatry* 132(7):716-719, 1975 1094841
- Glassman AH, Perel JM, Shostak M, et al: Clinical implications of imipramine plasma levels for depressive illness. *Arch Gen Psychiatry* 34(2):197-204, 1977 843179
- Glassman AH, Bigger JT Jr, Giardina EV, et al: Clinical characteristics of imipramine-induced orthostatic hypotension. *Lancet* 1(8114):468-472, 1979 85056
- Glassman AH, Roose SP, Bigger JT Jr: The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. *JAMA* 269(20):2673-2675, 1993 8487453
- Goldberg RS, Thornton WE: Combined tricyclic-MAOI therapy for refractory depression: a review, with guidelines for appropriate usage. *J Clin Pharmacol* 18(2-3):143-147, 1978 342553
- Goodwin FK, Bunney WE Jr: Depressions following reserpine: a reevaluation. *Semin Psychiatry* 3(4):435-448, 1971 4154501
- Goodwin GM, Green AR, Johnson P: 5-HT<sub>2</sub> receptor characteristics in frontal cortex and 5-HT<sub>2</sub> receptor-mediated head-twitch behaviour following antidepressant treatment to mice. *Br J Pharmacol* 83(1):235-242, 1984 6237705
- Gram LF: Inadequate dosing and pharmacokinetic variability as confounding factors in assessment of efficacy of antidepressants. *Clin Neuropharmacol* 13 (suppl 1): S35-S44, 1990 2199035
- Greenblatt DJ, Moltke LL, Shader RI: Pharmacokinetics of psychotropic drugs, in *Geriatric Psychopharmacology*. Edited by Nelson JC. New York, Marcel Dekker, 1998, pp 27-41
- Greist JH, Jefferson JW, Kobak KA, et al: Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. *Arch Gen Psychiatry* 52(1):53-60, 1995 7811162
- Hammer W, Sjöqvist F: Plasma levels of monomethylated tricyclic antidepressants during treatment with imipramine-like compounds. *Life Sci* 6(17):1895-1903, 1967 6052684
- Himmelhoch JM, Detre T, Kupfer DJ, et al: Treatment of previously intractable depressions with tranylcypromine and lithium. *J Nerv Ment Dis* 155(3):216-220, 1972 5053920

- Himmelhoch JM, Thase ME, Mallinger AG, Houck P: Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry* 148(7):910-916, 1991 2053632
- Horst DA, Grace ND, LeCompte PM: Prolonged cholestasis and progressive hepatic fibrosis following imipramine therapy. *Gastroenterology* 79(3):550-554, 1980 7429116
- Ji L, Pan S, Marti-Jaun J, et al: Single-step assays to analyze CYP2D6 gene polymorphisms in Asians: allele frequencies and a novel \*14B allele in mainland Chinese. *Clin Chem* 48(7):983-988, 2002 12089164
- Jick H, Dinan BJ, Hunter JR, et al: Tricyclic antidepressants and convulsions. *J Clin Psychopharmacol* 3(3):182-185, 1983 6875026
- Jobson K, Linnoila M, Gillam J, Sullivan JL: Successful treatment of severe anxiety attacks with tricyclic antidepressants: a potential mechanism of action. *Am J Psychiatry* 135(7):863-864, 1978 665806
- Johannessen Landmark C, Henning O, Johannessen SI: Proconvulsant effects of antidepressants—What is the current evidence? *Epilepsy Behav* 61:287-291, 2016 26926001
- Katz IR, Simpson GM, Jethanandani V, et al: Steady state pharmacokinetics of nortriptyline in the frail elderly. *Neuropsychopharmacology* 2(3):229-236, 1989 2789662
- Katz IR, Simpson GM, Curlik SM, et al: Pharmacologic treatment of major depression for elderly patients in residential care settings. *J Clin Psychiatry* 51 (7 suppl):41-47, discussion 48, 1990 2195013
- Keller MB, Gelenberg AJ, Hirschfeld RMA, et al: The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. *J Clin Psychiatry* 59(11):598-607, 1998 9862606
- Klein DF: Delineation of two drug responsive anxiety syndromes. *Psychopharmacology (Berl)* 5:397-408, 1964 14194683
- Kocsis JH, Frances AJ, Voss C, et al: Imipramine treatment for chronic depression. *Arch Gen Psychiatry* 45(3):253-257, 1988 3277579
- Kuhn R: The treatment of depressive states with G 22355 (imipramine hydrochloride). *Am J Psychiatry* 115(5):459-464, 1958 13583250
- Kuhn R: The imipramine story, in *Discoveries in Biological Psychiatry*. Edited by Ayd FJ, Blackwell B. Philadelphia, PA, JB Lippincott, 1970, pp 205-217
- Kupfer DJ, Spiker DG: Refractory depression: prediction of non-response by clinical indicators. *J Clin Psychiatry* 42(8):307-312, 1981 7251567
- Lakoski JM, Aghajanian GK: Effects of ketanserin on neuronal responses to serotonin in the prefrontal cortex, lateral geniculate and dorsal raphe nucleus. *Neuropharmacology* 24(4):265-273, 1985 3158835
- Leonard HL, Swedo S, Rapoport JL, et al: Treatment of obsessive compulsive disorder in children and adolescents with clomipramine and desipramine: a double-blind crossover comparison. *Arch Gen Psychiatry* 46:1088-1092, 1989 2686576
- Lesch KP, Manji HK: Signal-transducing G proteins and antidepressant drugs: evidence for modulation of alpha subunit gene expression in rat brain. *Biol Psychiatry* 32(7):549-579, 1992 1333286
- Liang J, Liu X, Pan M, et al: Blockade of Nav1.8 currents in nociceptive trigeminal neurons contributes to anti-trigeminal nociceptive effect of amitriptyline. *Neuromolecular Med* 16(2):308-321, 2014 24292897
- Liebowitz MR, Quitkin FM, Stewart JW, et al: Phenelzine vs imipramine in atypical depression. *Arch Gen Psychiatry* 41:669-677, 1984 6375621
- Liebowitz MR, Quitkin FM, Stewart JW, et al: Antidepressant specificity in atypical depression. *Arch Gen Psychiatry* 45(2):129-137, 1988 3276282
- Livingston RL, Zucker DK, Isenberg K, Wetzel RD: Tricyclic antidepressants and delirium. *J Clin Psychiatry* 44(5):173-176, 1983 6853452
- Manji HK, Potter WZ, Lenox RH: Signal transduction pathways. Molecular targets for lithium's actions. *Arch Gen Psychiatry* 52(7):531-543, 1995 7598629

- Marek GJ, Carpenter LL, McDougale CJ, Price LH: Synergistic action of 5-HT<sub>2A</sub> antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. *Neuropsychopharmacology* 28(2):402-412, 2003 12589395
- Max MB, Lynch SA, Muir J, et al: Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 326(19):1250-1256, 1992 1560801
- McGrath PJ, Stewart JW, Harrison W, Quitkin FM: Treatment of tricyclic refractory depression with a monoamine oxidase inhibitor antidepressant. *Psychopharmacol Bull* 23(1):169-172, 1987 3602314
- Miller NL, Kocsis JH, Leon AC, et al: Maintenance desipramine for dysthymia: a placebo-controlled study. *J Affect Disord* 64(2-3):231-237, 2001 11313089
- Mochizuki D: Serotonin and noradrenaline reuptake inhibitors in animal models of pain. *Hum Psychopharmacol* 19 (suppl 1):S15-S19, 2004 15378668
- Montgomery SA: The efficacy of fluoxetine as an antidepressant in the short and long term. *Int Clin Psychopharmacol* 4 (suppl 1):113-119, 1989 2644336
- Moskovitz R, DeVane CL, Harris R, Stewart RB: Toxic hepatitis and single daily dosage imipramine therapy. *J Clin Psychiatry* 43(4):165-166, 1982 7068550
- Mowry JB, Spyker DA, Cantilena LR Jr, et al: 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. *Clin Toxicol (Phila)* 52(10):1032-1283, 2014 25559822
- Munjack DJ, Usigli R, Zulueta A, et al: Nortriptyline in the treatment of panic disorder and agoraphobia with panic attacks. *J Clin Psychopharmacol* 8(3):204-207, 1988 3379145
- Nelson JC: Use of desipramine in depressed inpatients. *J Clin Psychiatry* 45(10 Pt 2): 10-16, 1984 6384205
- Nelson JC: The use of antipsychotic drugs in the treatment of depression, in *Treating Resistant Depression*. Edited by Zohar J, Belmaker RH. New York, PMA Publishing, 1987, pp 131-146
- Nelson JC, Jatlow PI: Nonlinear desipramine kinetics: prevalence and importance. *Clin Pharmacol Ther* 41(6):666-670, 1987 3581650
- Nelson JC, Jatlow P, Quinlan DM, Bowers MB Jr: Desipramine plasma concentration and antidepressant response. *Arch Gen Psychiatry* 39(12):1419-1422, 1982 7149903
- Nelson JC, Jatlow PI, Quinlan DM: Subjective complaints during desipramine treatment. Relative importance of plasma drug concentrations and the severity of depression. *Arch Gen Psychiatry* 41(1): 55-59, 1984 6691785
- Nelson JC, Jatlow PI, Mazure C: Desipramine plasma levels and response in elderly melancholic patients. *J Clin Psychopharmacol* 5(4):217-220, 1985 4019810
- Nelson JC, Jatlow PI, Mazure C: Rapid desipramine dose adjustment using 24-hour levels. *J Clin Psychopharmacol* 7(2):72-77, 1987 3584524
- Nelson JC, Atillasoy E, Mazure C, Jatlow PI: Hydroxydesipramine in the elderly. *J Clin Psychopharmacol* 8(6):428-433, 1988a 3235701
- Nelson JC, Mazure C, Jatlow PI: Antidepressant activity of 2-hydroxydesipramine. *Clin Pharmacol Ther* 44(3):283-288, 1988b 3416551
- Nelson JC, Mazure CM, Jatlow PI: Characteristics of desipramine-refractory depression. *J Clin Psychiatry* 55(1):12-19, 1994 8294386
- Nelson JC, Mazure CM, Jatlow PI: Desipramine treatment of major depression in patients over 75 years of age. *J Clin Psychopharmacol* 15(2):99-105, 1995 7782495
- Nemeroff CB, DeVane CL, Pollock BG: Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 153(3):311-320, 1996 8610817
- Nibuya M, Nestler EJ, Duman RS: Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci* 16(7):2365-2372, 1996 8601816
- Nordin C, Bertilsson L, Siwers B: Clinical and biochemical effects during treatment of depression with nortriptyline: the role of 10-hydroxynortriptyline. *Clin Pharmacol Ther* 42(1):10-19, 1987 2439250



- O'Brien FE, Dinan TG, Griffin BT, Cryan JF: Interactions between antidepressants and P-glycoprotein at the blood-brain barrier: clinical significance of in vitro and in vivo findings. *Br J Pharmacol* 165(2):289-312, 2012 21718296
- O'Malley PG, Jackson JL, Santoro J, et al: Antidepressant therapy for unexplained symptoms and symptom syndromes. *J Fam Pract* 48(12):980-990, 1999 10628579
- Panerai AE, Monza G, Movilia P, et al: A randomized, within-patient, cross-over, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. *Acta Neurol Scand* 82(1):34-38, 1990 2239134
- Peck AW, Stern WC, Watkinson C: Incidence of seizures during treatment with tricyclic antidepressant drugs and bupropion. *J Clin Psychiatry* 44(5 Pt 2):197-201, 1983 6406457
- Peroutka SJ, Snyder SH: Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. *Science* 210(4465):88-90, 1980 6251550
- Pollock BG: Drug interactions, in *Geriatric Psychopharmacology*. Edited by Nelson JC. New York, Marcel Dekker, 1997, pp 43-60
- Potter WZ, Calil HM, Manian AA, et al: Hydroxylated metabolites of tricyclic antidepressants: preclinical assessment of activity. *Biol Psychiatry* 14(4):601-613, 1979 486616
- Powell WJ Jr, Koch-Weser J, Williams RA: Lethal hepatic necrosis after therapy with imipramine and desipramine. *JAMA* 206(3):642-645, 1968 4234079
- Prange AJ Jr: The pharmacology and biochemistry of depression. *Dis Nerv Syst* 25:217-221, 1964 14140032
- Preskorn SH, Irwin HA: Toxicity of tricyclic antidepressants—kinetics, mechanism, intervention: a review. *J Clin Psychiatry* 43(4):151-156, 1982 7068546
- Preskorn SH, Simpson S: Tricyclic-antidepressant-induced delirium and plasma drug concentration. *Am J Psychiatry* 139(6):822-823, 1982 7081500
- Preskorn SH, Beber JH, Faul JC, Hirschfeld RM: Serious adverse effects of combining fluoxetine and tricyclic antidepressants. *Am J Psychiatry* 147(4):532, 1990 2107764
- Preskorn SH, Alderman J, Chung M, et al: Pharmacokinetics of desipramine coadministered with sertraline or fluoxetine. *J Clin Psychopharmacol* 14(2):90-98, 1994 8195463
- Price LH, Nelson JC, Waltrip RW: Desipramine-associated hepatitis. *J Clin Psychopharmacol* 3(4):243-246, 1983 6886037
- Price LH, Nelson JC, Jatlow PI: Effects of desipramine on clinical liver function tests. *Am J Psychiatry* 141(6):798-800, 1984 6731623
- Priest BT, Kaczorowski GJ: Blocking sodium channels to treat neuropathic pain. *Expert Opin Ther Targets* 11(3):291-306, 2007 17298289
- Randrup A, Braestrup C: Uptake inhibition of biogenic amines by newer antidepressant drugs: relevance to the dopamine hypothesis of depression. *Psychopharmacology (Berl)* 53(3):309-314, 1977 408861
- Rapoport J, Potter WZ: Tricyclic antidepressants: use in pediatric psychopharmacology, in *Pharmacokinetics: Youth and Age*. Edited by Raskin A, Robinson D. Amsterdam, The Netherlands, Elsevier, 1981, pp 105-123
- Rapoport JL, Mikkelsen EJ, Zavadil A, et al: Childhood enuresis. II. Psychopathology, tricyclic concentration in plasma, and antienuretic effect. *Arch Gen Psychiatry* 37(10):1146-1152, 1980 7000030
- Reynolds CF 3rd, Butters MA, Lopez O, et al: Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Arch Gen Psychiatry* 68(1):51-60, 2011 21199965
- Richelson E, Nelson A: Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. *J Pharmacol Exp Ther* 230(1):94-102, 1984 6086881

- Riddle MA, Nelson JC, Kleinman CS, et al: Sudden death in children receiving Norpramin: a review of three reported cases and commentary. *J Am Acad Child Adolesc Psychiatry* 30(1):104-108, 1991 2005044
- Riddle MA, Geller B, Ryan N: Another sudden death in a child treated with desipramine. *J Am Acad Child Adolesc Psychiatry* 32(4):792-797, 1993 8340300
- Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: a meaningful difference. *J Clin Psychopharmacol* 1(5):316-319, 1981 6277997
- Roose SP, Glassman AH, Walsh BT, Woodring S: Tricyclic nonresponders: phenomenology and treatment. *Am J Psychiatry* 143(3):345-348, 1986 3953869
- Roose SP, Glassman AH, Giardina EG, et al: Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol* 7(4):247-251, 1987a 3114333
- Roose SP, Glassman AH, Giardina EG, et al: Tricyclic antidepressants in depressed patients with cardiac conduction disease. *Arch Gen Psychiatry* 44(3):273-275, 1987b 3827520
- Roose SP, Laghrissi-Thode F, Kennedy JS, et al: Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 279(4):287-291, 1998 9450712
- Rosenstein DL, Nelson JC: Heart rate during desipramine treatment as an indicator of beta<sub>1</sub>-adrenergic function. Society of Biological Psychiatry Scientific Program. *Biol Psychiatry* 29:132A, 1991
- Rosenstein DL, Nelson JC, Jacobs SC: Seizures associated with antidepressants: a review. *J Clin Psychiatry* 54(8):289-299, 1993 8253696
- Rudorfer MV, Potter WZ: The role of metabolites of antidepressant in the treatment of depression. *CNS Drugs* 7:273-312, 1997
- Rudorfer MV, Robins E: Amitriptyline overdose: clinical effects on tricyclic antidepressant plasma levels. *J Clin Psychiatry* 43(11):457-460, 1982 7174623
- Rudorfer MV, Young RC: Desipramine: cardiovascular effects and plasma levels. *Am J Psychiatry* 137(8):984-986, 1980 7416309
- Ryan ND: The pharmacologic treatment of child and adolescent depression. *Psychiatr Clin North Am* 15(1):29-40, 1992 1549547
- Salerno SM, Browning R, Jackson JL: The effect of antidepressant treatment on chronic back pain: a meta-analysis. *Arch Intern Med* 162(1):19-24, 2002 11784215
- Schildkraut JJ: The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 122(5): 509-522, 1965 5319766
- Schuckit M, Robins E, Feighner J: Tricyclic antidepressants and monoamine oxidase inhibitors. *Arch Gen Psychiatry* 24(6):509-514, 1971 5578096
- Schwaninger M, Schöfl C, Blume R, et al: Inhibition by antidepressant drugs of cyclic AMP response element-binding protein/cyclic AMP response element-directed gene transcription. *Mol Pharmacol* 47(6):1112-1118, 1995 7603449
- Shoaf SE, Linnoila M: Interaction of ethanol and smoking on the pharmacokinetics and pharmacodynamics of psychotropic medications. *Psychopharmacol Bull* 27(4):577-594, 1991 1813903
- Siris SG, van Kammen DP, Docherty JP: Use of antidepressant drugs in schizophrenia. *Arch Gen Psychiatry* 35(11):1368-1377, 1978 30429
- Spiker DG, Weiss AN, Chang SS, et al: Tricyclic antidepressant overdose: clinical presentation and plasma levels. *Clin Pharmacol Ther* 18(5 Pt 1):539-546, 1975 1183139
- Spiker DG, Weiss JC, Dealy RS, et al: The pharmacological treatment of delusional depression. *Am J Psychiatry* 142(4):430-436, 1985 3883815
- Sulser F, Vetulani J, Mobley PL: Mode of action of antidepressant drugs. *Biochem Pharmacol* 27(3):257-261, 1978 202286

- Szabo ST, Blier P: Effect of the selective noradrenergic reuptake inhibitor reboxetine on the firing activity of noradrenaline and serotonin neurons. *Eur J Neurosci* 13(11):2077-2087, 2001 11422448
- Tatsumi M, Groshan K, Blakely RD, Richelson E: Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol* 340(2-3):249-258, 1997 9537821
- Thase ME, Mallinger AG, McKnight D, Himmelhoch JM: Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *Am J Psychiatry* 149(2):195-198, 1992 1734739
- Thase ME, Fava M, Halbreich U, et al: A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. *Arch Gen Psychiatry* 53(9):777-784, 1996 8792754
- Thayssen P, Bjerre M, Kragh-Sørensen P, et al: Cardiovascular effect of imipramine and nortriptyline in elderly patients. *Psychopharmacology (Berl)* 74(4):360-364, 1981 6794083
- Tremblay P, Blier P: Catecholaminergic strategies for the treatment of major depression. *Curr Drug Targets* 7(2):149-158, 2006 16475956
- Uhr M, Tontsch A, Namendorf C, et al: Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. *Neuron* 57(2): 203-209, 2008 18215618
- von Moltke LL, Greenblatt DJ, Harmatz JS, et al: Psychotropic drug metabolism in old age: principles and problems of assessment, in *Psychopharmacology: The Fourth Generation of Progress*. Edited by Bloom FE, Kupfer DJ. New York, Raven, 1995, pp 1461-1469
- Walsh BT, Hadigan CM, Wong LM: Increased pulse and blood pressure associated with desipramine treatment of bulimia nervosa. *J Clin Psychopharmacol* 12(3):163-168, 1992 1629381
- Weaver GA, Pavlinac D, Davis JS: Hepatic sensitivity to imipramine. *Am J Dig Dis* 22(6):551-553, 1977 868834
- Weiss J, Dormann SM, Martin-Facklam M, et al: Inhibition of P-glycoprotein by newer antidepressants. *J Pharmacol Exp Ther* 305(1):197-204, 2003 12649369
- Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry* 144(11): 1403-1411, 1987 3314536
- Wilens TE, Biederman J, Baldessarini RJ, et al: Developmental changes in serum concentrations of desipramine and 2-hydroxydesipramine during treatment with desipramine. *J Am Acad Child Adolesc Psychiatry* 31(4):691-698, 1992 1644733
- Wilens TE, Biederman J, Prince J, et al: Six-week, double-blind, placebo-controlled study of desipramine for adult attention deficit hyperactivity disorder. *Am J Psychiatry* 153(9):1147-1153, 1996 8780417
- Yoshimura M, Furue H: Mechanisms for the anti-nociceptive actions of the descending noradrenergic and serotonergic systems in the spinal cord. *J Pharmacol Sci* 101(2):107-117, 2006 16766858
- Young RC, Alexopoulos GS, Shamoian CA, et al: Plasma 10-hydroxynortriptyline in elderly depressed patients. *Clin Pharmacol Ther* 35(4):540-544, 1984 6705454
- Yue QY, Zhong ZH, Tybring G, et al: Pharmacokinetics of nortriptyline and its 10-hydroxy metabolite in Chinese subjects of different CYP2D6 genotypes. *Clin Pharmacol Ther* 64(4):384-390, 1998 9797795
- Zitrin CM, Klein DF, Woerner MG: Treatment of agoraphobia with group exposure in vivo and imipramine. *Arch Gen Psychiatry* 37(1):63-72, 1980 6101535

# CHAPTER 10

## Fluoxetine

Jerrold F. Rosenbaum, M.D.

Dawn F. Ionescu, M.D.

The introduction of fluoxetine as the first selective serotonin reuptake inhibitor (SSRI) approved in the United States—initially for the treatment of depression—represents an important advance in psychopharmacology and has been the catalyst for much subsequent basic and clinical research. Considerable evidence has demonstrated that fluoxetine, like other SSRIs, has a broad spectrum of clinical indications. There is a consensus, however, that the commercial success of fluoxetine (and subsequently marketed SSRIs) derived from its advantageous safety profile, which propelled the SSRIs to dominance in the antidepressant drug market. Fluoxetine, under the brand name Prozac, became a cultural icon—a symbol of the growth in antidepressant prescribing and depression recognition. Consequently, it also became a focus of controversies about rare events attributed to side effects,

such as violent acts and suicide, and a symbol of the medicalization of mental health concerns. Fluoxetine was also the first of the SSRI blockbuster drugs to become available in generic form; ironically, with decreased cost came decreased market share, likely reflecting the reduction in marketing and availability of office samples. Although SSRIs, as a class, share several common features, individual agents (such as fluoxetine) also have unique characteristics.

---

## History and Discovery

---

Serotonin (5-HT) is an indoleamine with wide distribution in plants, animals, and humans. Pioneering histochemistry by [Falck et al. \(1962\)](#) found that 5-HT was localized within specific neuronal pathways and cell bodies. These originate principally from two discrete nuclei: the medial and dorsal raphe. Across animal species, 5-HT innervation is widespread. Although regional variations exist, several limbic structures manifest especially high levels of 5-HT ([Amin et al. 1954](#)).

However, the 5-HT levels in the central nervous system (CNS) represent only a small fraction of the 5-HT levels in the body ([Bradley 1989](#)). Because 5-HT does not cross the blood-brain barrier, it must be synthesized locally. 5-HT is released into the synapse from the cytoplasmic and vesicular reservoirs ([Elks et al. 1979](#)). Following its release, 5-HT is principally inactivated by reuptake into nerve terminals through a sodium/potassium ( $\text{Na}^+/\text{K}^+$ ) adenosine triphosphatase (ATPase)-dependent carrier ([Shaskan and Snyder 1970](#)). The transmitter is subsequently subject to

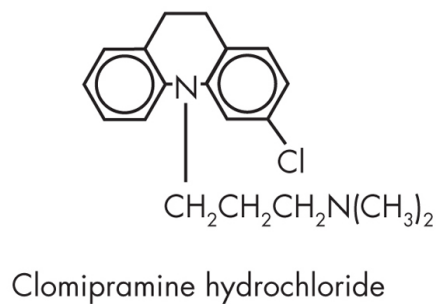
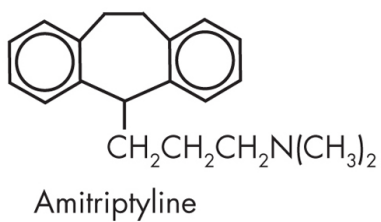
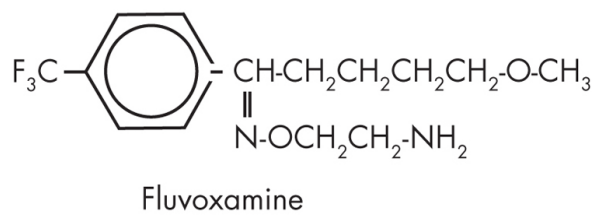
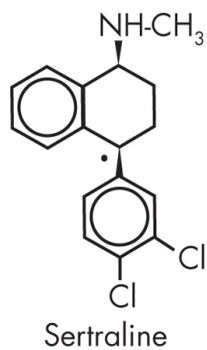
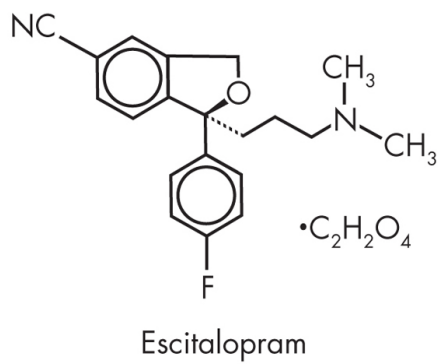
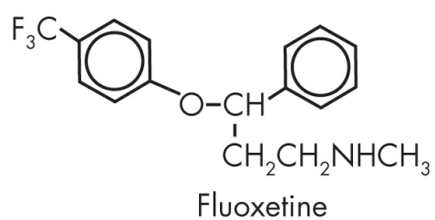
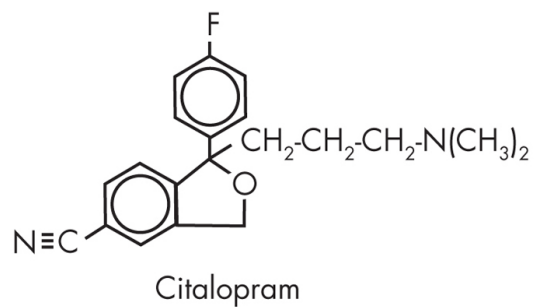
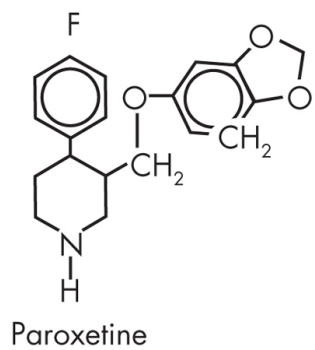
either degradation by monoamine oxidase (MAO) or vesicular restorage. Abnormalities in central 5-HT function have been hypothesized to underlie disturbances in mood, anxiety, satiety, cognition, aggression, and sexual drives, to highlight a few. As described by [Fuller \(1985\)](#), there are several loci at which therapeutic drugs might alter 5-HT neurotransmission. The explosion of knowledge regarding the serotonergic system can largely be traced to the development of compounds, such as fluoxetine, that block the reuptake of this neurotransmitter.

---

## Structure-Activity Relations

---

Drugs that inhibit 5-HT reuptake vary in their selectivity. Despite the tendency to lump the contemporary SSRIs into the same class designation, significant structural and activity differences exist. Their chemical structures help illustrate this diversity ([Figure 10-1](#)). In contrast to paroxetine and sertraline, which exist as single isomers, fluoxetine, like citalopram, is a racemate. The family of SSRIs manifests diverse structural and activity relations. Such data are in vitro and thus subject to methodological variability ([Thomas et al. 1987](#)). Fluoxetine is less potent than paroxetine in vitro and less selective for 5-HT reuptake inhibition (relative to norepinephrine) than citalopram. However, note that in vitro potency does not necessarily equate with in vivo dosing experience, clinical efficacy, or adverse-event profile.



---

**FIGURE 10-1.** Chemical structures of selective serotonin reuptake inhibitors and selected tricyclic antidepressants.

Although the tricyclic antidepressants (TCAs), like the SSRIs, antagonize 5-HT receptors ([Dempsey et al. 2005](#); [Eisensamer et al. 2003](#)), they also exhibit inhibitory activity at other receptor targets, mediating their adverse-event profile ([Hall and Ogren 1981](#); [Snyder and Yamamura 1977](#); [U'Prichard et al. 1978](#)). These other targets include histaminergic,  $\alpha_1$ -adrenergic, and muscarinic receptors. For fluoxetine, the median inhibitory concentration ( $IC_{50}$ ) at histaminergic and adrenergic sites is in the micromolar range and thus unlikely to be of clinical significance. Activity at the muscarinic receptor is negligible for fluoxetine. [Stauderman et al. \(1992\)](#) reported that fluoxetine and paroxetine inhibit the binding of  $^3H$ -labeled nitrendipine to L-type calcium channels; however, this was at concentrations that were probably in excess of those achieved during in vivo treatment of depression.

In summary, in vitro radioligand-binding techniques showed that fluoxetine had a lower probability of many of the troublesome side effects associated with TCAs and was relatively selective in its 5-HT reuptake inhibition.

---

## Pharmacological Profile

---

### Serotonin



The action of any SSRI extends beyond the inhibition of 5-HT reuptake. At least 14 different 5-HT receptor subtypes reside at pre- and postsynaptic locations ([Fuller 1996](#)). Serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) binding sites include both somatodendritic and presynaptic auto-receptors (which inhibit 5-HT firing) and postsynaptic receptors. The latter are predominantly hippocampal, and their sensitivity is increased after chronic antidepressant exposure ([Aghajanian et al. 1988](#); [Castro et al. 2003](#)).

After chronic administration, many antidepressants downregulate or reduce the density of serotonin<sub>2</sub> (5-HT<sub>2</sub>) binding sites in rat frontal cortex ([Peroutka and Snyder 1980](#)). Some, but not all, SSRIs have been associated with this effect ([Fraser et al. 1988](#)), and fluoxetine has been demonstrated to normalize 5-HT<sub>1A</sub> density in rats ([Sodero et al. 2006](#)). SSRIs, as a drug class, have been reported to normalize both 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptor density among patients with depression ([Leonard 1992](#)).

The mechanisms by which fluoxetine and other SSRIs interact with the human serotonin transporter (SERT) are not fully understood. Some evidence suggests that fluoxetine's effect on SERT is partially based on SERT promoter polymorphism; it can lead to increased or decreased SERT expression, depending on an individual's genotype ([Little et al. 2006](#)). Further studies have shown that SERT may also be inhibited at the posttranslational stage, likely through multiple binding sites on the SERT molecule itself ([Henry et al. 2006](#); [Iceta et al. 2007](#)).

Fluoxetine transiently inhibits dorsal raphe firing, decreases terminal autoreceptor function, and ultimately increases net 5-HT synaptic transmission within CA3 pyramidal cells in the hippocampus ([Blier et al. 1988](#)).

Electrophysiological studies indicate that most antidepressants enhance net 5-HT transmission after chronic administration ([Blier et al. 1990](#)), albeit at different loci: the TCAs via enhanced sensitivity of postsynaptic 5-HT<sub>1A</sub> receptors, and the SSRIs (and MAO inhibitors [MAOIs]) via reduced sensitivity of somatodendritic (5-HT<sub>1A</sub>) and terminal (serotonin<sub>1D</sub> [5-HT<sub>1D</sub>]) autoreceptors. SSRIs and TCAs also exert an inhibitory effect on serotonin<sub>3</sub> (5-HT<sub>3</sub>) receptors in a noncompetitive fashion ([Eisensamer et al. 2003](#)). These observations of different mechanisms may help to explain why certain depressive symptoms that do not respond to one class of antidepressant will respond to another class and may also explain the enhanced response reported when combinations of antidepressant agents are used.

## Norepinephrine

Chronic administration of most somatic treatments for depression downregulates or reduces the density of  $\beta$ -adrenergic binding sites in the brain ([Bergstrom and Kellar 1979](#)). These treatments include traditional norepinephrine-specific and mixed uptake inhibitors ([Charney et al. 1981](#)). However, results with the SSRIs have been less consistent ([Johnson 1991](#)). Despite its in vitro 5-HT selectivity, fluoxetine has been observed, with autoradiography, to induce  $\beta$ -adrenergic receptor downregulation. It has also been shown in at least one study to increase extracellular norepinephrine concentrations in rat prefrontal cortex after acute systemic administration; this effect was not observed with other SSRIs tested ([Bymaster et al. 2002](#)). Fluoxetine has also

been demonstrated to potentiate the noradrenergic effects of bupropion ([Li et al. 2002](#)).

Most studies with SSRIs have not shown a consistent change in  $\beta$ -adrenergic binding or  $\beta$ -adrenergic-stimulated cyclic adenosine monophosphate (cAMP) production. However, [Baron et al. \(1988\)](#) reported that fluoxetine, when it was coadministered with desipramine, augmented the reduction in cortical  $\beta$ -adrenergic receptors expected with desipramine alone. In contrast, investigations with fluvoxamine, paroxetine, and citalopram have not yielded consistent results. In general, the greater the 5-HT selectivity of a compound, the less in vitro evidence for  $\beta$ -adrenergic downregulation has been seen. Thus,  $\beta$ -adrenergic downregulation may not be essential for clinical efficacy.

Current data do not support a significant effect on  $\alpha$ -adrenergic receptor affinity or density by the SSRIs. Studies using radiolabeling to investigate fluoxetine ([Wong et al. 1985](#)) have shown relative inactivity at this site. Fluoxetine has been reported to reduce desipramine-induced release of growth hormone after 4 weeks of treatment ([O'Flynn et al. 1991](#)). This effect suggests possible indirect activity at the  $\alpha_2$ -adrenergic receptor.

In summary, although relative differences in adrenoceptor affinity exist across the SSRI class, and fluoxetine may have more adrenergic activity than some of the other SSRIs, the clinical significance of these differences appears to be negligible.

## Dopamine

Animal studies provide evidence that the serotonergic system may exert tonic inhibition on the central dopaminergic system. Serotonin has also been shown to decrease the generation of dopaminergic cells from mesencephalic precursors in rats, an effect mediated by serotonin<sub>4</sub> (5-HT<sub>4</sub>) and serotonin<sub>7</sub> (5-HT<sub>7</sub>) receptors found on glial cells ([Parga et al. 2007](#)). Thus, fluoxetine might diminish dopaminergic transmission, consistent with anecdotes of extrapyramidal side effects (EPS) occurring during fluoxetine therapy ([Bouchard et al. 1989](#)). 5-HT agonists, however, also exert a facilitatory influence on dopamine release ([Benloucif and Galloway 1991](#)), which can be antagonized by the 5-HT<sub>1</sub> blocker pindolol, and evidence suggests that SSRIs may actually sensitize mesolimbic dopamine receptors ([Arnt et al. 1984a, 1984b](#)). Furthermore, repeated administration of fluoxetine, citalopram, or paroxetine to rats increased spontaneous dopaminergic neuronal activity ([Sekine et al. 2007](#)), and chronic fluoxetine treatment also increased brain-derived neurotrophic factor (BDNF) expression within rat dopaminergic regions ([Molteni et al. 2006](#)).

## Summary of Neurotransmitter Effects

Fluoxetine enhances central 5-HT transmission through increased output and/or increased postsynaptic receptor sensitivity ([Blier et al. 1987](#)). Fluoxetine's overall effects on the noradrenergic and dopaminergic systems are less straightforward and are also less likely to play a role in the drug's antidepressant effects. However, such changes

alone, in any of the neurotransmitter systems, do not guarantee a clinically meaningful response ([Charney et al. 1984](#)). A change in baseline 5-HT function or a “permissive” set of interactions with other collocated neurotransmitter receptors is likely involved in the highly individualized responses in patients with depression.

---

## Pharmacokinetics and Disposition

---

Considerable pharmacokinetic variability exists within the SSRI class ([Leonard 1992](#)). Of particular note, discussion of drug half-life must also include consideration of the presence or absence of active metabolites. Fluoxetine is extensively metabolized by the liver’s cytochrome P450 (CYP) system to its active metabolite, norfluoxetine. Fluoxetine is a potent CYP2D6 inhibitor, and norfluoxetine has a moderate inhibitory effect on CYP3A4 ([Hemeryck and Belpaire 2002](#)). The elimination half-life of norfluoxetine (4–16 days) is significantly longer than that of fluoxetine (4–6 days); in fact, norfluoxetine’s half-life is the longest of any of the SSRIs or their active metabolites. Half-life is not significantly affected by hemodialysis or renal impairment ([Aronoff et al. 1984](#)).

The relatively long half-life of fluoxetine confers greater protection from the discontinuation syndrome that is associated with abrupt discontinuation or noncompliance related to interruption of treatment than more rapidly cleared SSRIs. Conversely, more prolonged vigilance for drug-drug interactions following discontinuation is required for fluoxetine; for example, a 5-week washout

from fluoxetine is recommended before initiating an MAOI (Ciraulo and Shader 1990; Lane and Baldwin 1997). Variability in drug half-life is associated with a range in time to steady-state plasma concentrations, which does not clearly predict or correlate with onset of antidepressant activity.

---

## Mechanism of Action

---

In the absence of pharmacological manipulation, the reuptake of 5-HT into the presynaptic nerve terminal typically leads to its inactivation. Fluoxetine, through blockade of the reuptake process, acutely enhances serotonergic neurotransmission by permitting 5-HT to act for an extended period of time at synaptic binding sites. A net result is an acute increase in synaptic 5-HT. One difference separating SSRIs from direct-acting agonists is that SSRIs are dependent on neuronal release of 5-HT for their action—that is, SSRIs can be considered augmenters of basal physiological signals, but they are not direct stimulators of postsynaptic receptor function, and they are dependent on presynaptic neuronal integrity. These pharmacodynamic features might explain SSRI nonresponse. If the release of 5-HT from presynaptic neuronal storage sites is substantially compromised and, in turn, if net synaptic 5-HT concentration is negligible, a clinically meaningful response to an SSRI would not be expected.

Serotonin receptors also include a family of presynaptic autoreceptors that suppresses the further release of 5-HT, thus limiting the degree of postsynaptic receptor

stimulation that can be achieved. [de Montigny et al. \(1989\)](#) investigated the mechanism of action of several SSRIs and suggested that the enhanced efficacy of serotonergic synaptic transmission is not the result of increased postsynaptic sensitivity. Rather, longer-term SSRI treatment induced a desensitization of somatodendritic and terminal 5-HT autoreceptors. This desensitization would permit 5-HT neurons to reestablish a normal rate of firing, despite sustained reuptake blockade. These neurons could then release a greater amount of 5-HT (per impulse) into the synaptic cleft. This modification reportedly occurs over a time course that is compatible with the antidepressant response.

---

## Indications and Efficacy

---

The U.S. Food and Drug Administration (FDA)-labeled indications for fluoxetine are major depressive disorder, obsessive-compulsive disorder (OCD), panic disorder, bulimia nervosa, and premenstrual dysphoric disorder (PMDD). We will review these as well as some other disorders for which fluoxetine is commonly used.

### Major Depressive Disorder

Placebo-controlled, double-blind trials have established the superiority of fluoxetine over placebo in depression ([Kasper et al. 1992](#)). Statistically significant reductions from baseline in the Hamilton Rating Scale for Depression (Ham-D; [Hamilton 1960](#)) score have been seen as early as the second week of treatment; however, the rate and quality of

response to any SSRI are highly individualized (range, 10–42 days). Overall, the efficacy of fluoxetine has been found to be comparable to or slightly better than that of the conventional TCAs ([Cipriani et al. 2005](#); [Wernicke et al. 1987](#)) and comparable to that of venlafaxine ([Nemeroff et al. 2007](#); [Schatzberg and Roose 2006](#)). Notwithstanding, in a survey of 439 clinicians, about one-quarter indicated that they believed SSRIs to be the most efficacious antidepressant class, despite a lack of clear empirical evidence ([Petersen et al. 2002](#)). Within the class of SSRIs, there is no clear and consistent evidence for superior effectiveness of one agent over another in primary care settings ([Kroenke et al. 2001](#)).

In general, the range for dose titration with most SSRIs is relatively narrow, and higher dosages are more often associated with increased adverse events ([Altamura et al. 1988](#); [Amin et al. 1989](#)). [Schweizer et al. \(1990\)](#) reported that in a study of 108 subjects treated with 20 mg of fluoxetine for 3 weeks and then randomly assigned to receive either 20 mg or 60 mg for another 5 weeks, both groups did equally well after 8 weeks.

However, early implementation of high-dose therapy may be appropriate in some circumstances. Conversion of nonresponders by prescribing at the higher end of the dose range has been described with fluoxetine ([Fava et al. 1992](#)). Unfortunately, plasma-level studies have contributed little to the understanding of the dose–response relationship. Most studies have failed to confirm any relationship between clinical response and plasma concentration with fluoxetine ([Kelly et al. 1989](#)). This suggests that synaptic concentrations and/or pharmacodynamic effects are not accurately reflected by plasma levels.



Continued efficacy of fluoxetine during maintenance therapy has been established in several trials ([Danion 1989](#); [Dufour 1987](#); [Ferrey et al. 1989](#); [Montgomery et al. 1988](#); [Reimherr et al. 1998](#)). One trial reported a recurrence in 54 of 94 placebo subjects (57%) versus 23 of 88 fluoxetine-maintained subjects (26%) ( $P < 0.0001$ ) who had at least 4.5 months of recovery before randomization ([Montgomery et al. 1988](#)). Study participants were required to have had at least two previous episodes.

Although fluoxetine is perceived as “activating,” considerable evidence supports its utility in depression with anxious features. [Montgomery \(1989a\)](#) conducted a meta-analysis of several fluoxetine trials that indicated efficacy in depression featuring anxiety and psychomotor agitation. Similar findings have been reported by [Jouvent et al. \(1989\)](#) and [Beasley et al. \(1991\)](#).

In an attempt to improve compliance with long-term antidepressant treatment, a once-weekly formulation of fluoxetine was developed and approved. Although the concept appears reasonable and the preparation, a once-weekly enteric-coated 90-mg tablet, is safe and efficacious for continuation treatment ([Schmidt et al. 2000](#)), this formulation has not attracted widespread use, which suggests that a once-daily formulation may be convenient enough for most patients.

## Obsessive-Compulsive Disorder

Clomipramine, a potent inhibitor of both 5-HT and norepinephrine reuptake, was observed more than 30 years ago to reduce obsessive-compulsive symptoms ([Van Renynghe de Voxvrie 1968](#)). The superior benefit of this

potent serotonergic TCA over desipramine represents a cornerstone in the 5-HT hypothesis of OCD ([Benkelfat et al. 1989](#)). Fluoxetine has been shown to be effective in OCD independent of a patient's comorbid mood status ([Jenike et al. 1989](#)). Patients who have OCD may require higher doses of medication and longer treatment periods than do patients with depression to determine response. Currently, clomipramine and the SSRIs are considered to be the first-line agents for treatment of OCD ([Kaplan and Hollander 2003](#)).

Because OCD is a chronic disorder, prolonged fluoxetine therapy may be necessary. In patients whose symptoms have been minimally or only moderately reduced with SSRI treatment, numerous augmentation strategies have been proposed and include tryptophan, fenfluramine, lithium, buspirone, trazodone, or an antipsychotic (see [Goodman et al. 1992](#)). In addition, fluoxetine has shown efficacy in children and adolescents with OCD ([Geller et al. 2001](#)). In so-called OCD spectrum disorders (now grouped, in DSM-5 [[American Psychiatric Association 2013](#)], under obsessive-compulsive and related disorders), such as skin picking ([Bloch et al. 2001](#)) and body dysmorphic disorder ([Phillips et al. 2002](#)), controlled trials also indicate efficacy for fluoxetine.

## Panic Disorder

SSRIs are the drugs of choice in the prevention of panic attacks and in the treatment of panic disorder. Positive results from double-blind, placebo-controlled trials in patients with panic disorder are available for fluoxetine ([Michelson et al. 2001](#)). In general, patients with panic

disorder need a low initial dose of fluoxetine (e.g., 10 mg); however, often usual antidepressant dosing for optimal response (e.g., 20–80 mg) is required. The initial low dose serves to minimize early side effects in anxious patients who are particularly sensitive to somatic symptoms of anxiety, and it sets the stage for long-term compliance. The recurrent and chronic nature of panic disorder requires individual medication regimens that may include multiple agents as well as variable dosages.

## Eating Disorders

Manipulation of central 5-HT results in significantly altered feeding behaviors (e.g., an increased satiety response) ([Carruba et al. 1986](#)). [Blundell \(1986\)](#) reported that pharmacological enhancement of 5-HT reduced meal size, rate of eating, and body weight. The predominant locus of this 5-HT effect is likely within the hypothalamus and may be mediated through gene expression of neuropeptide Y (NPY) and pro-opiomelanocortin (POMC) ([Myung et al. 2005](#)). In general, the ability of an antidepressant to diminish appetite and, in turn, to reduce weight is related to its ability to block 5-HT uptake ([Angel et al. 1988](#)).

### **Bulimia Nervosa**

Agents with at least some degree of 5-HT uptake inhibition have been useful in bulimia nervosa (see [Brewerton et al. 1990](#)). Clinical trials with fluoxetine have found a positive treatment effect on binge eating and purging behaviors ([Goldstein et al. 1995](#)). In a large placebo-controlled trial, [Enas et al. \(1989\)](#) studied dosing of 20 mg versus 60 mg of fluoxetine in 382 female outpatients with bulimia. A clinical

benefit was observed in binge frequency, purging, mood, and carbohydrate craving. In a smaller study of 91 female patients in a primary care setting, women assigned to receive fluoxetine kept more physician appointments, exhibited greater reductions in binge eating and vomiting, and had a greater improvement in psychological symptoms than those assigned to receive placebo ([Walsh et al. 2004](#)). Continued treatment with fluoxetine is associated with improvement and decreased risk of relapse ([Romano et al. 2002](#)).

## **Anorexia Nervosa**

Pharmacological trials with SSRIs in patients with anorexia nervosa have been relatively sparse. [Kaye et al. \(1991\)](#) suggested that fluoxetine may help maintain body weight in patients with anorexia nervosa who have gained weight. This group also completed a similar study with fluoxetine under controlled conditions, suggesting some benefit for fluoxetine in improving outcome and preventing relapse ([Kaye et al. 2001](#)). On the other hand, [Walsh et al. \(2006\)](#) found no benefit for continued treatment with fluoxetine after weight restoration in a randomized, double-blind, placebo-controlled trial of 93 patients. Efficacy of SSRIs has been linked to the food obsessions of many patients with eating disorders.

## **Premenstrual Dysphoric Disorder**

Several randomized, blinded, placebo-controlled trials that used various diagnostic criteria and outcome measures have established the efficacy and tolerability of fluoxetine in the treatment of PMDD ([Menkes et al. 1993](#); [Pearlstein et](#)

al. 1997; Steiner et al. 1995; Su et al. 1993, 1997; Wood et al. 1992). In the largest study, 313 women with DSM-III-R late luteal phase dysphoric disorder ([American Psychiatric Association 1987](#)) received 20 mg of fluoxetine, 60 mg of fluoxetine, or placebo daily for six menstrual cycles after a two-cycle placebo washout period ([Steiner et al. 1995](#)). One hundred eighty women completed the study. Both doses of fluoxetine were superior to placebo, beginning at the first menstrual cycle and continuing throughout the six cycles. More patients treated with 60 mg of fluoxetine discontinued because of adverse events than did patients treated with 20 mg of fluoxetine or placebo. More patients treated with placebo discontinued because of lack of response than did patients treated with either fluoxetine dose. In a subsequent study of 34 women, fluoxetine was significantly superior to bupropion and placebo in treating PMDD ([Pearlstein et al. 1997](#)).

## Anger and Aggression

Diminished serotonergic activity has been implicated in the personality features of impulsivity, anger, hostility, and aggression ([Coccaro et al. 1989](#)). These clinical attributes best associate with DSM-IV ([American Psychiatric Association 1994](#)) Cluster B personality disorders. Fluoxetine reduced impulsivity in small groups of patients with borderline personality disorder ([Cornelius et al. 1991](#); [Norden 1989](#)). Fluoxetine significantly reduced anger attacks in patients with and without depression ([Fava et al. 1991, 1993, 1996](#); [Rubey et al. 1996](#); [Salzman et al. 1995](#)).

# Posttraumatic Stress Disorder

Fluoxetine significantly reduced symptoms of posttraumatic stress disorder (PTSD), compared with placebo, in 64 patients (veterans and nonveterans), as measured by the Clinician-Administered PTSD Scale (CAPS; [van der Kolk et al. 1994](#)). It also showed efficacy by week 6 in a large double-blind, placebo-controlled trial ([Martenyi et al. 2002](#)).

## Premature (Early) Ejaculation

SSRIs, including fluoxetine, are effective in the treatment of premature ejaculation, although increased latency to ejaculation is highest with paroxetine ([Waldinger et al. 1998](#)). In a 1-year follow-up study, patients treated with fluoxetine (20 mg/day or less) in combination with sexual behavior therapy reported significant improvement in ejaculation latency ([Graziottin et al. 1996](#)). Another study demonstrated efficacy from a weekly fluoxetine dose of 90 mg ([Manasia et al. 2003](#)). Clear-cut dosing recommendations have not been clarified, however, and titration (upward or downward) may be necessary.

## Pain Syndromes

Fluoxetine has shown efficacy in reducing pain associated with diabetic neuropathy ([Max et al. 1992](#)). Fluoxetine (20 mg/day) improved scores on measures of pain and discomfort in subjects with fibromyalgia, compared with subjects on placebo ([Arnold et al. 2002](#); [Goldenberg et al. 1996](#)). The effect of fluoxetine combined with amitriptyline was superior to the effect of either agent used alone.

Fluoxetine reduced the number of attacks in patients with migraine headaches ([Saper et al. 1994](#)). More recent work has demonstrated that antidepressants that also affect the norepinephrine system (i.e., serotonin-norepinephrine reuptake inhibitors [SNRIs]) are more effective than the SSRIs in treating neuropathic pain ([Mochizuki 2004](#); [Pedersen et al. 2005](#)). In fact, the SNRI duloxetine has received FDA approval for the treatment of neuropathic pain.

## Alcohol Use Disorder

A substantial amount of evidence supports a 5-HT dysfunction in alcohol abuse and dependence. Animal studies have shown that increased 5-HT levels reduce alcohol consumption ([Farren 1995](#)). For example, [Murphy et al. \(1988\)](#) reported beneficial effects with fluoxetine and fluvoxamine in reducing alcohol intake in a rat model.

Although results are not consistent, some clinical trials with SSRIs have reported reduced alcohol consumption in patients with and without depression, in contrast to patients treated with TCAs, which have less robust efficacy ([Cornelius et al. 1997](#); [Lejoyeux 1996](#)). A precise mechanism for the role of SSRIs in the treatment of alcohol dependence is not understood. To date, the beneficial effect, if any, appears to be independent of antidepressant activity ([Naranjo et al. 1986, 1990](#)). More work is needed to determine the specific patient subpopulations that might benefit most from SSRIs (see [Gorelick 1989](#)).

From a risk-benefit assessment, it is reassuring that fluoxetine does not appear to potentiate the effects of ethanol ([Lemberger et al. 1985](#)) and does not carry a high

risk of fatal poisoning when taken in combination with alcohol ([Koski et al. 2005](#)). SSRIs may help selected patients with alcohol dependence in recovery when these drugs are used as part of a multifaceted treatment program.

## Obesity

SSRIs have been extensively investigated for an effect on food consumption. This interest stems from evidence that perturbation of 5-HT receptors modifies animal feeding behavior ([Garattini et al. 1986](#)). This modification appears to be independent of a local gastrointestinal effect (e.g., the perception of nausea). 5-HT innervation to the hypothalamus influences satiety and may selectively affect carbohydrate consumption ([Wurtman et al. 1981](#)). In one large trial, 458 patients were treated for 52 weeks with fluoxetine (60 mg/day) or placebo ([Goldstein et al. 1994](#)). Weight loss was significantly greater in the fluoxetine-treated group at 28 weeks, but not at 52 weeks. Long-term benefits may be better sustained when fluoxetine is combined with behavior modification ([Marcus et al. 1990](#)).

The broad involvement of the serotonergic system in modulating behavior and cognition supports the wide potential utility of SSRIs.

## Other Medical Conditions

Fluoxetine has been evaluated and observed to be efficacious in a variety of conditions, including poststroke depression and motor dysfunction, fibromyalgia, chronic pain, migraine, hot flashes in menopause, repetitions and



compulsions in autism spectrum disorder, and depression in cancer patients. It has also proved useful in some patients with chronic fatigue syndrome. Interestingly, fluoxetine also appears to have antiviral properties ([Zuo et al. 2012](#)).

---

## Side Effects and Toxicology

---

Safety and a favorable side-effect profile, as well as the lack of multiple receptor affinity that mediates adverse events associated with TCAs, distinguish fluoxetine and other SSRIs from TCAs. Medications in the SSRI class generally have similar side-effect profiles.

For most patients, SSRIs are better tolerated than TCAs, based on the number of early trial discontinuations attributable to an adverse event (see [Boyer and Feighner 1991](#)). In general, for three-arm trials, the incidence of early discontinuation due to an adverse event was 5%–10% for placebo, 10%–20% for SSRIs, and 30%–35% for TCAs. The SSRIs, presumably by enhancement of 5-HT within the CNS, may induce agitation, anxiety, sleep disturbance, tremor, sexual dysfunction (primarily anorgasmia), or headache. Baseline clinical features do not appear to predispose patients to these adverse events ([Montgomery 1989b](#)). Although CNS adverse events may occur with SSRIs, [Kerr et al. \(1991\)](#) suggested that these drugs have a more favorable profile of behavioral toxicity overall than do conventional TCAs.

Because the enteric nervous system is richly innervated by 5-HT, adverse events may include altered gastrointestinal motility and nausea. Certain autonomic adverse events, including dry mouth, sweating, and weight

change, also occur. Furthermore, the use of SSRIs (including fluoxetine) during the perioperative period has been associated with a higher risk of adverse events, particularly bleeding events; however, the extent to which patient factors (e.g., medical illness) as opposed to SSRIs themselves are responsible for the elevated risks remains unknown ([Auerbach et al. 2013](#)). Fluoxetine decreases rapid eye movement (REM) and increases non-rapid eye movement (NREM) sleep at dosage ranges of 5–40 mg/kg in rodent models ([Gao et al. 1992](#)). This is a common property of many antidepressant medications. Of interest, fluoxetine induces higher rates of sedation as dosages are increased.

As was discussed earlier in this chapter (see section “Summary of Neurotransmitter Effects”), fluoxetine is unlikely to alter dopamine function; nonetheless, some side effects, such as hyperprolactinemia, extrapyramidal symptoms, sexual and cognitive dysfunction, galactorrhea, mammary hypertrophy, and gynecomastia, have been attributed to SSRI effects on the dopaminergic system ([Damsa et al. 2004](#)). Anecdotal reports of EPS ([Meltzer et al. 1979](#)) associated with SSRIs are not more frequent than those reported historically with TCAs ([Fann et al. 1976](#); [Zubenko et al. 1987](#)), MAOIs ([Teusink et al. 1984](#)), or trazodone ([Papini et al. 1982](#)). Very rare events, including arthralgia, lymphadenopathy, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, agranulocytosis, and hypoglycemia, have been reported during clinical trials or postmarketing surveillance; however, causality typically is uncertain.

One additional rare and life-threatening event associated with all SSRIs (and more prominently, their interaction with MAOIs or other 5-HT enhancers) is the central 5-HT syndrome. This phenomenon appears to represent an

overactivation of central 5-HT receptors and may manifest with features such as abdominal pain, diarrhea, sweating, fever, tachycardia, elevated blood pressure, altered mental state (e.g., delirium), myoclonus, increased motor activity, irritability, hostility, and mood change. Severe manifestations of this syndrome can induce hyperpyrexia, cardiovascular shock, or death. When a switch is being made from an SSRI to an MAOI, drug half-life (and that of any active metabolite, where applicable) should serve as a guide to the length of the washout period. A standard recommendation is to wait at least five times the half-life of the SSRI or its metabolite, whichever is longer, before administering the next serotonergic agent (for a review, see [Lane and Baldwin 1997](#)). For fluoxetine, this means a minimum 5-week washout period.

Tolerance to an adverse event may change with dose and/or length of exposure; higher doses are typically associated with higher rates of adverse events ([Bressa et al. 1989](#)). Many events, such as activation, are transient, usually beginning early in the course of therapy and then remitting ([Beasley et al. 1991](#)). Comparisons between A.M. and P.M. administration did not identify differences in efficacy ([Usher et al. 1991](#)). Individual patient differences suggest the need for some flexibility in dosing schedules. TCAs behave like type IA antiarrhythmics; therefore, in a dose-dependent fashion, they may retard His-Purkinje conduction. SSRIs are essentially devoid of this property. In clinical trials, the incidence of increased heart rate or conduction disturbance has been very low with fluoxetine ([Fisch 1985](#)). For a review of the relative side-effect profiles of TCAs and SSRIs, see the article by [Brambilla et al. \(2005\)](#).

---

## Specific Issues

---

### Suicidality

Evidence implicating 5-HT in suicide or violence is compelling. Reduced cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations correlate highly with completed suicides in patients with depression (Edman et al. 1986; Ninan et al. 1984). In vitro binding assays have shown an increased density ( $B_{\max}$ ) of 5-HT<sub>2</sub> receptors in individuals with depression and suicidal tendencies (Pandey et al. 1990). Both observations are consistent with a relative state of 5-HT depletion among subjects with suicidal tendencies. The American College of Neuropsychopharmacology (1992) reviewed evidence showing that antidepressants result in substantial improvement or remission of suicidal ideation and impulses in the vast majority of patients; SSRIs were thought to potentially “carry a lower risk for suicide than older tricyclic antidepressants” (p. 181) when taken in overdose. Furthermore, the task force stated that no evidence indicated that SSRIs triggered emergent suicidal ideation above base rates associated with depression. In addition, Warshaw and Keller (1996) determined that fluoxetine use did not increase the rate of suicide in a group of 654 patients with anxiety disorders. In a large retrospective review of patients receiving one or more of 10 antidepressants (including fluoxetine), Jick et al. (1995) concluded that the risk for suicide was similar among all agents.

Concern about suicidality surged in 2003 after the industry alerted the FDA that there might be an increased risk of suicide-related adverse events in children being treated with paroxetine. The FDA's review of available data found that approximately 4% of children taking SSRI medications reported or exhibited suicidal thinking or behavior (including suicide attempts)—twice the rate of those taking placebo. No completed suicides occurred among nearly 2,200 children treated with SSRIs, however.

The FDA's review was followed by a number of other studies examining this issue, including a meta-analysis of 24 pediatric trials of nine antidepressant drugs by [Hammad et al. \(2006\)](#). These authors found a modestly increased risk of suicidality (risk ratio=1.66) for SSRIs in depression trials (95% confidence interval=1.02-2.68). This risk must be balanced against the benefit—in the form of general improvement in mood and overall functioning—experienced by most depressed patients when they are placed on antidepressant therapy. In most cases, the therapeutic benefit of SSRIs will outweigh the risk of increased suicidal thoughts or behaviors ([Bridge et al. 2007](#)).

## Black Box Warning

On March 22, 2004, the FDA issued a public health advisory warning of the risk of worsened depression and suicidality in children and adolescents being treated with antidepressant medications. This was followed by placement of a black box warning on the packaging of all antidepressant medications, revised in 2006 to include adults through age 25 years (for the full text of the 2007 revision, see

<http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm173233.pdf>). After the black box warning was placed, prescriptions for antidepressants went down, and suicide attempts in children and adolescents increased. After antidepressant prescriptions dropped, suicide attempts increased by 22% in adolescents and by 34% in young adults (Lu et al. 2014).

## Use in Pregnancy and Lactation

Given the widespread use of SSRIs and the high prevalence of mood disorders during the childbearing years, it is likely that these agents are being used during pregnancy and breast-feeding. Published information about the use and safety of SSRIs in this special population is greatest for fluoxetine. Goldstein et al. (1997) evaluated the outcomes of 796 prospectively identified pregnancies with confirmed first-trimester exposure to fluoxetine. Historical reports of newborn surveys were used for comparison. Abnormalities were observed in 5% of the fluoxetine-exposed newborns, which was consistent with rates in historical controls. A review of the literature showed a statistically increased risk of persistent pulmonary hypertension of the newborn for infants exposed to SSRIs in late pregnancy, although clinically the absolute risk was low (Grigoriadis et al. 2014). A longitudinal observational study found no differences in growth variables (weight, length, head circumference) from birth to 12 months of age between infants exposed to SSRIs and those not exposed (Wisner et al. 2013). Pregnancy outcomes and follow-up cognitive and behavioral assessments for 135 children exposed in utero to a TCA or fluoxetine (55 infants) were compared with those for

children in a control group of mother–infant pairs ([Nulman et al. 1997](#)). The incidence of major malformations and perinatal complications was similar among the three groups. No statistically significant differences in mean global intelligence quotient (IQ) scores or language development were found in the children of mothers who received a TCA or fluoxetine compared with the children of control mothers. There were also no differences among the groups on several behavioral assessments. The results of children exposed during the first trimester were not different from those of children exposed throughout the pregnancy. Prospectively derived data are not available for paroxetine, sertraline, fluvoxamine, or citalopram. A recent study failed to find a significant association between risk of autism spectrum disorders in offspring and maternal use of SSRIs—including fluoxetine—during pregnancy ([Hviid et al. 2013](#)).

Fluoxetine is secreted into breast milk ([Hendrick et al. 2001](#)). The implications of this minimal exposure are unclear, but one naturalistic study ([Taddio et al. 1996](#)) and two case reports ([Burch and Wells 1992](#); [Isenberg 1990](#)), involving a total of 13 infants, noted no adverse effects in these infants during the short-term study periods. One case report did describe adverse events in a breast-fed infant whose mother was taking fluoxetine ([Lester et al. 1993](#)).

## SSRI Discontinuation Syndrome

Discontinuation symptoms have been described with several classes of antidepressants, including TCAs and MAOIs. SSRI discontinuation symptoms have been reported most frequently with paroxetine (short elimination half-life

and no active metabolite) and least frequently with fluoxetine (long elimination half-lives of parent compound and active metabolite) ([Haddad 1997](#); [Stahl et al. 1997](#)). SSRIs are not drugs of abuse; when these agents are discontinued, patients show neither the characteristic abstinence syndrome of CNS-depressant withdrawal nor drug-seeking behavior. The most common physical symptoms are dizziness, nausea and vomiting, fatigue, lethargy, flulike symptoms (e.g., aches and chills), and sensory and sleep disturbances. The psychological symptoms most commonly reported are anxiety, irritability, and crying spells. For most patients, the discontinuation symptoms are different from the adverse effects that they may have experienced while taking an SSRI. Discontinuation symptoms most often emerge within 1-3 days ([Schatzberg et al. 1997](#)).

Until recently, most information about SSRI discontinuation syndrome came from case reports or retrospective analyses. [Rosenbaum et al. \(1998\)](#) compared the effects of a 5- to 8-day abrupt discontinuation period from fluoxetine, paroxetine, or sertraline in three groups of patients with depression receiving maintenance therapy. Patients from the paroxetine and sertraline groups had a significant increase in adverse events, whereas patients in the fluoxetine group experienced no increase in adverse events.

In a more extended evaluation, the effects of abrupt discontinuation of fluoxetine were studied in 195 patients with depression ([Zajacka et al. 1998](#)). Patients whose depression remitted while they were taking fluoxetine were randomly assigned to continue fluoxetine (20 mg/day) or to discontinue abruptly and begin placebo, and they were



monitored for 6 weeks. Reports of adverse events were similar for both groups.

In summary, SSRIs with short half-lives (paroxetine and fluvoxamine) and related drugs, such as venlafaxine, should be tapered. Fluoxetine does not require tapering because of its extended half-life.

## Overdose

A major advantage of SSRIs, relative to other antidepressants, has been their superior therapeutic index ([Cooper 1988](#); [Pedersen et al. 1982](#)). The number of deaths per 1 million prescriptions, across several SSRIs (0–6), is substantially lower than that for conventional TCAs (8–53) or MAOIs (0–61) ([Leonard 1992](#)).

[Borys et al. \(1992\)](#) reported on 234 cases of fluoxetine overdose (serum level=232–1,390 ng/mL) obtained in a prospective multicenter study. Fluoxetine was the sole ingested in 87 cases; in the remaining 147 cases, it was taken in combination with alcohol and/or other drugs. Common symptoms included tachycardia, sedation, tremor, nausea, and emesis. The authors concluded that the emergent symptoms were minor and of short duration; thus, aggressive supportive care “is the only intervention necessary” ([Borys et al. 1992](#), p. 115).

---

## Drug-Drug Interactions

---

Although the potential for significant interactions exists, SSRIs are unlikely to be associated with many of the conventional problems seen with the earlier

antidepressants. These problems include the cumulative CNS-depressant effects with alcohol, anticholinergic agents, or antihistaminic compounds. The structural differences among SSRIs offer a basis for some intraclass differences. Lithium concentrations are generally unaffected.

One potential for clinically relevant antidepressant pharmacokinetic interactions is based on the drug effect on the CYP family of enzymes ([Brøsen and Gram 1989](#)). For example, SSRIs are both substrates for and inhibitors of oxidation via CYP2D6. [Crewe et al. \(1992\)](#) ranked the potency of CYP2D6 inhibition for serotonergic antidepressants, revealing the most clinically relevant effects on 2D6 for paroxetine and fluoxetine and less relevant effects for sertraline, fluvoxamine, citalopram, clomipramine, and amitriptyline.

Through inhibition of CYP2D6, fluoxetine may elevate the concentration of concomitantly administered drugs that rely on this enzyme for metabolism. This has particular clinical relevance when the second agent has a narrow therapeutic index. Examples of such agents include flecainide, quinidine, carbamazepine, propafenone, TCAs, and several antipsychotics ([Rudorfer and Potter 1989](#)). The clinical consequence of such an interaction may either enhance or impair efficacy and/or heighten the adverse-event profile.

The data with respect to fluoxetine's inhibition of other CYP enzymes, such as 3A3/4, 2C9, and 2C19, are less consistent, but the potential for such interaction exists.

---

## Conclusion

---

Fluoxetine has been shown to be a safe and effective drug that has proved to be better tolerated than TCAs and to have a superior safety profile in overdose for patients with comorbid medical illness. Evidence suggests a broad utilitarian role for fluoxetine across a spectrum of psychopathology.

---

## References

---

- Aghajanian JK, Sprouse JS, Rasmussen K: Electrophysiology of central serotonin receptor subtypes, in *The Serotonin Receptors*. Edited by Sanders-Bush E. Clifton, NJ, Humana Press, 1988, pp 225-252
- Altamura AC, Montgomery SA, Wernicke JF: The evidence for 20mg a day of fluoxetine as the optimal dose in the treatment of depression. *Br J Psychiatry Suppl* (3):109-112, 1988 3074862
- American College of Neuropsychopharmacology: Suicidal behavior and psychotropic medication. Accepted as a consensus statement by the ACNP Council, March 2, 1992. *Neuropsychopharmacology* 8(2):177-183, 1992 8471130
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Amin AH, Crawford TBB, Gaddum JH: The distribution of substance P and 5-hydroxytryptamine in the central

nervous system of the dog. *J Physiol* 126(3):596-618, 1954 13222357

Amin M, Lehmann H, Mirmiran J: A double-blind, placebo-controlled dose-finding study with sertraline. *Psychopharmacol Bull* 25(2):164-167, 1989 2690162

Angel I, Taranger MA, Claustre Y, et al: Anorectic activities of serotonin uptake inhibitors: correlation with their potencies at inhibiting serotonin uptake in vivo and 3H-mazindol binding in vitro. *Life Sci* 43(8):651-658, 1988 3261828

Arnold LM, Hess EV, Hudson JI, et al: A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *Am J Med* 112(3):191-197, 2002 11893345

Arnt J, Hyttel J, Overø KF: Prolonged treatment with the specific 5-HT-uptake inhibitor citalopram: effect on dopaminergic and serotonergic functions. *Pol J Pharmacol Pharm* 36(2-3):221-230, 1984a 6591152

Arnt J, Overø KF, Hyttel J, et al: Changes in rat dopamine- and serotonin function in vivo after prolonged administration of the specific 5-HT uptake inhibitor, citalopram. *Psychopharmacology (Berl)* 84(4):457-465, 1984b 6441945

Aronoff GR, Bergstrom RF, Pottratz ST, et al: Fluoxetine kinetics and protein binding in normal and impaired renal function. *Clin Pharmacol Ther* 36(1):138-144, 1984 6610522

Auerbach AD, Vittinghoff E, Maselli J, et al: Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery. *JAMA Intern Med* 173(12):1075-1081, 2013 23699725

Baron BM, Ogden AM, Siegel BW, et al: Rapid down regulation of beta-adrenoceptors by co-administration of desipramine and fluoxetine. *Eur J Pharmacol* 154(2):125-134, 1988 2465908

- Beasley CM Jr, Sayler ME, Bosomworth JC, et al: High-dose fluoxetine: efficacy and activating-sedating effects in agitated and retarded depression. *J Clin Psychopharmacol* 11(3):166-174, 1991 2066455
- Benkelfat C, Murphy DL, Zohar J, et al: Clomipramine in obsessive-compulsive disorder. Further evidence for a serotonergic mechanism of action. *Arch Gen Psychiatry* 46(1):23-28, 1989 2910220
- Benloucif S, Galloway MP: Facilitation of dopamine release in vivo by serotonin agonists: studies with microdialysis. *Eur J Pharmacol* 200(1):1-8, 1991 1769366
- Bergstrom DA, Kellar KJ: Adrenergic and serotonergic receptor binding in rat brain after chronic desmethylinipramine treatment. *J Pharmacol Exp Ther* 209(2):256-261, 1979 220405
- Blier P, de Montigny C, Chaput Y: Modifications of the serotonin system by antidepressant treatments: implications for the therapeutic response in major depression. *J Clin Psychopharmacol* 7 (6 suppl): 24S-35S, 1987 3323264
- Blier P, Chaput Y, de Montigny C: Long-term 5-HT reuptake blockade, but not monoamine oxidase inhibition, decreases the function of terminal 5-HT autoreceptors: an electrophysiological study in the rat brain. *Naunyn Schmiedeberg's Arch Pharmacol* 337(3):246-254, 1988 3260661
- Blier P, de Montigny C, Chaput Y: A role for the serotonin system in the mechanism of action of antidepressant treatments: preclinical evidence. *J Clin Psychiatry* 51 (suppl 4):14-20, 1990 2157700
- Bloch MR, Elliott M, Thompson H, et al: Fluoxetine in pathologic skin-picking: open-label and double-blind results. *Psychosomatics* 42(4):314-319, 2001 11496020
- Blundell JE: Serotonin manipulations and the structure of feeding behaviour. *Appetite* 7 (suppl):39-56, 1986 3527061

- Borys DJ, Setzer SC, Ling LJ, et al: Acute fluoxetine overdose: a report of 234 cases. *Am J Emerg Med* 10(2):115-120, 1992 1586402
- Bouchard RH, Pourcher E, Vincent P: Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* 146(10):1352-1353, 1989 2604792
- Boyer WF, Feighner JP: The efficacy of selective serotonin uptake inhibitors in depression, in *Selective Serotonin Uptake Inhibitors*. Edited by Feighner JP, Boyer WF. Chichester, UK, Wiley, 1991, pp 89-108
- Bradley PB: *Introduction to Neuropharmacology*. Boston, MA, Wright, 1989
- Brambilla P, Cipriani A, Hotopf M, et al: Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. *Pharmacopsychiatry* 38(2):69-77, 2005 15744630
- Bressa GM, Brugnoli R, Pancheri P: A double-blind study of fluoxetine and imipramine in major depression. *Int Clin Psychopharmacol* 4 (suppl 1):69-73, 1989 2783701
- Brewerton TD, Brandt HA, Lessem MD, et al: Serotonin in eating disorders, in *Serotonin in Major Psychiatric Disorders*. Edited by Coccaro EF, Murphy DL. Washington, DC, American Psychiatric Press, 1990, pp 153-184
- Bridge JA, Iyengar S, Salary CB, et al: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 297(15):1683-1696, 2007 17440145
- Brøsen K, Gram LF: Clinical significance of the sparteine/debrisoquine oxidation polymorphism. *Eur J Clin Pharmacol* 36(6):537-547, 1989 2570698
- Burch KJ, Wells BG: Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics* 89(4 pt 1):676-677, 1992 1557252

- Bymaster FP, Zhang W, Carter PA, et al: Fluoxetine, but not other selective serotonin uptake inhibitors, increases norepinephrine and dopamine extracellular levels in prefrontal cortex. *Psychopharmacology* (Berl) 160(4):353-361, 2002 11919662
- Carruba MO, Mantegazza P, Memo M, et al: Peripheral and central mechanisms of action of serotonergic anorectic drugs. *Appetite* 7 (suppl):105-113, 1986 3740835
- Castro M, Diaz A, del Olmo E, et al: Chronic fluoxetine induces opposite changes in G protein coupling at pre and postsynaptic 5-HT<sub>1A</sub> receptors in rat brain. *Neuropharmacology* 44(1):93-101, 2003 12559126
- Charney DS, Menkes DB, Heninger GR: Receptor sensitivity and the mechanism of action of antidepressant treatment. Implications for the etiology and therapy of depression. *Arch Gen Psychiatry* 38(10): 1160-1180, 1981 6271089
- Charney DS, Heninger GR, Sternberg DE: Serotonin function and mechanism of action of antidepressant treatment. Effects of amitriptyline and desipramine. *Arch Gen Psychiatry* 41(4):359-365, 1984 6703855
- Cipriani A, Brambilla P, Furukawa T, et al: Fluoxetine versus other types of pharmacotherapy for depression. *Cochrane Database Syst Rev* (4):CD004185, 2005 16235353
- Ciraulo DA, Shader RI: Fluoxetine drug-drug interactions, I: antidepressants and antipsychotics. *J Clin Psychopharmacol* 10(1):48-50, 1990 1968472
- Coccaro EF, Siever LJ, Klar HM, et al: Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry* 46(7):587-599, 1989 2735812
- Cooper GL: The safety of fluoxetine—an update. *Br J Psychiatry Suppl* (3):77-86, 1988 3074869

- Cornelius JR, Soloff PH, Perel JM, et al: A preliminary trial of fluoxetine in refractory borderline patients. *J Clin Psychopharmacol* 11(2):116-120, 1991 2056138
- Cornelius JR, Salloum IM, Ehler JG, et al: Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 54(8):700-705, 1997 9283504
- Crewe HK, Lennard MS, Tucker GT, et al: The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Clin Pharmacol* 34(3):262-265, 1992 1389951
- Damsa C, Bumb A, Bianchi-Demicheli F, et al: "Dopamine-dependent" side effects of selective serotonin reuptake inhibitors: a clinical review. *J Clin Psychiatry* 65(8):1064-1068, 2004 15323590
- Danion JM: The effectiveness of fluoxetine in acute studies and long-term treatment, in *Psychiatry Today: VIII World Congress of Psychiatry Abstracts*. Edited by Stefanis CN, Soldatos CR, Rabavilas AD. New York, Elsevier, 1989, p 334
- de Montigny C, Chaput Y, Blier P: Long-term tricyclic and electroconvulsive treatment increases responsiveness of dorsal hippocampus 5-HT<sub>1A</sub> receptors: an electrophysiological study. *Soc Neurosci Abstracts* 15:854, 1989
- Dempsey CM, Mackenzie SM, Gargus A, et al: Serotonin (5HT), fluoxetine, imipramine and dopamine target distinct 5HT receptor signaling to modulate *Caenorhabditis elegans* egg-laying behavior. *Genetics* 169(3):1425-1436, 2005 15654117
- Dufour H: Fluoxetine: long-term treatment and prophylaxis in depression. Paper presented at the International Fluoxetine Symposium, Tyrol, Austria, October 13-17, 1987
- Edman G, Åsberg M, Levander S, et al: Skin conductance habituation and cerebrospinal fluid 5-



- hydroxyindoleacetic acid in suicidal patients. *Arch Gen Psychiatry* 43(6):586-592, 1986 2423049
- Eisensamer B, Rammes G, Gimpl G, et al: Antidepressants are functional antagonists at the serotonin type 3 (5-HT<sub>3</sub>) receptor. *Mol Psychiatry* 8(12):994-1007, 2003 14647397
- Elks ML, Youngblood WW, Kizer JS: Serotonin synthesis and release in brain slices: independence of tryptophan. *Brain Res* 172(3):471-486, 1979 113050
- Enas GG, Pope HJ, Levine LR: Fluoxetine and bulimia nervosa: double-blind study, in 1989 New Research Program and Abstracts, American Psychiatric Association 142nd Annual Meeting, San Francisco, CA, May 6-11, 1989. Washington, DC, American Psychiatric Association, 1989, p 204
- Falck B, Hillarp NA, Thieme G, Torp A: Fluorescence of catechol amines and related compounds condensed with formaldehyde. *J Histochem Cytochem* 10(3):348-354, 1962 doi: 10.1177/10.3.348
- Fann WE, Sullivan JL, Richman BW: Dyskinesias associated with tricyclic antidepressants. *Br J Psychiatry* 128:490-493, 1976 1276554
- Farren CK: Serotonin and alcoholism: clinical and experimental research. *Journal of Serotonin Research* 1:9-26, 1995
- Fava M, Rosenbaum JF, McCarthy M, et al: Anger attacks in depressed outpatients and their response to fluoxetine. *Psychopharmacol Bull* 27(3):275-279, 1991 1775598
- Fava M, Rosenbaum JF, Cohen L, et al: High-dose fluoxetine in the treatment of depressed patients not responsive to a standard dose of fluoxetine. *J Affect Disord* 25(4):229-234, 1992 1430659
- Fava M, Rosenbaum JF, Pava JA, et al: Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *Am J Psychiatry* 150(8): 1158-1163, 1993 7848377

- Fava M, Alpert J, Nierenberg AA, et al: Fluoxetine treatment of anger attacks: a replication study. *Ann Clin Psychiatry* 8(1):7-10, 1996 8743642
- Ferrey G, Gailledrau J, Beuzen JN: The interest of fluoxetine in prevention of depressive recurrences, in *Psychiatry Today: VIII World Congress of Psychiatry Abstracts*. Edited by Stefanis CN, Soldatos CR, Rabavilas AD. New York, Elsevier, 1989, p 99
- Fisch C: Effect of fluoxetine on the electrocardiogram. *J Clin Psychiatry* 46(3 Pt 2):42-44, 1985 3871766
- Fraser A, Offord SJ, Lucki I: Regulation of serotonin receptors and responsiveness in the brain, in *The Serotonin Receptors*. Edited by Sanders-Bush E. Clifton, NJ, Humana Press, 1988, pp 319-362
- Fuller RW: Drugs altering serotonin synthesis and metabolism, in *Neuropharmacology of Serotonin*. Edited by Green AR. New York, Oxford University Press, 1985, pp 1-20
- Fuller RW: Mechanisms and functions of serotonin neuronal systems: opportunities for neuropeptide interactions. *Ann N Y Acad Sci* 780:176-184, 1996 8602731
- Gao B, Duncan WC Jr, Wehr TA: Fluoxetine decreases brain temperature and REM sleep in Syrian hamsters. *Psychopharmacology (Berl)* 106(3):321-329, 1992 1570377
- Garattini S, Mennini T, Bendotti C, et al: Neurochemical mechanism of action of drugs which modify feeding via the serotonergic system. *Appetite* 7 (suppl):15-38, 1986 2427023
- Geller DA, Hoog SL, Heiligenstein JH, et al; Fluoxetine Pediatric OCD Study Team: Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry* 40(7):773-779, 2001 11437015
- Goldenberg D, Mayskiy M, Mossey C, et al: A randomized, double-blind crossover trial of fluoxetine and

- amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 39(11):1852-1859, 1996 8912507
- Goldstein DJ, Rampey AH Jr, Enas GG, et al: Fluoxetine: a randomized clinical trial in the treatment of obesity. *Int J Obes Relat Metab Disord* 18(3):129-135, 1994 8186809
- Goldstein DJ, Wilson MG, Thompson VL, et al; Fluoxetine Bulimia Nervosa Research Group: Long-term fluoxetine treatment of bulimia nervosa. *Br J Psychiatry* 166(5):660-666, 1995 7620754
- Goldstein DJ, Corbin LA, Sundell KL: Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol* 89(5 pt 1):713-718, 1997 9166307
- Goodman WK, McDougle CJ, Price LH: Pharmacotherapy of obsessive compulsive disorder. *J Clin Psychiatry* 53 (suppl):29-37, 1992 1532962
- Gorelick DA: Serotonin uptake blockers and the treatment of alcoholism. *Recent Dev Alcohol* 7:267-281, 1989 2648494
- Graziottin A, Montorsi F, Guazzoni G, et al: Combined fluoxetine and sexual behavioral therapy for premature ejaculation: one-year follow-up analysis of results, complications and success predictors (abstract). *J Urol* 155 (5 suppl):497A, 1996
- Grigoriadis S, Vonderporten EH, Mamisashvili L, et al: Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. *BMJ* 348:f6932, 2014 24429387
- Haddad P: Newer antidepressants and the discontinuation syndrome. *J Clin Psychiatry* 58 (suppl 7):17-21, discussion 22, 1997 9219489
- Hall H, Ogren SO: Effects of antidepressant drugs on different receptors in the brain. *Eur J Pharmacol* 70(3):393-407, 1981 6262100
- Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56-62, 1960 14399272

- Hammad TA, Laughren T, Racoosin J: Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 63(3):332-339, 2006 16520440
- Hemeryck A, Belpaire FM: Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 3(1):13-37, 2002 11876575
- Hendrick V, Stowe ZN, Altshuler LL, et al: Fluoxetine and norfluoxetine concentrations in nursing infants and breast milk. *Biol Psychiatry* 50(10):775-782, 2001 11720696
- Henry LK, Field JR, Adkins EM, et al: Tyr-95 and Ile-172 in transmembrane segments 1 and 3 of human serotonin transporters interact to establish high affinity recognition of antidepressants. *J Biol Chem* 281(4):2012-2023, 2006 16272152
- Hviid A, Melbye M, Pasternak B: Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. *N Engl J Med* 369(25):2406-2415, 2013 24350950
- Iceta R, Mesonero JE, Alcalde AI: Effect of long-term fluoxetine treatment on the human serotonin transporter in Caco-2 cells. *Life Sci* 80(16):1517-1524, 2007 17289086
- Isenberg KE: Excretion of fluoxetine in human breast milk (letter). *J Clin Psychiatry* 51(4):169, 1990 2324084
- Jenike MA, Buttolph L, Baer L, et al: Open trial of fluoxetine in obsessive-compulsive disorder. *Am J Psychiatry* 146(7):909-911, 1989 2787123
- Jick SS, Dean AD, Jick H: Antidepressants and suicide. *BMJ* 310(6974):215-218, 1995 7677826
- Johnson AM: The comparative pharmacological properties of selective serotonin reuptake inhibitors in animals, in *Selective Serotonin Uptake Inhibitors*. Edited by Feighner JP, Boyer WF. Chichester, UK, Wiley, 1991, pp 37-70

- Jouvent R, Baruch P, Ammar S, et al: Fluoxetine efficacy in depressives with impulsivity vs blunted affect, in *Psychiatry Today: VIII World Congress of Psychiatry Abstracts*. Edited by Stefanis CN, Soldatos CR, Rabavilas AD. New York, Elsevier, 1989, p 398
- Kaplan A, Hollander E: A review of pharmacologic treatments for obsessive-compulsive disorder. *Psychiatr Serv* 54(8):1111-1118, 2003 12883138
- Kasper S, Fuger J, Möller H-J: Comparative efficacy of antidepressants. *Drugs* 43 (suppl 2):11-22, discussion 22-23, 1992 1378369
- Kaye WH, Weltzin TE, Hsu LK, et al: An open trial of fluoxetine in patients with anorexia nervosa. *J Clin Psychiatry* 52(11): 464-471, 1991 1744064
- Kaye WH, Nagata T, Weltzin TE, et al: Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 49(7):644-652, 2001 11297722
- Kelly MW, Perry PJ, Holstad SG, et al: Serum fluoxetine and norfluoxetine concentrations and antidepressant response. *Ther Drug Monit* 11(2):165-170, 1989 2785723
- Kerr JS, Sherwood N, Hindmarch I: The comparative psychopharmacology of 5-HT reuptake inhibitors. *Hum Psychopharmacol* 6(4):313-317, 1991 doi: 10.1002/hup.470060408
- Koski A, Vuori E, Ojanperä I: Newer antidepressants: evaluation of fatal toxicity index and interaction with alcohol based on Finnish postmortem data. *Int J Legal Med* 119(6):344-348, 2005 15739105
- Kroenke K, West SL, Swindle R, et al: Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. *JAMA* 286(23):2947-2955, 2001 11743835
- Lane R, Baldwin D: Selective serotonin reuptake inhibitor-induced serotonin syndrome: review (review). *J Clin*

- Psychopharmacol 17(3):208-221, 1997 9169967
- Lejoyeux M: Use of serotonin (5-hydroxytryptamine) reuptake inhibitors in the treatment of alcoholism. Alcohol Alcohol 31 (suppl 1):69-75, 1996 8737004
- Lemberger L, Rowe H, Bergstrom RF, et al: Effect of fluoxetine on psychomotor performance, physiologic response, and kinetics of ethanol. Clin Pharmacol Ther 37(6):658-664, 1985 3874037
- Leonard BE: Pharmacological differences of serotonin reuptake inhibitors and possible clinical relevance. Drugs 43 (suppl 2): 3-9, discussion 9-10, 1992 1378371
- Lester BM, Cucca J, Andreozzi L, et al: Possible association between fluoxetine hydrochloride and colic in an infant. J Am Acad Child Adolesc Psychiatry 32(6):1253-1255, 1993 8282672
- Li SX, Perry KW, Wong DT: Influence of fluoxetine on the ability of bupropion to modulate extracellular dopamine and norepinephrine concentrations in three mesocorticolimbic areas of rats. Neuropharmacology 42(2):181-190, 2002 11804614
- Little KY, Zhang L, Cook E: Fluoxetine-induced alterations in human platelet serotonin transporter expression: serotonin transporter polymorphism effects. J Psychiatry Neurosci 31(5):333-339, 2006 16951736
- Lu CY, Zhang F, Lakoma MD, et al: Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. BMJ 348:g3596, 2014 24942789
- Manasia P, Pomerol J, Ribè N, et al: Comparison of the efficacy and safety of 90 mg versus 20 mg fluoxetine in the treatment of premature ejaculation. J Urol 170(1):164-165, 2003 12796671
- Marcus MD, Wing RR, Ewing L, et al: A double-blind, placebo-controlled trial of fluoxetine plus behavior modification in the treatment of obese binge-eaters and

- non-binge-eaters. *Am J Psychiatry* 147(7): 876-881, 1990 2192563
- Martenyi F, Brown EB, Zhang H, et al: Fluoxetine versus placebo in posttraumatic stress disorder. *J Clin Psychiatry* 63(3): 199-206, 2002 11926718
- Max MB, Lynch SA, Muir J, et al: Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 326(19):1250-1256, 1992 1560801
- Meltzer HY, Young M, Metz J, et al: Extrapyrarnidal side effects and increased serum prolactin following fluoxetine, a new antidepressant. *J Neural Transm* 45(2):165-175, 1979 313977
- Menkes DB, Taghavi E, Mason PA, et al: Fluoxetine's spectrum of action in premenstrual syndrome. *Int Clin Psychopharmacol* 8(2):95-102, 1993 8345163
- Michelson D, Allgulander C, Dantendorfer K, et al: Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder: randomised, placebo-controlled trial. *Br J Psychiatry* 179:514-518, 2001 11731354
- Mochizucki D: Serotonin and noradrenaline reuptake inhibitors in animal models of pain. *Hum Psychopharmacol* 19 (suppl 1):S15-S19, 2004 15378668
- Molteni R, Calabrese F, Bedogni F, et al: Chronic treatment with fluoxetine up-regulates cellular BDNF mRNA expression in rat dopaminergic regions. *Int J Neuropsychopharmacol* 9(3):307-317, 2006 16035958
- Montgomery SA: Fluoxetine in the treatment of anxiety, agitation and suicidal thoughts, in *Psychiatry Today: VIII World Congress of Psychiatry Abstracts*. Edited by Stefanis CN, Soldatos CR, Rabavilas AD. New York, Elsevier, 1989a, p 335
- Montgomery SA: New antidepressants and 5-HT uptake inhibitors. *Acta Psychiatr Scand Suppl* 350:107-116, 1989b 2530760

- Montgomery SA, Dufour H, Brion S, et al: The prophylactic efficacy of fluoxetine in unipolar depression. *Br J Psychiatry Suppl* 153(3):69-76, 1988 3150694
- Murphy JM, Waller MB, Gatto GJ, et al: Effects of fluoxetine on the intragastric self-administration of ethanol in the alcohol preferring P line of rats. *Alcohol* 5(4):283-286, 1988 3265874
- Myung CS, Kim BT, Choi SH, et al: Role of neuropeptide Y and proopiomelanocortin in fluoxetine-induced anorexia. *Arch Pharm Res* 28(6):716-721, 2005 16042082
- Naranjo CA, Sellers EM, Lawrin MO: Modulation of ethanol intake by serotonin uptake inhibitors. *J Clin Psychiatry* 47 (suppl):16-22, 1986 3007443
- Naranjo CA, Kadlec KE, Sanhueza P, et al: Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clin Pharmacol Ther* 47(4):490-498, 1990 2328557
- Nemeroff CB, Thase ME; EPIC 014 Study Group: A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. *J Psychiatr Res* 41(3-4):351-359, 2007 16165158
- Ninan PT, van Kammen DP, Scheinin M, et al: CSF 5-hydroxyindoleacetic acid levels in suicidal schizophrenic patients. *Am J Psychiatry* 141(4):566-569, 1984 6199986
- Norden MJ: Fluoxetine in borderline personality disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 13(6):885-893, 1989 2813806
- Nulman I, Rovet J, Stewart DE, et al: Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 336(4):258-262, 1997 8995088
- O'Flynn K, O'Keane V, Lucey JV, et al: Effect of fluoxetine on noradrenergic mediated growth hormone release: a double blind, placebo-controlled study. *Biol Psychiatry* 30(4):377-382, 1991 1912129



- Pandey GN, Pandey SC, Janicak PG, et al: Platelet serotonin-2 receptor binding sites in depression and suicide. *Biol Psychiatry* 28(3):215-222, 1990 2378926
- Papini M, Martinetti MG, Pasquinelli A: Trazodone symptomatic extrapyramidal disorders of infancy and childhood. *Ital J Neurol Sci* 3(2):161-162, 1982 7118529
- Parga J, Rodriguez-Pallares J, Muñoz A, et al: Serotonin decreases generation of dopaminergic neurons from mesencephalic precursors via serotonin type 7 and type 4 receptors. *Dev Neurobiol* 67(1):10-22, 2007 17443768
- Pearlstein TB, Stone AB, Lund SA, et al: Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol* 17(4):261-266, 1997 9241004
- Pedersen LH, Nielsen AN, Blackburn-Munro G: Antinociception is selectively enhanced by parallel inhibition of multiple subtypes of monoamine transporters in rat models of persistent and neuropathic pain. *Psychopharmacology (Berl)* 182(4): 551-561, 2005 16133135
- Pedersen OL, Kragh-Sørensen P, Bjerre M, et al: Citalopram, a selective serotonin reuptake inhibitor: clinical antidepressive and long-term effect—a phase II study. *Psychopharmacology (Berl)* 77(3):199-204, 1982 6812140
- Peroutka SJ, Snyder SH: Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. *Science* 210(4465):88-90, 1980 6251550
- Petersen T, Dording C, Neault NB, et al: A survey of prescribing practices in the treatment of depression. *Prog Neuropsychopharmacol Biol Psychiatry* 26(1):177-187, 2002 11853110
- Phillips KA, Albertini RS, Rasmussen SA: A randomized placebo-controlled trial of fluoxetine in body dysmorphic

- disorder. Arch Gen Psychiatry 59(4):381-388, 2002 11926939
- Reimherr FW, Amsterdam JD, Quitkin FM, et al: Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. Am J Psychiatry 155(9):1247-1253, 1998 9734550
- Romano SJ, Halmi KA, Sarkar NP, et al: A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful acute fluoxetine treatment. Am J Psychiatry 159(1):96-102, 2002 11772696
- Rosenbaum JF, Fava M, Hoog SL, et al: Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 44(2):77-87, 1998 9646889
- Rubey RN, Johnson MR, Emmanuel N, et al: Fluoxetine in the treatment of anger: an open clinical trial. J Clin Psychiatry 57(9): 398-401, 1996 9746447
- Rudorfer MV, Potter WZ: Combined fluoxetine and tricyclic antidepressants. Am J Psychiatry 146(4):562-564, 1989 2784634
- Salzman C, Wolfson AN, Schatzberg A, et al: Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J Clin Psychopharmacol 15(1):23-29, 1995 7714224
- Saper JR, Silberstein SD, Lake AE 3rd, et al: Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache 34(9):497-502, 1994 8002320
- Schatzberg A, Roose S: A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. Am J Geriatr Psychiatry 14(4):361-370, 2006 16582045
- Schatzberg AF, Haddad P, Kaplan EM, et al: Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. Discontinuation Consensus panel. J Clin Psychiatry 58 (suppl 7):5-10, 1997 9219487

- Schmidt ME, Fava M, Robinson JM, et al: The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. *J Clin Psychiatry* 61(11):851-857, 2000 11105738
- Schweizer E, Rickels K, Amsterdam JD, et al: What constitutes an adequate antidepressant trial for fluoxetine? *J Clin Psychiatry* 51(1):8-11, 1990 2403998
- Sekine Y, Suzuki K, Ramachandran PV, et al: Acute and repeated administration of fluoxetine, citalopram, and paroxetine significantly alters the activity of midbrain dopamine neurons in rats: an in vivo electrophysiological study. *Synapse* 61(2):72-77, 2007 17117425
- Shaskan EG, Snyder SH: Kinetics of serotonin accumulation into slices from rat brain: relationship to catecholamine uptake. *J Pharmacol Exp Ther* 175(2):404-418, 1970 5481708
- Snyder SH, Yamamura HI: Antidepressants and the muscarinic acetylcholine receptor. *Arch Gen Psychiatry* 34(2):236-239, 1977 14603
- Sodero AO, Orsingher OA, Ramírez OA: Altered serotonergic function of dorsal raphe nucleus in perinatally protein-deprived rats: effects of fluoxetine administration. *Eur J Pharmacol* 532(3):230-235, 2006 16472801
- Stahl MMS, Lindquist M, Pettersson M, et al: Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. *Eur J Clin Pharmacol* 53(3-4):163-169, 1997 9476026
- Stauderman KA, Gandhi VC, Jones DJ: Fluoxetine-induced inhibition of synaptosomal [3H]5-HT release: possible Ca(2+)-channel inhibition. *Life Sci* 50(26):2125-2138, 1992 1608295
- Steiner M, Steinberg S, Stewart D, et al; Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group: Fluoxetine in the treatment of premenstrual

- dysphoria. N Engl J Med 332(23):1529-1534, 1995 7739706
- Su T-P, Danaceau M, Schmidt PJ, et al: Fluoxetine in the treatment of patients with premenstrual syndrome. Biol Psychiatry 33:159A-160A, 1993
- Su T-P, Schmidt PJ, Danaceau MA, et al: Fluoxetine in the treatment of premenstrual dysphoria. Neuropsychopharmacology 16(5):346-356, 1997 9109106
- Taddio A, Ito S, Koren G: Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. J Clin Pharmacol 36(1):42-47, 1996 8932542
- Teusink JP, Alexopoulos GS, Shamoian CA: Parkinsonian side effects induced by a monoamine oxidase inhibitor. Am J Psychiatry 141(1):118-119, 1984 6691428
- Thomas DR, Nelson DR, Johnson AM: Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxytryptamine uptake inhibitor. Psychopharmacology (Berl) 93(2):193-200, 1987 2962217
- U'Prichard DC, Greenberg DA, Sheehan PP, et al: Tricyclic antidepressants: therapeutic properties and affinity for alpha-noradrenergic receptor binding sites in the brain. Science 199(4325):197-198, 1978 202024
- Usher RW, Beasley CM Jr, Bosomworth JC: Efficacy and safety of morning versus evening fluoxetine administration. J Clin Psychiatry 52(3):134-136, 1991 2005078
- van der Kolk BA, Dreyfuss D, Michaels M, et al: Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry 55(12):517-522, 1994 7814344
- Van Renynghe de Voxvrie G: [Use of anafranil (G 34586) in obsessive neuroses]. Acta Neurol Psychiatr Belg 68(10):787-792, 1968 4976729
- Waldinger MD, Hengeveld MW, Zwinderman AH, et al: Effect of SSRI antidepressants on ejaculation: a double-

- blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol* 18(4):274-281, 1998 9690692
- Walsh BT, Fairburn CG, Mickley D, et al: Treatment of bulimia nervosa in a primary care setting. *Am J Psychiatry* 161(3): 556-561, 2004 14992983
- Walsh BT, Kaplan AS, Attia E, et al: Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *JAMA* 295(22):2605-2612, 2006 16772623
- Warshaw MG, Keller MB: The relationship between fluoxetine use and suicidal behavior in 654 subjects with anxiety disorders. *J Clin Psychiatry* 57(4):158-166, 1996 8601551
- Wernicke JF, Bremner JD, Bosomworth J, et al: The efficacy and safety of fluoxetine in the long-term treatment of depression. Paper presented at the International Fluoxetine Symposium, Tyrol, Austria, October 13-17, 1987
- Wisner KL, Bogen DL, Sit D, et al: Does fetal exposure to SSRIs or maternal depression impact infant growth? *Am J Psychiatry* 170(5):485-493, 2013 23511234
- Wong DT, Reid LR, Bymaster FP, et al: Chronic effects of fluoxetine, a selective inhibitor of serotonin uptake, on neurotransmitter receptors. *J Neural Transm* 64(3-4):251-269, 1985 3003252
- Wood SH, Mortola JF, Chan Y-F, et al: Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. *Obstet Gynecol* 80(3 pt 1):339-344, 1992 1495689
- Wurtman JJ, Wurtman RJ, Growdon JH, et al: Carbohydrate craving in obese people: suppression by treatments affecting serotonergic transmission. *Int J Eat Disord* 1(1):2-15, 1981
- Zajacka J, Fawcett J, Amsterdam J, et al: Safety of abrupt discontinuation of fluoxetine: a randomized, placebo-

controlled study. J Clin Psychopharmacol 18(3):193-197, 1998 9617977

Zubenko GS, Cohen BM, Lipinski JF Jr: Antidepressant-related akathisia. J Clin Psychopharmacol 7(4):254-257, 1987 3624508

Zuo J, Quinn KK, Kye S, et al: Fluoxetine is a potent inhibitor of coxsackievirus replication. Antimicrob Agents Chemother 56(9):4838-4844, 2012 22751539

# CHAPTER 11

## Sertraline

Linda L. Carpenter, M.D.

Alan F. Schatzberg, M.D.

---

### History and Discovery

---

Research has implicated dysregulation of serotonin (5-hydroxytryptamine [5-HT]) in mood and anxiety disorders. Researchers therefore identified compounds that are selective in blocking neurotransmitter reuptake and yet have little agonist and antagonist activity at receptors thought to be associated with adverse effects. Sertraline, a naphthylamino compound that is structurally different from monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), is a member of this class of drugs ([Guthrie 1991](#); [Heym and Koe 1988](#)).

For the 12 months ending June 2006, it was estimated that sales of sertraline (under the brand name Zoloft) in the United States exceeded \$3 billion ([Rancourt 2006](#)). In August 2006, a generic formulation of sertraline became

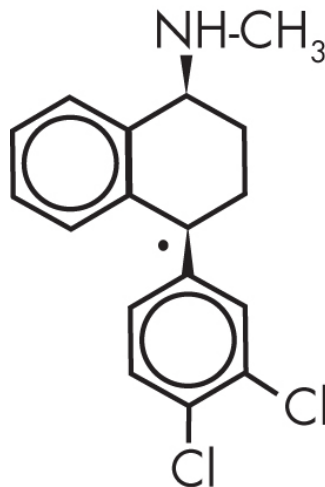
available in the United States, and within the first 2 weeks of its availability, the substitution rate exceeded 77% ([Block 2006](#)).

---

## Structure-Activity Relations

---

Sertraline [(+)-*cis*-(1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthylamine] ([Figure 11-1](#)) specifically blocks the reuptake of 5-HT in the soma and terminal regions of serotonergic neurons. The ability of sertraline to inhibit 5-HT reuptake is approximately 20-fold higher than its capacity to inhibit uptake of either norepinephrine or dopamine ([Heym and Koe 1988](#)). However, sertraline is more potent at blocking dopamine receptor uptake than are other selective serotonin reuptake inhibitors (SSRIs) and TCAs ([Hiemke and Härtter 2000](#); [Richelson 1994](#)).



---

**FIGURE 11-1.** Chemical structure of sertraline.



Serotonin neurons in the midbrain raphe nuclei have inhibitory autoreceptors in both the soma (serotonin<sub>1A</sub> [5-HT<sub>1A</sub>] receptors) and terminal area (serotonin<sub>1B</sub> [5-HT<sub>1B</sub>] receptors) that are stimulated by the acute increase in 5-HT. The immediate effect of serotonin transporter (5-HTT) blockade is to increase the amount of 5-HT in axosomatic synapses and to decrease neuronal firing ([Blier 2001](#); [Blier et al. 1990](#); [Heym and Koe 1988](#)). Over several weeks, these autoreceptors are desensitized and firing rates increase.

Unlike the older TCAs, sertraline has little appreciable antagonistic effect on histamine<sub>1</sub> (H<sub>1</sub>), muscarinic, or dopamine<sub>2</sub> (D<sub>2</sub>) receptors and thus is associated with few difficulties with severe constipation, drowsiness, and dry mouth ([Hiemke and Härter 2000](#); [Richelson 1994](#)). The antagonism of  $\alpha_1$ -adrenoreceptors by sertraline is at least 10-fold more potent than that of other SSRIs ([Hiemke and Härter 2000](#)), although this antagonism does not translate into clinically meaningful hypotension or reflex tachycardia. However, there is a report suggesting that sertraline decreases sympathetic nervous system activity, a property consistent with  $\alpha$  receptor blockade ([Shores et al. 2001](#)). It is also possible that the decrease in sympathetic response is related to stimulation of the 5-HT<sub>1A</sub> receptors noted above.

Sertraline is metabolized to desmethylsertraline (see section “Pharmacokinetics and Distribution” below). This compound is approximately one-tenth as active in blocking the reuptake of 5-HT; it also lacks antidepressant activity in animal models ([Heym and Koe 1988](#)).

---

## Pharmacological Profile

---

Among the various antidepressant agents that block the 5-HTT, sertraline is second only to paroxetine in potency for 5-HT reuptake blockade, as demonstrated in animal models ([Hiemke and Härtter 2000](#); [Owens et al. 2001](#); [Richelson 1994](#)). The selectivity of sertraline for norepinephrine follows that of escitalopram ([Hiemke and Härtter 2000](#); [Owens et al. 2001](#)), although other work suggests greater selectivity for fluvoxamine than for sertraline ([Richelson 1994](#)). The relative selectivity for the 5-HTT, compared with the dopamine transporter (DAT), is lowest for sertraline ([Owens et al. 2001](#)).

Sertraline exhibits inhibitory activity on several cytochrome P450 (CYP) enzymes. The ability of the compound to slightly elevate dextromethorphan and desipramine supports modest inhibition of CYP2D6 ([Hiemke and Härtter 2000](#); [Ozdemir et al. 1998](#); [Preskorn 1996](#)). It has little appreciable inhibition of CYP1A2, even when used at higher dosages ([Ozdemir et al. 1998](#)). A very mild elevation of CYP2C9/10 substrates has been found in several studies ([Preskorn 1996](#)). Sertraline has complex effects on the CYP3A3/4 enzyme system: it initially shows slight inhibition, but it also induces this system, albeit modestly, over time ([Preskorn 1996](#)).

---

## Pharmacokinetics and Disposition

---

Sertraline is absorbed slowly via the gastrointestinal tract, with peak plasma levels occurring between 6 and 8 hours after ingestion ([Warrington 1991](#)). The delay may be the result of enterohepatic circulation ([Hiemke and Härtter](#)

2000; van Harten 1993). When sertraline is taken with food, the peak plasma level occurs earlier, at about 5.5 hours (Pfizer 2016). The medication is more than 95% protein bound; however, because it binds weakly to  $\alpha_1$ -glycoproteins, it does not cause substantial displacement of other protein-bound drugs (Preskorn 1996).

The volume of distribution ( $V_d$ ) of sertraline is large, exceeding 20 L/kg. The distribution is larger in young females than in young males (Warrington 1991). In animal models, the concentration of sertraline is 40 times higher in brain than in plasma (Hiemke and Härtter 2000).

The elimination half-life of sertraline is 26–32 hours, and steady-state levels are achieved after 7 days. Sertraline shows linear pharmacokinetics within a range of 50–200 mg/day (Warrington 1991) and does not appear to inhibit or induce its own metabolism. Peak plasma levels are somewhat lower in young males than in young females, older females, or older males (Pfizer 2016; Ronfeld et al. 1997; Warrington 1991), and the elimination rate constant is higher in young males than in young females, older females, or older males (0.031/hour in young males, 0.022/hour in young females, and 0.019/hour in older males and females). Maximal plasma concentrations of sertraline may be significantly reduced following a gastric bypass procedure (Roerig et al. 2012).

In children between the ages of 6 and 17 years, weight-corrected metabolism is more rapid. The maximum concentration and area under the curve (AUC) are 22% lower in children than in adults. Despite this relatively more efficient metabolism, the smaller body mass of most children suggests that lower dosages of sertraline should be used in pediatric populations (Pfizer 2016).

Sertraline is metabolized in the liver via oxidative metabolism; the concentration of the primary metabolite, desmethylsertraline, is up to threefold higher than that of the parent compound ([Hiemke et al. 1991](#); [Ronfeld et al. 1997](#); [Warrington 1991](#)). Desmethylsertraline levels are also lower in young males than in young females, elderly females, or elderly males. The peak concentration ( $t_{\max}$ ) of desmethylsertraline is attained more quickly in young females than in young males, older females, and older males (6 hours in young females vs. 9 hours in young males, 8 hours in older females, and 14 hours in older males) ([Warrington 1991](#)). The half-life of desmethylsertraline is 1.6–2.0 times that of the parent compound ([Warrington 1991](#)).

Whereas desmethylsertraline is the major metabolite of sertraline, other minor metabolites include a ketone and an alcohol compound ([Warrington 1991](#)). Less than 0.2% of an oral dose of sertraline is excreted unchanged in urine, whereas approximately 50% is found in feces. The enzymes involved in metabolism of sertraline to desmethylsertraline remain unclear ([Greenblatt et al. 1999](#)). Although six different CYP enzymes have the capacity to catalyze this reaction, none accounts for more than 25% of sertraline's clearance. The contribution of each CYP enzyme is dependent not only on the protein's activity on the substrate, as evidenced through in vitro models, but also on the abundance of the enzyme. Given these properties, one computer model identified 2C9 as the greatest contributor (~23%) to sertraline demethylation, with 3A4 and 2C19 each contributing about 15%, 2D6 adding 5%, and 2B6 contributing 2% to the process ([Greenblatt et al. 1999](#); [Lee et al. 1999](#)). These percentages can vary across individuals, depending on the amount of enzyme that is available or

enzyme inhibition that occurs. Because multiple CYP enzymes are involved in sertraline's metabolism, concurrent use of medications with specific CYP inhibition is unlikely to substantially impair the process ([Greenblatt et al. 1999](#)). However, increased CYP2B activity was seen in mice as a consequence of sertraline coadministration with bupropion ([Molnari et al. 2012](#)).

Patients with liver disease experience decreased sertraline metabolism ([Hiemke and Härter 2000](#)). For individuals with mild liver impairment, the half-life of the drug may be increased threefold ([Pfizer 2016](#)), and concentrations are likely to be greater in patients with severe impairment. Although renal impairment does not appreciably influence the metabolism of sertraline ([Hiemke and Härter 2000](#)), hemodialysis patients with severe end-stage renal disease do not appear to tolerate sertraline 25 mg/day without risk of significant toxicity ([Chander et al. 2011](#)).

---

## Mechanism of Action

---

The means by which all antidepressants exert their therapeutic action is largely unknown, although some of the properties noted above have been related to hypothetical mechanisms ([Blier 2001](#); [Blier et al. 1990](#)). As previously mentioned, the immediate effect of sertraline is to decrease neuronal firing rates. This is followed by normalization and an increase in firing rates, as autoreceptors are desensitized. As activity in the presynaptic neuron increases, noradrenergic neurons are stimulated by postsynaptic 5-HT receptors located on noradrenergic

nerve terminals, leading to eventual downregulation of  $\beta$ -adrenergic receptors, an effect produced by many, but not all, antidepressant agents ([Frazer and Scott 1994](#); [Guthrie 1991](#)).

Not inconsistent with the above are findings suggesting that SSRI treatment decreases production of 5-HT<sub>1B</sub> messenger RNA (mRNA), the message for a regulatory autoreceptor on dorsal raphe neurons that controls the amount of 5-HT released with each impulse ([Anthony et al. 2000](#)). Again, the decrease in mRNA production coincides temporally with the time frame for SSRI therapeutic effects. In addition to inhibition of 5-HT reuptake, preclinical research demonstrated that sertraline inhibits hippocampal presynaptic sodium channels to control neurotransmitter release ([Aldana and Sitges 2012](#)), and sertraline's ability to increase extracellular dopamine concentration in nucleus accumbens and striatum differentiated it from other SSRIs ([Kitaichi et al. 2010](#)).

---

## Indications and Efficacy

---

### Approved Clinical Indications

Sertraline is currently approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of major depressive disorder (MDD), obsessive-compulsive disorder (OCD) and pediatric OCD, posttraumatic stress disorder (PTSD), panic disorder, premenstrual dysphoric disorder (PMDD), and social anxiety disorder. Some of the pivotal

studies using this compound for these indications are reviewed in the following subsections.

## **Major Depressive Disorder**

Sertraline's efficacy in the treatment of MDD was established by a number of placebo-controlled trials for acute-phase therapy ([Fabre et al. 1995](#); [Olie et al. 1997](#); [Reimherr et al. 1990](#)). In a multicenter trial, 369 patients were randomly assigned to a fixed dosage of sertraline (50 mg/day, 100 mg/day, or 200 mg/day) or placebo for 6 weeks ([Fabre et al. 1995](#)). Patients at all dosages of sertraline showed approximately equivalent improvement, which was greater than that shown with placebo for most measures.

Sertraline was compared with amitriptyline and placebo in a multicenter trial of 448 patients ([Reimherr et al. 1990](#)). Sertraline was dosed flexibly up to 200 mg/day, and amitriptyline was administered at dosages as high as 150 mg/day. Both active treatments were superior to placebo, as indicated by Hamilton Rating Scale for Depression (Ham-D) and Clinical Global Impressions (CGI) Scale scores; similarly, response rates (rates at which patients attained a 50% decrease in the Ham-D or a CGI Scale score of 1 or 2) were higher with the active treatment compared with placebo.

In a multicenter study of 235 men and 400 women with either chronic MDD (enduring at least 2 years) or MDD superimposed on DSM-IV ([American Psychiatric Association 1994](#)) dysthymic disorder, subjects were randomly assigned to 12 weeks of either sertraline or imipramine in a 2-to-1 ratio ([Kornstein et al. 2000](#)). Treatment was double-blinded, and the study medication was titrated to a flexible maximum daily dosage of 200 mg sertraline or 300 mg imipramine. Response to both drugs was similar, but

sertraline was better tolerated. Results revealed that many who benefited had not achieved response until after 8 weeks of treatment, underscoring the need for extended sertraline trials in patients with chronic depression ([Keller et al. 1998a](#)). Another interesting finding from this study is that men and women had differential response rates to sertraline and imipramine ([Kornstein et al. 2000](#)). Remission and response outcomes were combined in an intent-to-treat analysis that showed that 57% of women but only 46% of men benefited from sertraline. Among men, response was somewhat better with imipramine than with sertraline (62% and 45%, respectively). Response rates were more rapid for men assigned to imipramine and for women assigned to sertraline. Premenopausal women were more likely to respond to sertraline, whereas postmenopausal women were equally likely to respond to either agent.

Sertraline was significantly more effective than placebo in reducing depressive symptoms of postpartum depression ([Hantsoo et al. 2014](#)), particularly in women whose symptoms began within 4 weeks of giving birth. In another recent trial, a specialized cognitive-behavioral therapy (CBT) was significantly more effective than sertraline in postpartum depressed women ([Milgrom et al. 2015](#)).

Sertraline has been shown to be effective for maintenance-phase treatment, both in patients with MDD ([Doogan and Caillard 1992](#)) and in patients with chronic MDD (defined as a major depressive episode enduring at least 2 years or co-occurring with dysthymic disorder) ([Keller et al. 1998b](#)). The [Doogan and Caillard \(1992\)](#) study followed 300 patients throughout 44 weeks of double-blind, placebo-controlled maintenance therapy and found that



13% of sertraline-treated patients, compared with 46% of placebo-treated patients, experienced a relapse.

The utility of sertraline in preventing illness recurrence among chronic MDD patients who responded to acute antidepressant therapy ( $n=161$ ) was examined in the [Keller et al. \(1998b\)](#) study, in which subjects were randomly assigned to receive 52 weeks of maintenance treatment with either placebo or sertraline. More than 60% of the sample was female and had a current episode duration that exceeded 8 years. Sertraline significantly outperformed placebo on all outcome measures; 6% of sertraline-treated patients and 23% of placebo-treated patients experienced depressive episode recurrence, and clinically significant depressive symptom re-emergence was observed in 26% of sertraline-treated patients versus 50% of patients receiving placebo.

Sertraline can be used to treat MDD in special populations. In addition to the trials just described, several studies found sertraline to be at least as effective as TCAs in treating younger adults ([Cohn et al. 1990](#); [Lydiard et al. 1997](#); [Möller et al. 1998](#)) and elderly patients ([Bondareff et al. 2000](#); [Finkel et al. 1999](#); [Forlenza et al. 2001](#)) with MDD. Sertraline has been shown to be as beneficial as nortriptyline in women with postpartum MDD ([Wisner et al. 2006](#)). Furthermore, sertraline may confer a prophylactic advantage in women at high risk for developing postpartum episodes of MDD ([Wisner et al. 2004](#)), and sertraline is one of three antidepressants judged to be evidence-based choices for MDD in women who are breast feeding ([Lanza di Scalea and Wisner 2009](#)). Several trials have shown roughly equivalent efficacy for sertraline and other SSRIs ([Aguglia et al. 1993](#); [Franchini et al. 1997](#); [Nemeroff et al. 1996](#); [Newhouse et al. 2000](#); [Stahl 2000](#)); however, a

recent Cochrane Database review and meta-analysis of all randomized controlled trials of sertraline against an active antidepressant comparator concluded that sertraline was superior to other agents for the treatment of MDD in terms of both efficacy and acceptability ([Cipriani et al. 2010](#)).

## **Premenstrual Dysphoric Disorder**

In one of the first multicenter trials to test the efficacy of an antidepressant agent for PMDD, sertraline was compared with placebo ([Yonkers et al. 1997](#)). Either placebo or sertraline (at a flexible daily dosage of 50–150 mg) was given to 243 women. After three menstrual cycles of treatment, total daily rating scores had decreased by 32% and 11% in the sertraline- and placebo-treated groups, respectively. Both emotional and physical symptom clusters improved by 32% with sertraline treatment, a reduction nearly threefold higher than that seen with placebo. At the endpoint, CGI-I scores of 1 or 2 were achieved by 62% and 34% of those assigned to sertraline and placebo, respectively.

In a second multicenter trial, it was shown that sertraline treatment could be commenced halfway through the menstrual cycle (i.e., at ovulation) and still be more effective than placebo ([Halbreich et al. 2002](#)). In this three-cycle flexible-dosage study, 281 women were randomly assigned to receive daily dosages of 50–100 mg of sertraline or placebo. The responder rates in this study, after three cycles of luteal-phase treatment, were 50% and 26% for sertraline and placebo, respectively. As with the daily treatment study, functional improvement paralleled symptomatic improvement. Only 8% of the women taking sertraline and 1% of the women receiving placebo discontinued the study because of side effects. The efficacy

of this drug administration schedule for women with PMDD has the potential to revolutionize treatment approaches, because many women with PMDD prefer to avoid taking medication during nonsymptomatic periods.

A secondary analysis of data from three large federally sponsored trials ( $n=447$ ) indicated that women with premenstrual syndrome (PMS) showed positive responses to sertraline, similar to outcomes observed in women with PMDD ([Freeman et al. 2011](#)). Examination of symptom-based subtypes in that analysis revealed that predominantly psychological symptoms or mixed psychological/physical symptoms predicted better response to sertraline than did predominantly physical symptoms.

### **Social Anxiety Disorder (Social Phobia)**

Several studies have established the efficacy of sertraline in the treatment of social anxiety disorder (also known as social phobia). In one of the earliest studies ([Katzelnick et al. 1995](#)), sertraline treatment (at flexible dosages of 50–100 mg/day) produced a statistically significant improvement compared with placebo, as measured by Liebowitz Social Anxiety Scale (LSAS) scores. A large double-blind, placebo-controlled study followed more than 200 Canadian outpatients with generalized social phobia for 20 weeks, measuring response on CGI-I scores and mean reductions on the social phobia subscale of the Marks Fear Questionnaire and the Brief Social Phobia scale ([Van Ameringen et al. 2001](#)). Fifty-three percent of patients treated with sertraline, compared with only 29% of patients receiving placebo, were either much or very much improved by the study's end, as measured by CGI-I scores. When subjects who responded to sertraline were randomly assigned to continue sertraline or switch to placebo for an

additional 24 weeks, the relative risk of relapse for those who were randomly assigned to placebo was greater than 10 ([Walker et al. 2000](#)).

[Liebowitz et al. \(2003\)](#) demonstrated that sertraline produced a significant reduction in LSAS scores and resulted in a greater proportion of responders after 12 weeks of treatment (at dosages up to 200 mg/day) compared with placebo. In a placebo-controlled study that compared sertraline, exposure therapy, and combined treatment and involved more than 380 Norwegian patients with generalized social phobia, sertraline alone or in combination with exposure therapy yielded statistically significant improvements in CGI social phobia scores, whereas exposure therapy alone did not ([Blomhoff et al. 2001](#)). While not FDA approved in the pediatric population, sertraline has been well tolerated and has shown efficacy in childhood social anxiety disorder ([Compton et al. 2001](#)).

## **Panic Disorder**

Sertraline's efficacy in the treatment of panic disorder has been demonstrated in several studies. In a 12-week randomized, placebo-controlled, flexible-dose multicenter trial in outpatients with panic disorder (with and without agoraphobia) but without depression ([Pohl et al. 1998](#)), sertraline was superior to placebo on a number of efficacy measures. One hundred sixty-eight patients meeting diagnostic criteria for panic disorder without depression were randomly assigned to receive sertraline or placebo after a 2-week single-blind lead-in. The mean sertraline dosage at endpoint was 126 mg/day (SD=62 mg/day), and the reduction in frequency of panic attacks was significantly greater for the sertraline group (77% vs. 51% for the placebo group), with significantly fewer panic symptom

episodes occurring in that group. Similar results supporting sertraline's efficacy for panic disorder were reported by [Pollack et al. \(1998\)](#), who randomly assigned 178 patients to sertraline or placebo.

A fixed-dosage study of sertraline (50 mg/day, 100 mg/day, or 200 mg/day) or placebo for 12 weeks ([Londborg et al. 1998](#)) demonstrated sertraline's superiority over placebo in numerous trial outcomes, including number of panic attacks and limited-symptom attacks, severity of anticipatory anxiety, dimensional anxiety measures, and global measures of improvement. Pooled sertraline data indicated a 65% reduction in the number of panic attacks, compared with a 39% decrease in the placebo group. Effect sizes, reflecting the magnitude of difference between the two treatments, for the three different sertraline dosages tested were 0.58 (50 mg/day), 0.41 (100 mg/day), and 0.60 (200 mg/day), but response rates did not differ significantly among dosage groups. In the panic studies described above, the authors reported a low incidence of attrition secondary to sertraline adverse events, concluding that sertraline is a safe and effective treatment for patients with panic disorder. Sertraline's beneficial effects in panic disorder may be further enhanced when the drug is used in combination with self-administered CBT ([Koszycki et al. 2011](#)).

## **Obsessive-Compulsive Disorder in Adults**

Several multicenter trials found benefit for sertraline over placebo in the acute- and maintenance-phase treatment of OCD in adults. One study failed to show superiority of sertraline over placebo, perhaps because of the limited sample size ( $n=19$ ) or the treatment-resistant characteristics of the cohort ([Jenike et al. 1990](#)). Larger-

scale studies with diverse patients had differing results. By week 3 of a 12-week flexible-dose study in 167 patients ([Kronig et al. 1999](#)), sertraline (mean 165 mg/day) differentiated from placebo. At study endpoint, 41% of patients receiving sertraline and 23% of those receiving placebo had achieved a CGI-Improvement scale (CGI-I) score of 1 or 2.

A fixed-dose study ([Greist et al. 1995](#)) also found superior results with three different daily dosages (50, 100, or 200 mg) of sertraline, compared with placebo, over 1 year of treatment in a multisite trial. OCD patients ( $n=325$ ) were randomly assigned to 12 weeks of double-blind treatment after a 1-week washout period. Responders (40% of sertraline-treated patients and 26% of placebo-treated patients) were offered enrollment in an additional 40 weeks of continuation treatment. Over the 52 weeks of the study, sertraline-treated subjects demonstrated significantly greater improvement than did subjects given placebo.

Some evidence suggests that higher daily dosages of sertraline may be helpful for patients whose symptoms do not respond to standard dosages. In one study, 66 patients with OCD that was unresponsive to sertraline therapy at dosages of 200 mg/day after 16 weeks of treatment were randomly assigned to continue on the same dosage for an additional 12 weeks or to increase their dosage to 250–400 mg/day ([Ninan et al. 2006](#)). At the end of the trial, those receiving higher dosages had greater improvement in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores, although rates of response were similar for the two groups.

Other studies supporting the utility of sertraline in OCD have included head-to-head comparisons with other antidepressants ([Bergeron et al. 2002](#); [Bisserbe et al. 1997](#); [Hoehn-Saric et al. 2000](#)). In a comparison of lower-dosage

sertraline with cognitive-behavioral group therapy, both treatments were shown to be efficacious, although OCD patients treated with group therapy had greater reductions in symptoms ([Sousa et al. 2006](#)). Continuation of CBT versus sertraline initiation in children and adolescents with OCD who had not responded to an initial trial of CBT resulted in similar efficacy ([Skarphedinsson et al. 2015](#)).

## **Obsessive-Compulsive Disorder in Children and Adolescents**

Sertraline is approved for use in children for the treatment of OCD. In a 12-week double-blind, placebo-controlled, parallel-group multicenter trial in 187 pediatric subjects (107 children ages 6–12 years, and 80 adolescents ages 13–17 years), [March et al. \(1998\)](#) found that subjects treated with sertraline (mean endpoint dosage 167 mg/day) showed significant improvement on Y-BOCS, National Institute of Mental Health—Global Obsessive-Compulsive Scale (NIMH-GOCS), and CGI-I scores, compared with subjects receiving placebo. There were few dropouts due to adverse events, and the authors concluded that sertraline is a safe, well-tolerated treatment in this age group. A subsequent study in children and adolescents treated with sertraline (50–200 mg/day) over 12 months found that many who responded to acute treatment could achieve full or partial remission status with longer-term treatment ([Wagner et al. 2003](#)).

## **Posttraumatic Stress Disorder**

Sertraline's efficacy in the treatment of PTSD is supported by two large acute-phase, double-blind, placebo-controlled multicenter studies ([Brady et al. 2000](#); [Davidson et al. 2001b](#)), a long-term treatment study ([Londborg et al.](#)



2001), and a relapse prevention trial (Davidson et al. 2001a).

In the first acute-phase trial (Davidson et al. 2001b), 208 civilian patients were randomly assigned to receive either sertraline or placebo for 12 weeks. Observed symptom reductions with active treatment were about 50% for re-experiencing/intrusion, just under 50% for avoidance/numbing, and 40% for arousal. The probability of response, defined as a CGI Scale score of 1 or 2 and a minimal 30% decrease in the Clinician-Administered PTSD Scale—Part 2 (CAPS-2), was 0.65 in sertraline-treated patients and 0.38 in placebo-treated patients at the 12-week endpoint. Approximately 40% of each group had comorbid MDD, with mean baseline 21-item Ham-D scores around 21. Of interest, there were no significant differences among groups in depression symptom severity. The second acute-phase study (Brady et al. 2000) yielded similarly positive results.

In a pediatric sample with PTSD, 10 weeks of treatment with sertraline 50–200 mg/day appeared generally safe but did not produce outcomes superior to those with placebo (Robb et al. 2010).

Whereas the overall acute-phase efficacy of sertraline for PTSD was significant for women in the large controlled studies reviewed above (Brady et al. 2000; Davidson et al. 2001b), sertraline failed to differentiate from placebo in men. Some research suggests that treatment efficacy may vary by gender and by type of traumas experienced. Other research has shown no significant gender differences in sertraline's efficacy in patients with combat-related PTSD (Friedman et al. 2007). Reasons for the sex differences in efficacy findings are not clear, although one possible explanation is that women are more likely than men to



experience sexual or physical trauma and childhood abuse. It is possible that the nature of the trauma itself (age at exposure, chronicity, contextual factors) may alter the biology of the disorder and its responsiveness to medication ([Stein et al. 2006](#)). Some data suggest that certain serotonin transporter genotypes may be associated with better outcomes ([Mushtaq et al. 2012](#)).

Findings from a U.S. Department of Veterans Affairs (VA) medical center study failed to demonstrate that sertraline was superior to placebo in patients with predominantly combat-related PTSD ([Friedman et al. 2007](#)), but a subsequent trial in Iranian combat veterans ( $n=70$ ) did show robust efficacy for sertraline compared with placebo ([Panahi et al. 2011](#)).

Sertraline long-term benefit for PTSD was demonstrated in a prospective study in which patients with PTSD who had completed 12 weeks of double-blind, placebo-controlled acute-phase treatment with sertraline ([Brady et al. 2000](#)) were enrolled in a 24-week open-label continuation phase ([Londborg et al. 2001](#)). It was observed that about 20%–25% of the total improvement in PTSD symptoms occurred during the continuation phase (weeks 12–36). The greatest improvement over time was among patients who were originally considered “nonresponders” in the acute phase, leading the authors to conclude that as many as one-third of PTSD patients may require longer treatment to achieve a clinically significant response. Sertraline’s efficacy in sustaining improvement and preventing PTSD relapse was also examined in a 28-week double-blind continuation study ( $n=96$ ) ([Davidson et al. 2001a](#)). Sertraline was found to be superior to placebo on the three primary outcome measures: full syndrome relapse (sertraline vs. placebo, 5.3% and 26.1%, respectively), relapse or discontinuation

due to clinical deterioration (sertraline vs. placebo, 15.8% and 45.7%, respectively), and acute exacerbation (sertraline vs. placebo, 15.8% and 52.2%, respectively). The relative risk of relapse (RR) after discontinuing sertraline was 6.35.

## Off-Label Use and Special Populations

Sertraline has also been studied for off-label use in the treatment of a variety of disorders.

### **Mood Symptoms in Neurological Conditions**

Sertraline has been used to treat mood symptoms associated with a number of neurological conditions, including depression associated with Parkinson's disease ([Antonini et al. 2006](#); [Hauser and Zesiewicz 1997](#); [Meara and Hobson 1998](#)) and depression-linked fatigue in multiple sclerosis ([Mohr et al. 2003](#)). A study in children and adolescents with epilepsy and depression demonstrated sertraline's efficacy in treating depressive symptoms while maintaining good seizure control ([Thomé-Souza et al. 2007](#)). A 10-week study of sertraline in patients with chronic tension headaches showed a decline in analgesic medication use, suggesting that sertraline may be a good alternative for patients who cannot tolerate the adverse events associated with TCAs ([Singh and Misra 2002](#)). Sertraline also has been used to improve pathological crying and pseudobulbar-type affects ([Benedek and Peterson 1995](#); [Mukand et al. 1996](#); [Okun et al. 2001](#); [Peterson et al. 1996](#)).

## Depression and Cognitive Dysfunction in Elderly Patients With and Without Dementia

Following initial results suggesting a possible role for sertraline in Alzheimer's disease ([Lyketsos et al. 2000](#); [Magai et al. 2000](#)), subsequent studies failed to demonstrate the drug's superiority to placebo at 12, 13, and 24 weeks ([Banerjee et al. 2011](#); [Rosenberg et al. 2010](#); [Weintraub et al. 2010](#)). A recent small study comparing sertraline, venlafaxine, and desipramine in depressed patients with Alzheimer's disease reported significant improvement over baseline in cognitive test performance for all three drugs, with the most widespread effects noted for sertraline ([Mokhber et al. 2014](#)). Sertraline additionally appears to improve subsyndromal depressive symptoms and cognitive function in elderly patients without dementia ([Rocca et al. 2005](#)).

## Substance Use Disorders

Numerous studies have examined the potential for sertraline to benefit patients with substance use disorders. An acute-phase trial of sertraline in DSM-IV alcohol dependence did not indicate its benefit over placebo ([Kranzler et al. 2006](#)), but subsequent analyses and follow-up data suggested potential benefit for alcohol-dependent patients with certain genotypes ([Kranzler et al. 2012](#)). The combination of sertraline plus naltrexone may be particularly useful for treating depressive symptoms and maintaining sobriety in individuals with co-occurring depression and alcohol dependence ([Pettinati et al. 2010](#)). Most studies of sertraline for dependence on other substances of abuse—such as methamphetamine ([Shoptaw et al. 2006](#)), opiates ([Carpenter et al. 2004](#)), or cocaine

([Winhusen et al. 2005](#))—do not suggest any benefit from sertraline in helping to curb substance use. However, a recent trial did find that in comparison with placebo, sertraline delayed the time to relapse in cocaine-dependent patients with depressive symptoms ([Oliveto et al. 2012](#)).

## **Depression in Cardiovascular Disease**

Sertraline is one of the few antidepressants shown to be safe for the treatment of depression in patients with cardiovascular disease. In a well-publicized study by the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group, 369 patients with a recent myocardial infarction or hospitalization for unstable angina who also met criteria for a current major depressive episode were randomly assigned to receive sertraline (at flexible dosages of 50–200 mg/day) or placebo for 24 weeks ([Glassman et al. 2002](#)). There were no significant treatment-emergent effects of sertraline on cardiac measures (including change from baseline left ventricular ejection fraction [LVEF], runs of ventricular premature complexes, or prolonged QTc intervals). For the entire sample, sertraline was superior to placebo in improving rates of response when defined by CGI ratings, but not when defined by Ham-D scores ([Glassman et al. 2002](#)). A separate analysis of the SADHART data showed a trend for sertraline-treated patients to have fewer psychiatric or cardiovascular hospitalizations during the treatment period ([O'Connor et al. 2005](#)) and indicated that sertraline was most beneficial for those patients whose depressive episodes predated the acute cardiac syndrome, those who had a past history of MDD, and those whose episodes were of greater severity ([Glassman et al. 2006](#)). However, although sertraline's safety was again demonstrated in a study of 469 SADHART patients with

chronic heart failure (CHF), in this sample there was no evidence of antidepressant superiority of sertraline over placebo ([O'Connor et al. 2010](#)). Compared with nonremitting patients, CHF patients who achieved remission from depression had fewer cardiovascular events at pretreatment baseline and went on to have better cardiovascular outcomes over a 5-year period ([Jiang et al. 2011](#)).

Sertraline alone and sertraline in combination with coping skills training showed efficacy in treating noncardiac chest pain, including associated symptoms of catastrophizing and anxiety ([Keefe et al. 2011](#)).

Other data relevant to cardiac health include a sertraline trial in nondepressed patients with chronic ischemic heart failure, in which the drug appeared to decrease ventricular extrasystoles ([Leftheriotis et al. 2010](#)). Although the potential mechanism of its cardiovascular benefit is not entirely clear, sertraline may decrease platelet adherence, thereby reducing the likelihood of recurrent myocardial events ([McFarlane et al. 2001](#); [Shapiro et al. 1999](#)).

A review of the literature relevant to abnormal bleeding associated with sertraline and other SSRIs suggested increased risk for gastrointestinal bleeding may be caused by an SSRI-induced increase in gastric acid secretion, whereas a protective effect against ischemic heart disease may be attributable to SSRI effects on platelet reactivity, endothelial reactivity, and inflammatory markers ([Andrade et al. 2010](#)). Of note, examination of pretreatment inflammatory markers in a sample ( $n=122$ ) with coronary heart disease (CHD) and comorbid depression did not suggest that elevated baseline inflammatory markers predicted inferior response to sertraline ([Bot et al. 2011](#)), but depressed CHD patients with comorbid obstructive

sleep apnea/hypopnea syndrome had inferior outcomes with sertraline ([Roest et al. 2012](#)). Other studies have demonstrated that sertraline can improve quality of life in depressed patients with acute coronary syndrome ([Swenson et al. 2003](#)) or a recent stroke ([Murray et al. 2005](#)).

A meta-analysis of 16 studies involving about 4,300 patients reported that TCAs and citalopram were associated with significantly greater QTc prolongation than were sertraline, paroxetine, or fluvoxamine ([Beach et al. 2014](#)).

## **Depression in Cancer**

Sertraline has been studied in patients with cancer and depression. A 12-week open-label, flexible-dose trial of sertraline in patients undergoing chemotherapy demonstrated positive effects on depressed mood ([Torta et al. 2008](#)), but in a controlled trial of almost 200 patients with advanced disease who did not have MDD, sertraline had no mood benefit over placebo ([Stockler et al. 2007](#)).

## **Vasomotor Symptoms**

Another proposed off-label use for sertraline is the alleviation of hot flashes associated with menopause ([Aedo et al. 2011](#); [Gordon et al. 2006](#); [Grady et al. 2007](#)) or with tamoxifen treatment for breast cancer ([Kimmick et al. 2006](#)) in women, as well as in men following medical castration for advanced prostate cancer ([Roth and Scher 1998](#)). One study suggested that a positive response to sertraline for hot flashes is related to activity level, education, and menopausal status ([Kerwin et al. 2007](#)).

Sertraline was superior to placebo in a study that examined its potential for controlling hot flashes in women with or at high risk of breast cancer, for whom hormone therapy was not recommended ([Wu et al. 2009](#)).

## Other Uses

There has been some research investigating sertraline's potential benefit in a variety of other conditions.

Sertraline has been used successfully in the treatment of children and adolescents with MDD and dysthymic disorder ([Ambrosini et al. 1999](#); [Nixon et al. 2001](#)), and it has demonstrated some utility in the treatment of depression in patients with schizophrenia ([Addington et al. 2002](#); [Kirli and Caliskan 1998](#); [Mulholland et al. 2003](#)). One study in patients with MDD showed that sertraline increased adaptive traits associated with psychopathic personality (social charm and interpersonal and physical boldness) and reduced maladaptive traits associated with psychopathy (dysregulated impulsivity and externalization), independent of its antidepressant effects ([Dunlop et al. 2011](#)).

Sertraline has also shown some benefit in the treatment of generalized anxiety disorder (GAD). Two randomized GAD trials showed that sertraline had superiority over placebo ([Allgulander et al. 2004](#); [Brawman-Mintzer et al. 2006](#)) and efficacy similar to that of paroxetine ([Ball et al. 2005](#)). In a placebo-controlled trial ([Rynn et al. 2001](#)), sertraline was both effective and safe in children with GAD.

Results from some investigations suggest a role for sertraline in the treatment of various eating disorders, including anorexia nervosa ([Santonastaso et al. 2001](#)), bulimia nervosa ([Milano et al. 2004](#)), binge-eating disorder ([Leombruni et al. 2006](#); [McElroy et al. 2000](#)), and night-eating syndrome ([O'Reardon et al. 2006](#)).

Several studies have reported sertraline's benefit in treating premature ejaculation ([Arafa and Shamloul 2006](#); [Biri et al. 1998](#)).

Trials of sertraline for DSM-IV impulse-control disorders have yielded mixed results; positive outcomes were observed in a trichotillomania sample ([Dougherty et al. 2006](#)), but no therapeutic effect was demonstrated for gambling disorders ([Saiz-Ruiz et al. 2005](#)).

A number of studies have highlighted the effective use of sertraline in treating aggressive and self-harming behaviors ([Buck 1995](#); [Feder 1999](#)), specifically in patients with personality disorders ([Kavoussi et al. 1994](#)), patients with Huntington's disease ([Ranen et al. 1996](#)), and adults with intellectual disability or autism spectrum disorder ([Hellings et al. 1996](#); [McDougle et al. 1998](#)).

Sertraline has proved useful in preventing dialysis-induced hypotension, a condition that can be exacerbated by other antidepressive agents ([Perazella 2001](#)). Sertraline also has been of benefit in treating pruritus associated with cholestatic liver disease ([Mayo et al. 2007](#)). Finally, it has been shown to reduce symptom severity in refractory tinnitus ([Zöger et al. 2006](#)).

---

## Side Effects and Toxicology

---

Sertraline has been demonstrated to have a low incidence of anticholinergic, sedative, and cardiovascular effects because of its low affinity for adrenergic, cholinergic, histaminergic, and benzodiazepine receptors. However, in premarketing evaluations, sertraline was associated with a number of adverse effects. The most commonly reported



side effects were gastrointestinal disturbance (nausea, 27%; diarrhea/loose stools, 21%), sleep disturbance (insomnia, 22%; somnolence, 14%), headache (26%), dry mouth (15%), and sexual dysfunction (ejaculation failure, 14%; decreased libido, 6%). Other side effects reported by subjects and described as frequent (i.e., occurring in at least 1 of 100 subjects) in premarketing pooled data from clinical trials included impotence, palpitations, chest pain, hypertonia, hypoesthesia, increased appetite, back pain, asthenia, malaise, weight gain, myalgia, yawning, rhinitis, and tinnitus ([Pfizer 2016](#)).

## Hyponatremia

Sertraline and other SSRIs have been associated with cases of hyponatremia, as well as with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (see [Bouman et al. 1997](#); [Bradley et al. 1996](#); [Catalano et al. 1996](#); [Goldstein et al. 1996](#); [Kessler and Samuels 1996](#)). [Bradley et al. \(1996\)](#), in a review of the literature, noted that the average age of patients experiencing SIADH was greater than 70 years, suggesting that the elderly may be more vulnerable to age-related changes in water balance, which may make them more susceptible to developing SIADH with an SSRI.

## Extrapyramidal Side Effects

Extrapyramidal side effects (EPS), including dyskinesias, dystonias, and akathisia, have been observed with sertraline use, although they are infrequent ([Altshuler and Szuba 1994](#); [Lambert et al. 1998](#); [Madhusoodanan and](#)

[Brenner 1997](#); [Opler 1994](#)). [Hamilton and Opler \(1992\)](#) suggested that the underlying mechanism of SSRI-induced akathisia is serotonergic inhibition of the nigrostriatal dopamine pathway, which can be associated with parkinsonism ([Leo et al. 1995](#); [Pina Latorre et al. 2001](#)). [Madhusoodanan and Brenner \(1997\)](#), in a case report of choreiform dyskinesia and EPS associated with sertraline therapy, proposed that 5-HT-driven antagonism of dopaminergic transmission in the nigrostriatal pathway, as well as in the ventral tegmental area, might be responsible.

## Sexual Dysfunction

Sexual dysfunction is a well-known side effect of SSRIs, including sertraline. A Cochrane Database review noted that although limited evidence is available, some trials have suggested that the addition of sildenafil or bupropion can reduce antidepressant-induced erectile dysfunction in men ([Rudkin et al. 2004](#)).

## Rare Adverse Events

Other adverse events associated with sertraline are rare and include seizures ([Raju et al. 2000](#); [Saraf and Schrader 1999](#)), stuttering ([Brewerton et al. 1996](#); [Christensen et al. 1996](#); [McCall 1994](#)), altered platelet function and bleeding time ([Calhoun and Calhoun 1996](#); [Mendelson 2001](#)), and galactorrhea ([Bronzo and Stahl 1993](#); [Lesaca 1996](#)). Urinary hesitancy and retention have been reported in a few cases in women ([Lowenstein et al. 2007](#)). A study in GAD reported significantly greater bone density loss in

patients who received 12 months of sertraline treatment versus those treated with other SSRIs ([Ak et al. 2015](#)).

## Increased Risk of Suicidality

In common with all other antidepressants, sertraline carries an FDA black box warning regarding an increased risk of suicidality in children and adolescents, although there are no specific data indicating increased rates of suicide in children treated with sertraline. One specific study of suicidal thinking and behavior in more than 700 older adults with late-life depression showed no increase in suicidality with sertraline treatment versus placebo ([Nelson et al. 2007](#)).

## Discontinuation Syndrome

Sertraline has been associated with a discontinuation syndrome. [Leiter et al. \(1995\)](#) described two cases in which patients experienced alterations in mood, cognition, energy, gait, and equilibrium, in addition to gastrointestinal symptoms, headaches, and paresthesias. Elsewhere there have been reports of insomnia, impaired short-term memory, myalgias, dyspnea, and chills without fevers ([Louie et al. 1994](#)). In a systematic 28-week study in patients with panic disorder ([Rapaport et al. 2001](#)), abrupt discontinuation of sertraline was primarily associated only with insomnia (15.7% of patients randomly assigned to placebo vs. 4.3% continuing on sertraline) and dizziness (4.3% of patients continuing to take sertraline and 16.4% switched to placebo). There was no statistically significant

increase in headache or in general malaise in patients randomly assigned to switch to placebo.

## Use During Pregnancy and Lactation

The safety of sertraline and other SSRIs during pregnancy is discussed in [Chapter 57](#) of this volume (“Psychopharmacology During Pregnancy and Lactation,” by Ray-Griffith, Newport, and Stowe). A recent large-scale study in Quebec reported that exposure to sertraline during the first trimester was associated with an increased risk of cardiac (atrial/ventricular) effects and craniosyntosis ([Bérard et al. 2015](#)). In contrast, a recent major review of SSRIs in breast feeding concluded that sertraline and paroxetine are the preferred agents (in regard to the infant’s health) for nursing women who require antidepressant treatment ([Orsolini and Bellantuono 2015](#)).

---

## Drug-Drug Interactions

---

Sertraline has a number of potential drug-drug interactions. Because the drug is tightly bound to plasma proteins, caution should be employed when sertraline is used in combination with pharmaceuticals possessing similar characteristics, such as warfarin, and prothrombin time should be monitored when sertraline and warfarin are used concurrently ([Pfizer 2016](#)). The potential for serotonin syndrome may be increased when sertraline is used in combination with other SSRIs, serotonin-norepinephrine reuptake inhibitors, or triptans prescribed for the acute treatment of migraines. Coadministration of sertraline with

an MAOI is contraindicated because of the significant risk of serotonin syndrome with this combination.

The degree of sertraline's inhibition of the CYP system, most significantly CYP2D6, is relatively minor in comparison with that of other SSRIs, such as fluoxetine and paroxetine ([Preskorn et al. 2007](#)), although mouse data have shown a mild pharmacokinetic drug-drug interaction between bupropion and sertraline that leads to a small elevation in bupropion metabolism ([Molnari et al. 2012](#)). Because TCAs are substrates of CYP2D6, drug levels and dosages need to be closely monitored when TCAs are used in combination with sertraline.

Sertraline, in common with its fellow SSRIs citalopram and escitalopram, is also metabolized by the CYP2C19 isoenzyme, which is inhibited by proton pump inhibitors (PPIs). In a study examining the effect of PPIs on serum concentrations of SSRIs, coadministration of the PPI esomeprazole led to significant elevations (+38.5%;  $P=0.0014$ ) in sertraline blood levels but caused an almost twofold increase (+81.8%;  $P<0.001$ ) in escitalopram blood levels ([Gjestad et al. 2015](#)).

---

## Conclusion

---

Controlled clinical trials support sertraline's efficacy in the treatment of a variety of psychiatric conditions, including depressive and anxiety disorders, and uncontrolled studies suggest an expanded role for sertraline in a number of other conditions. Sertraline's safety profile is superior to that of older antidepressant agents, thus increasing the

potential target population of patients in whom sertraline treatment can be beneficial.

---

## References

---

- Addington DD, Azorin JM, Falloon IR, et al: Clinical issues related to depression in schizophrenia: an international survey of psychiatrists. *Acta Psychiatr Scand* 105(3):189-195, 2002 11939972
- Aedo S, Cavada G, Campodonico I, et al: Sertraline improves the somatic and psychological symptoms of the climacteric syndrome. *Climacteric* 14(5):590-595, 2011 21861771
- Aguglia E, Casacchia M, Cassano GB, et al: Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. *Int Clin Psychopharmacol* 8(3):197-202, 1993 8263318
- Ak E, Bulut SD, Bulut S, et al: Evaluation of the effect of selective serotonin reuptake inhibitors on bone mineral density: an observational cross-sectional study. *Osteoporos Int* 26(1):273-279, 2015 25187118
- Aldana BI, Sitges M: Sertraline inhibits pre-synaptic Na<sup>+</sup> channel-mediated responses in hippocampus-isolated nerve endings. *J Neurochem* 121(2):197-205, 2012 22288826
- Allgulander C, Dahl AA, Austin C, et al: Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry* 161(9):1642-1649, 2004 15337655
- Altshuler LL, Szuba MP: Course of psychiatric disorders in pregnancy. Dilemmas in pharmacologic management. *Neurol Clin* 12(3):613-635, 1994 7990794
- Ambrosini PJ, Wagner KD, Biederman J, et al: Multicenter open-label sertraline study in adolescent outpatients

- with major depression. *J Am Acad Child Adolesc Psychiatry* 38(5):566–572, 1999 10230188
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Andrade C, Sandarsh S, Chethan KB, et al: Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry* 71(12):1565–1575, 2010 21190637
- Anthony JP, Sexton TJ, Neumaier JF: Antidepressant-induced regulation of 5-HT(1b) mRNA in rat dorsal raphe nucleus reverses rapidly after drug discontinuation. *J Neurosci Res* 61(1):82–87, 2000 10861803
- Antonini A, Tesei S, Zecchinelli A, et al: Randomized study of sertraline and low-dose amitriptyline in patients with Parkinson's disease and depression: effect on quality of life. *Mov Disord* 21(8):1119–1122, 2006 16637039
- Arafa M, Shamloul R: Efficacy of sertraline hydrochloride in treatment of premature ejaculation: a placebo-controlled study using a validated questionnaire. *Int J Impot Res* 18(6):534–538, 2006 16554853
- Ball SG, Kuhn A, Wall D, et al: Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. *J Clin Psychiatry* 66(1):94–99, 2005 15669894
- Banerjee S, Hellier J, Dewey M, et al: Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 378(9789):403–411, 2011 21764118
- Beach SR, Kostis WJ, Celano CM, et al: Meta-analysis of selective serotonin reuptake inhibitor-associated QTc

- prolongation. *J Clin Psychiatry* 75(5):e441-e449, 2014 24922496
- Benedek DM, Peterson KA: Sertraline for treatment of pathological crying. *Am J Psychiatry* 152(6):953-954, 1995 7755132
- Bérard A, Zhao JP, Sheehy O: Sertraline use during pregnancy and the risk of major malformations. *Am J Obstet Gynecol* 212(6):795.e1-795.e12, 2015 25637841
- Bergeron R, Ravindran AV, Chaput Y, et al: Sertraline and fluoxetine treatment of obsessive-compulsive disorder: results of a double-blind, 6-month treatment study. *J Clin Psychopharmacol* 22(2):148-154, 2002 11910259
- Biri H, Isen K, Sinik Z, et al: Sertraline in the treatment of premature ejaculation: a double-blind placebo controlled study. *Int Urol Nephrol* 30(5):611-615, 1998 9934807
- Bisserbe J, Lane R, Flament M; Franco-Belgian OCD Study Group: A double-blind comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. *Eur Psychiatry* 12(2):82-93, 1997 19698511
- Blier P: Pharmacology of rapid-onset antidepressant treatment strategies. *J Clin Psychiatry* 62 (suppl 15):12-17, 2001 11444761
- Blier P, de Montigny C, Chaput Y: A role for the serotonin system in the mechanism of action of antidepressant treatments: preclinical evidence. *J Clin Psychiatry* 51 (4 suppl):14-20, discussion 21, 1990 2157700
- Block J: Zoloft erosion outpaces recent generic launches. "The Pink Sheet" Daily. September 5, 2006. Available at: <https://www.pharmamedtechbi.com/publications/the-pink-sheet-daily/2006/9/5/zoloft-erosion-outpaces-other-recent-generic-launches>. Accessed June 29, 2015.
- Blomhoff S, Haug TT, Hellström K, et al: Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *Br J Psychiatry* 179:23-30, 2001 11435264



- Bondareff W, Alpert M, Friedhoff AJ, et al: Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. *Am J Psychiatry* 157(5):729-736, 2000 10784465
- Bot M, Carney RM, Freedland KE, et al: Inflammation and treatment response to sertraline in patients with coronary heart disease and comorbid major depression. *J Psychosom Res* 71(1):13-17, 2011 21665007
- Bouman WP, Johnson H, Trescoli-Serrano C, et al: Recurrent hyponatremia associated with sertraline and lofepramine. *Am J Psychiatry* 154(4):580, 1997 9090354
- Bradley ME, Foote EF, Lee EN, et al: Sertraline-associated syndrome of inappropriate antidiuretic hormone: case report and review of the literature. *Pharmacotherapy* 16(4):680-683, 1996 8840376
- Brady K, Pearlstein T, Asnis GM, et al: Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* 283(14):1837-1844, 2000 10770145
- Brawman-Mintzer O, Knapp RG, Rynn M, et al: Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 67(6):874-881, 2006 16848646
- Brewerton TD, Markowitz JS, Keller SG, et al: Stuttering with sertraline. *J Clin Psychiatry* 57(2):90-91, 1996 8591976
- Bronzo MR, Stahl SM: Galactorrhea induced by sertraline (letter). *Am J Psychiatry* 150(8):1269-1270, 1993 8093119
- Buck OD: Sertraline for reduction of violent behavior. *Am J Psychiatry* 152(6):953, 1995 7755131
- Calhoun JW, Calhoun DD: Prolonged bleeding time in a patient treated with sertraline. *Am J Psychiatry* 153(3):443, 1996 8610842
- Carpenter KM, Brooks AC, Vosburg SK, et al: The effect of sertraline and environmental context on treating

depression and illicit substance use among methadone maintained opiate dependent patients: a controlled clinical trial. *Drug Alcohol Depend* 74(2):123-134, 2004 15099656

Catalano G, Kanfer SN, Catalano MC, et al: The role of sertraline in a patient with recurrent hyponatremia. *Gen Hosp Psychiatry* 18(4):278-283, 1996 8832263

Chander WP, Singh N, Mukhiya GK: Serotonin syndrome in maintenance haemodialysis patients following sertraline treatment for depression. *J Indian Med Assoc* 109(1):36-37, 2011 21888157

Christensen RC, Byerly MJ, McElroy RA: A case of sertraline-induced stuttering. *J Clin Psychopharmacol* 16(1):92-93, 1996 8834434

Cipriani A, La Ferla T, Furukawa TA, et al: Sertraline versus other antidepressive agents for depression. *Cochrane Database Syst Rev* (4):CD006117, 2010 20393946

Cohn CK, Shrivastava R, Mendels J, et al: Double-blind, multicenter comparison of sertraline and amitriptyline in elderly depressed patients. *J Clin Psychiatry* 51 (12 suppl B):28-33, 1990 2258379

Compton SN, Grant PJ, Chrisman AK, et al: Sertraline in children and adolescents with social anxiety disorder: an open trial. *J Am Acad Child Adolesc Psychiatry* 40(5):564-571, 2001 11349701

Davidson J, Pearlstein T, Lonnberg P, et al: Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry* 158(12):1974-1981, 2001a 11729012

Davidson JR, Rothbaum BO, van der Kolk BA, et al: Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry* 58(5):485-492, 2001b 11343529

- Doogan DP, Caillard V: Sertraline in the prevention of depression. *Br J Psychiatry* 160:217-222, 1992 1540762
- Dougherty DD, Loh R, Jenike MA, et al: Single modality versus dual modality treatment for trichotillomania: sertraline, behavioral therapy, or both? *J Clin Psychiatry* 67(7):1086-1092, 2006 6889452
- Dunlop BW, DeFife JA, Marx L, et al: The effects of sertraline on psychopathic traits. *Int Clin Psychopharmacol* 26(6):329-337, 2011 21909028
- Fabre LF, Abuzzahab FS, Amin M, et al: Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. *Biol Psychiatry* 38(9):592-602, 1995 8573661
- Feder R: Treatment of intermittent explosive disorder with sertraline in 3 patients. *J Clin Psychiatry* 60(3):195-196, 1999 10192598
- Finkel SI, Richter EM, Clary CM, et al: Comparative efficacy of sertraline vs. fluoxetine in patients age 70 or over with major depression. *Am J Geriatr Psychiatry* 7(3):221-227, 1999 10438693
- Forlenza OV, Almeida OP, Stoppe A Jr, et al: Antidepressant efficacy and safety of low-dose sertraline and standard-dose imipramine for the treatment of depression in older adults: results from a double-blind, randomized, controlled clinical trial. *Int Psychogeriatr* 13(1):75-84, 2001 11352337
- Franchini L, Gasperini M, Perez J, et al: A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. *J Clin Psychiatry* 58(3):104-107, 1997 9108811
- Frazer A, Scott PA: Onset of action of antidepressant treatments: neuropharmacological aspects, in *Critical Issues in the Treatment of Affective Disorders/Collegium Internationale Neuro-Psychopharmacologicum Regional Workshop*, Paris, March 12-14, 1994 (International

Academy for Biomedical and Drug Research [Series] Vol. 9; Racagni G, Brunello N, volume editors). New York, Karger, 1994, pp 82-89

Freeman EW, Sammel MD, Lin H, et al: Clinical subtypes of premenstrual syndrome and responses to sertraline treatment. *Obstet Gynecol* 118(6):1293-1300, 2011 22105258

Friedman MJ, Marmar CR, Baker DG, et al: Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry* 68(5):711-720, 2007 17503980

Gjestad C, Westin AA, Skogvoll E, et al: Effect of proton pump inhibitors on the serum concentrations of the selective serotonin reuptake inhibitors citalopram, escitalopram, and sertraline. *Ther Drug Monit* 37(1):90-97, 2015 24887634

Glassman AH, O'Connor CM, Califf RM, et al; Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group: Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 288(6):701-709, 2002 12169073

Glassman AH, Bigger JT, Gaffney M, et al: Onset of major depression associated with acute coronary syndromes: relationship of onset, major depressive disorder history, and episode severity to sertraline benefit. *Arch Gen Psychiatry* 63(3):283-288, 2006 16520433

Goldstein L, Barker M, Segall F, et al: Seizure and transient SIADH associated with sertraline (letter). *Am J Psychiatry* 153(5): 732, 1996 8615425

Gordon PR, Kerwin JP, Boesen KG, et al: Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population. *Menopause* 13(4):568-575, 2006 16837878

Grady D, Cohen B, Tice J, et al: Ineffectiveness of sertraline for treatment of menopausal hot flashes: a randomized

- controlled trial. *Obstet Gynecol* 109(4):823-830, 2007 17400842
- Greenblatt DJ, von Moltke LL, Harmatz JS, et al: Human cytochromes mediating sertraline biotransformation: seeking attribution. *J Clin Psychopharmacol* 19(6):489-493, 1999 10587282
- Greist JH, Jefferson JW, Kobak KA, et al: A 1 year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol* 10(2):57-65, 1995 7673657
- Guthrie SK: Sertraline: a new specific serotonin reuptake blocker. *DICP* 25(9):952-961, 1991 1949975
- Halbreich U, Bergeron R, Yonkers KA, et al: Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 100(6):1219-1229, 2002 12468166
- Hamilton MS, Opler LA: Akathisia, suicidality, and fluoxetine. *J Clin Psychiatry* 53(11):401-406, 1992 1364815
- Hantsoo L, Ward-O'Brien D, Czarkowski KA, et al: A randomized, placebo-controlled, double-blind trial of sertraline for postpartum depression. *Psychopharmacology (Berl)* 231(5):939-948, 2014 24173623
- Hauser RA, Zesiewicz TA: Sertraline for the treatment of depression in Parkinson's disease. *Mov Disord* 12(5):756-759, 1997 9380061
- Hellings JA, Kelley LA, Gabrielli WF, et al: Sertraline response in adults with mental retardation and autistic disorder. *J Clin Psychiatry* 57(8):333-336, 1996 8778118
- Heym J, Koe BK: Pharmacology of sertraline: a review. *J Clin Psychiatry* 49 (suppl):40-45, 1988 3045112
- Hiemke C, Härtter S: Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 85(1):11-28, 2000 10674711

- Hiemke C, Jussofie A, Jüptner M: Evidence that 3 alpha-hydroxy-5 alpha-pregnan-20-one is a physiologically relevant modulator of GABA-ergic neurotransmission. *Psychoneuroendocrinology* 16(6):517-523, 1991 1667336
- Hoehn-Saric R, Ninan P, Black DW, et al: Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Arch Gen Psychiatry* 57(1):76-82, 2000 10632236
- Jenike MA, Baer L, Summergrad P, et al: Sertraline in obsessive-compulsive disorder: a double-blind comparison with placebo. *Am J Psychiatry* 147(7):923-928, 1990 2192564
- Jiang W, Krishnan R, Kuchibhatla M, et al; SADHART-CHF Investigators: Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF Study). *Am J Cardiol* 107(4):545-551, 2011 21295172
- Katzelnick DJ, Kobak KA, Greist JH, et al: Sertraline for social phobia: a double-blind, placebo-controlled crossover study. *Am J Psychiatry* 152(9):1368-1371, 1995 7653696
- Kavoussi RJ, Liu J, Coccaro EF: An open trial of sertraline in personality disordered patients with impulsive aggression. *J Clin Psychiatry* 55(4):137-141, 1994 8071257
- Keefe FJ, Shelby RA, Somers TJ, et al: Effects of coping skills training and sertraline in patients with non-cardiac chest pain: a randomized controlled study. *Pain* 152(4):730-741, 2011 21324590
- Keller MB, Gelenberg AJ, Hirschfeld RM, et al: The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. *J Clin Psychiatry* 59(11):598-607, 1998a 9862606

- Keller MB, Kocsis JH, Thase ME, et al: Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* 280(19):1665-1672, 1998b 9831997
- Kerwin JP, Gordon PR, Senf JH: The variable response of women with menopausal hot flashes when treated with sertraline. *Menopause* 14(5):841-845, 2007 17413648
- Kessler J, Samuels SC: Sertraline and hyponatremia (letter). *N Engl J Med* 335(7):524, 1996 8676965
- Kimmick GG, Lovato J, McQuellon R, et al: Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *Breast J* 12(2):114-122, 2006 16509835
- Kirli S, Caliskan M: A comparative study of sertraline versus imipramine in postpsychotic depressive disorder of schizophrenia. *Schizophr Res* 33(1-2):103-111, 1998 9783350
- Kitaichi Y, Inoue T, Nakagawa S, et al: Sertraline increases extracellular levels not only of serotonin, but also of dopamine in the nucleus accumbens and striatum of rats. *Eur J Pharmacol* 647(1-3):90-96, 2010 20816814
- Kornstein SG, Schatzberg AF, Thase ME, et al: Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry* 157(9):1445-1452, 2000 10964861
- Koszycki D, Taljaard M, Segal Z, et al: A randomized trial of sertraline, self-administered cognitive behavior therapy, and their combination for panic disorder. *Psychol Med* 41(2):373-383, 2011 20462466
- Kranzler HR, Mueller T, Cornelius J, et al: Sertraline treatment of co-occurring alcohol dependence and major depression. *J Clin Psychopharmacol* 26(1):13-20, 2006 16415699
- Kranzler HR, Armeli S, Tennen H: Post-treatment outcomes in a double-blind, randomized trial of sertraline for

- alcohol dependence. *Alcohol Clin Exp Res* 36(4):739-744, 2012 21981418
- Kronig MH, Apter J, Asnis G, et al: Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. *J Clin Psychopharmacol* 19(2):172-176, 1999 10211919
- Lambert MT, Trutia C, Petty F: Extrapyramidal adverse effects associated with sertraline. *Prog Neuropsychopharmacol Biol Psychiatry* 22(5):741-748, 1998 9723116
- Lanza di Scalea T, Wisner KL: Antidepressant medication use during breastfeeding. *Clin Obstet Gynecol* 52(3):483-497, 2009 19661763
- Lee AJ, Chan WK, Harralson AF, et al: The effects of grapefruit juice on sertraline metabolism: an in vitro and in vivo study. *Clin Ther* 21(11):1890-1899, 1999 10890261
- Leftheriotis D, Flevari P, Ikonomidis I, et al: The role of the selective serotonin re-uptake inhibitor sertraline in nondepressive patients with chronic ischemic heart failure: a preliminary study. *Pacing Clin Electrophysiol* 33(10):1217-1223, 2010 20487349
- Leiter FL, Nierenberg AA, Sanders KM, et al: Discontinuation reactions following sertraline. *Biol Psychiatry* 38(10):694-695, 1995 8555382
- Leo RJ, Lichter DG, Hershey LA: Parkinsonism associated with fluoxetine and cimetidine: a case report. *J Geriatr Psychiatry Neurol* 8(4):231-233, 1995 8561837
- Leombruni P, Pierò A, Brustolin A, et al: A 12 to 24 weeks pilot study of sertraline treatment in obese women binge eaters. *Hum Psychopharmacol* 21(3):181-188, 2006 16625525
- Lesaca TG: Sertraline and galactorrhea. *J Clin Psychopharmacol* 16(4):333-334, 1996 8835712
- Liebowitz MR, DeMartinis NA, Weihs K, et al: Efficacy of sertraline in severe generalized social anxiety disorder:



- results of a double-blind, placebo-controlled study. *J Clin Psychiatry* 64(7):785-792, 2003 12934979
- Londborg PD, Wolkow R, Smith WT, et al: Sertraline in the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose investigation. *Br J Psychiatry* 173:54-60, 1998 9850204
- Londborg PD, Hegel MT, Goldstein S, et al: Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. *J Clin Psychiatry* 62(5):325-331, 2001 11411812
- Louie AK, Lannon RA, Ajari LJ: Withdrawal reaction after sertraline discontinuation. *Am J Psychiatry* 151(3):450-451, 1994 8109661
- Lowenstein L, Mueller ER, Sharma S, et al: Urinary hesitancy and retention during treatment with sertraline. *Int Urogynecol J Pelvic Floor Dysfunct* 18(7):827-829, 2007 17089079
- Lydiard RB, Stahl SM, Hertzman M, et al: A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. *J Clin Psychiatry* 58(11):484-491, 1997 9413414
- Lyketsos CG, Sheppard JM, Steele CD, et al: Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: initial results from the Depression in Alzheimer's Disease study. *Am J Psychiatry* 157(10):1686-1689, 2000 11007727
- Madhusoodanan S, Brenner R: Reversible choreiform dyskinesia and extrapyramidal symptoms associated with sertraline therapy. *J Clin Psychopharmacol* 17(2):138-139, 1997 10950491
- Magai C, Kennedy G, Cohen CI, et al: A controlled clinical trial of sertraline in the treatment of depression in nursing home patients with late-stage Alzheimer's

- disease. *Am J Geriatr Psychiatry* 8(1):66-74, 2000 10648297
- March JS, Biederman J, Wolkow R, et al: Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA* 280(20):1752-1756, 1998 9842950
- Mayo MJ, Handem I, Saldana S, et al: Sertraline as a first-line treatment for cholestatic pruritus. *Hepatology* 45(3):666-674, 2007 17326161
- McCall WV: Sertraline-induced stuttering. *J Clin Psychiatry* 55(7):316, 1994 8071298
- McDougle CJ, Brodtkin ES, Naylor ST, et al: Sertraline in adults with pervasive developmental disorders: a prospective open-label investigation. *J Clin Psychopharmacol* 18(1):62-66, 1998 9472844
- McElroy SL, Casuto LS, Nelson EB, et al: Placebo-controlled trial of sertraline in the treatment of binge eating disorder. *Am J Psychiatry* 157(6):1004-1006, 2000 10831483
- McFarlane A, Kamath MV, Fallen EL, et al: Effect of sertraline on the recovery rate of cardiac autonomic function in depressed patients after acute myocardial infarction. *Am Heart J* 142(4):617-623, 2001 11579351
- Meara J, Hobson P: Depression, anxiety and hallucinations in Parkinson's disease. *Elder Care* 10 (4 suppl 4-5), 1998 9855934
- Mendelson SD: Platelet function and sertraline. *Am J Psychiatry* 158(5):823-824, 2001 11329424
- Milano W, Petrella C, Sabatino C, et al: Treatment of bulimia nervosa with sertraline: a randomized controlled trial. *Adv Ther* 21(4):232-237, 2004 15605617
- Milgrom J, Gemmill AW, Ericksen J, et al: Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: a randomised controlled trial. *Aust N Z J Psychiatry* 49(3):236-245, 2015 25586754

- Mohr DC, Hart SL, Goldberg A: Effects of treatment for depression on fatigue in multiple sclerosis. *Psychosom Med* 65(4):542-547, 2003 12883103
- Mokhber N, Abdollahian E, Soltanifar A, et al: Comparison of sertraline, venlafaxine and desipramine effects on depression, cognition and the daily living activities in Alzheimer patients. *Pharmacopsychiatry* 47(4-5):131-140, 2014 24955552
- Möller HJ, Gallinat J, Hegerl U, et al: Double-blind, multicenter comparative study of sertraline and amitriptyline in hospitalized patients with major depression. *Pharmacopsychiatry* 31(5):170-177, 1998 9832348
- Molnari JC, Hassan HE, Myers AL: Effects of sertraline on the pharmacokinetics of bupropion and its major metabolite, hydroxybupropion, in mice. *Eur J Drug Metab Pharmacokinet* 37(1):57-63, 2012 21928040
- Mukand J, Kaplan M, Senno RG, et al: Pathological crying and laughing: treatment with sertraline. *Arch Phys Med Rehabil* 77(12):1309-1311, 1996 8976317
- Mulholland C, Lynch G, King DJ, et al: A double-blind, placebo-controlled trial of sertraline for depressive symptoms in patients with stable, chronic schizophrenia. *J Psychopharmacol* 17(1):107-112, 2003 12680747
- Murray V, von Arbin M, Bartfai A, et al: Double-blind comparison of sertraline and placebo in stroke patients with minor depression and less severe major depression. *J Clin Psychiatry* 66(6):708-716, 2005 15960563
- Mushtaq D, Ali A, Margoob MA, et al: Association between serotonin transporter gene promoter-region polymorphism and 4- and 12-week treatment response to sertraline in posttraumatic stress disorder. *J Affect Disord* 136(3):955-962, 2012 21962566
- Nelson JC, Delucchi K, Schneider L: Suicidal thinking and behavior during treatment with sertraline in late-life

- depression. *Am J Geriatr Psychiatry* 15(7):573–580, 2007 17586782
- Nemeroff CB, DeVane CL, Pollock BG: Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 153(3):311–320, 1996 8610817
- Newhouse PA, Krishnan KR, Doraiswamy PM, et al: A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. *J Clin Psychiatry* 61(8):559–568, 2000 10982198
- Ninan PT, Koran LM, Kiev A, et al: High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. *J Clin Psychiatry* 67(1):15–22, 2006 16426083
- Nixon MK, Milin R, Simeon JG, et al: Sertraline effects in adolescent major depression and dysthymia: a six-month open trial. *J Child Adolesc Psychopharmacol* 11(2):131–142, 2001 11436952
- Okun MS, Riestra AR, Nadeau SE: Treatment of ballism and pseudobulbar affect with sertraline. *Arch Neurol* 58(10):1682–1684, 2001 11594930
- Olie J, Gunn K, Katz E: A double-blind placebo-controlled multicentre study of sertraline in the acute and continuation treatment of major depression. *Eur Psychiatry* 12(1):34–41, 1997 19698503
- Oliveto A, Poling J, Mancino MJ, et al: Sertraline delays relapse in recently abstinent cocaine-dependent patients with depressive symptoms. *Addiction* 107(1):131–141, 2012 21707811
- Opler LA: Sertraline and akathisia. *Am J Psychiatry* 151(4):620–621, 1994 8147471
- Orsolini L, Bellantuono C: Serotonin reuptake inhibitors and breastfeeding: a systematic review. *Hum Psychopharmacol* 30(1):4–20, 2015 25572308
- O'Connor CM, Glassman AH, Harrison DJ: Pharmacoeconomic analysis of sertraline treatment of depression in patients with unstable angina or a recent

myocardial infarction. *J Clin Psychiatry* 66(3):346-352, 2005 15766301

O'Connor CM, Jiang W, Kuchibhatla M, et al; SADHART-CHF Investigators: Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol* 56(9):692-699, 2010 20723799

O'Reardon JP, Allison KC, Martino NS, et al: A randomized, placebo-controlled trial of sertraline in the treatment of night eating syndrome. *Am J Psychiatry* 163(5):893-898, 2006 16648332

Owens MJ, Knight DL, Nemeroff CB: Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. *Biol Psychiatry* 50(5):345-350, 2001 11543737

Ozdemir V, Naranjo CA, Herrmann N, et al: The extent and determinants of changes in CYP2D6 and CYP1A2 activities with therapeutic doses of sertraline. *J Clin Psychopharmacol* 18(1):55-61, 1998 9472843

Panahi Y, Moghaddam BR, Sahebkar A, et al: A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-traumatic stress disorder. *Psychol Med* 41(10):2159-2166, 2011 21349225

Perazella MA: Pharmacologic options available to treat symptomatic intradialytic hypotension. *Am J Kidney Dis* 38 (4 suppl 4):S26-S36, 2001 11602458

Peterson KA, Armstrong S, Moseley J: Pathologic crying responsive to treatment with sertraline (letter). *J Clin Psychopharmacol* 16(4):333, 1996 8835711

Pettinati HM, Oslin DW, Kampman KM, et al: A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *Am J Psychiatry* 167(6):668-675, 2010 20231324

- Pfizer: ZOLOFT (sertraline hydrochloride) tablets, full prescribing information. New York, NY, Roerig (division of Pfizer Inc), 2016. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=517>. Accessed January 22, 2016.
- Pina Latorre MA, Modrego PJ, Rodilla F, et al: Parkinsonism and Parkinson's disease associated with long-term administration of sertraline. *J Clin Pharm Ther* 26(2):111-112, 2001 11350533
- Pohl RB, Wolkow RM, Clary CM: Sertraline in the treatment of panic disorder: a double-blind multicenter trial. *Am J Psychiatry* 155(9):1189-1195, 1998 9734541
- Pollack MH, Otto MW, Worthington JJ, et al: Sertraline in the treatment of panic disorder: a flexible-dose multicenter trial. *Arch Gen Psychiatry* 55(11):1010-1016, 1998 9819070
- Preskorn SH: Effects of antidepressants on the cytochrome P450 system. *Am J Psychiatry* 153(12):1655-1657, 1996 8942473
- Preskorn SH, Shah R, Neff M, et al: The potential for clinically significant drug-drug interactions involving the CYP 2D6 system: effects with fluoxetine and paroxetine versus sertraline. *J Psychiatr Pract* 13(1):5-12, 2007 17242587
- Raju GV, Kumar TC, Khanna S: Seizures associated with sertraline. *Can J Psychiatry* 45(5):491, 2000 10900533
- Rancourt J: Teva launches first generic Zoloft. "The Pink Sheet" Daily. August 14, 2006. Available at: <https://www.pharmamedtechbi.com/publications/the-pink-sheet-daily/2006/8/14/teva-launches-first-generic-zoloft>. Accessed June 29, 2015.
- Ranen NG, Lipsey JR, Treisman G, et al: Sertraline in the treatment of severe aggressiveness in Huntington's disease. *J Neuropsychiatry Clin Neurosci* 8(3):338-340, 1996 8854307

- Rapaport MH, Wolkow R, Rubin A, et al: Sertraline treatment of panic disorder: results of a long-term study. *Acta Psychiatr Scand* 104(4):289-298, 2001 11722304
- Reimherr FW, Chouinard G, Cohn CK, et al: Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry* 51 (12 suppl B):18-27, 1990 2258378
- Richelson E: Pharmacology of antidepressants—characteristics of the ideal drug. *Mayo Clin Proc* 69(11):1069-1081, 1994 7967761
- Robb AS, Cueva JE, Sporn J, et al: Sertraline treatment of children and adolescents with posttraumatic stress disorder: a double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol* 20(6):463-471, 2010 21186964
- Rocca P, Calvarese P, Faggiano F, et al: Citalopram versus sertraline in late-life nonmajor clinically significant depression: a 1-year follow-up clinical trial. *J Clin Psychiatry* 66(3):360-369, 2005 15766303
- Roerig JL, Steffen K, Zimmerman C, et al: Preliminary comparison of sertraline levels in postbariatric surgery patients versus matched nonsurgical cohort. *Surg Obes Relat Dis* 8(1):62-66, 2012 21256091
- Roest AM, Carney RM, Stein PK, et al: Obstructive sleep apnea/hypopnea syndrome and poor response to sertraline in patients with coronary heart disease. *J Clin Psychiatry* 73(1):31-36, 2012 21903027
- Ronfeld RA, Tremaine LM, Wilner KD: Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers. *Clin Pharmacokinet* 32 (suppl 1):22-30, 1997 9068932
- Rosenberg PB, Drye LT, Martin BK, et al; DIADS-2 Research Group: Sertraline for the treatment of depression in Alzheimer disease. *Am J Geriatr Psychiatry* 18(2):136-145, 2010 20087081

- Roth AJ, Scher HI: Sertraline relieves hot flashes secondary to medical castration as treatment of advanced prostate cancer. *Psychooncology* 7(2):129-132, 1998 9589512
- Rudkin L, Taylor MJ, Hawton K: Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database Syst Rev* (4):CD003382, 2004 15495050
- Rynn MA, Siqueland L, Rickels K: Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry* 158(12):2008-2014, 2001 11729017
- Saiz-Ruiz J, Blanco C, Ibáñez A, et al: Sertraline treatment of pathological gambling: a pilot study. *J Clin Psychiatry* 66(1):28-33, 2005 15669885
- Santonastaso P, Friederici S, Favaro A: Sertraline in the treatment of restricting anorexia nervosa: an open controlled trial. *J Child Adolesc Psychopharmacol* 11(2): 143-150, 2001 11436953
- Saraf M, Schrader G: Seizure associated with sertraline. *Aust N Z J Psychiatry* 33(6): 944-945, 1999 10619229
- Shapiro PA, Lespérance F, Frasure-Smith N, et al: An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (the SADHAT Trial). *Sertraline Anti-Depressant Heart Attack Trial*. *Am Heart J* 137(6):1100-1106, 1999 10347338
- Shoptaw S, Huber A, Peck J, et al: Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug Alcohol Depend* 85(1):12-18, 2006 16621339
- Shores MM, Pascualy M, Lewis NL, et al: Short-term sertraline treatment suppresses sympathetic nervous system activity in healthy human subjects. *Psychoneuroendocrinology* 26(4):433-439, 2001 11259862



- Singh NN, Misra S: Sertraline in chronic tension-type headache. *J Assoc Physicians India* 50:873-878, 2002 12126338
- Skarphedinsson G, Weidle B, Thomsen PH, et al: Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: a randomized controlled trial. *Eur Child Adolesc Psychiatry* 24(5):591-602, 2015 25239489
- Sousa MB, Isolan LR, Oliveira RR, et al: A randomized clinical trial of cognitive-behavioral group therapy and sertraline in the treatment of obsessive-compulsive disorder. *J Clin Psychiatry* 67(7):1133-1139, 2006 16889458
- Stahl SM: Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry* 48(9):894-901, 2000 11074227
- Stein DJ, van der Kolk BA, Austin C, et al: Efficacy of sertraline in posttraumatic stress disorder secondary to interpersonal trauma or childhood abuse. *Ann Clin Psychiatry* 18(4):243-249, 2006 17162624
- Stockler MR, O'Connell R, Nowak AK, et al; Zolof's Effects on Symptoms and survival Time Trial Group: Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. *Lancet Oncol* 8(7):603-612, 2007 17548243
- Swenson JR, O'Connor CM, Barton D, et al; Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group: Influence of depression and effect of treatment with sertraline on quality of life after hospitalization for acute coronary syndrome. *Am J Cardiol* 92(11):1271-1276, 2003 14636902
- Thomé-Souza MS, Kuczynski E, Valente KD: Sertraline and fluoxetine: safe treatments for children and adolescents

- with epilepsy and depression. *Epilepsy Behav* 10(3):417-425, 2007 17306625
- Torta R, Siri I, Caldera P: Sertraline effectiveness and safety in depressed oncological patients. *Support Care Cancer* 16(1):83-91, 2008 17874143
- Van Ameringen MA, Lane RM, Walker JR, et al: Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. *Am J Psychiatry* 158(2):275-281, 2001 11156811
- van Harten J: Clinical pharmacokinetics of selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 24(3):203-220, 1993 8384945
- Wagner KD, Cook EH, Chung H, et al: Remission status after long-term sertraline treatment of pediatric obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol* 13 (suppl 1):S53-S60, 2003 12880500
- Walker JR, Van Ameringen MA, Swinson R, et al: Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. *J Clin Psychopharmacol* 20(6):636-644, 2000 11106135
- Warrington SJ: Clinical implications of the pharmacology of sertraline. *Int Clin Psychopharmacol* 6 (suppl 2):11-21, 1991 1806626
- Weintraub D, Rosenberg PB, Drye LT, et al; DIADS-2 Research Group: Sertraline for the treatment of depression in Alzheimer disease: week-24 outcomes. *Am J Geriatr Psychiatry* 18(4):332-340, 2010 20220589
- Winhusen TM, Somoza EC, Harrer JM, et al: A placebo-controlled screening trial of tiagabine, sertraline and donepezil as cocaine dependence treatments. *Addiction* 100 (suppl 1):68-77, 2005 15730351
- Wisner KL, Perel JM, Peindl KS, et al: Prevention of postpartum depression: a pilot randomized clinical trial. *Am J Psychiatry* 161(7):1290-1292, 2004 15229064

- Wisner KL, Hanusa BH, Perel JM, et al: Postpartum depression: a randomized trial of sertraline versus nortriptyline. *J Clin Psychopharmacol* 26(4):353-360, 2006 16855451
- Wu MF, Hilsenbeck SG, Tham YL, et al: The efficacy of sertraline for controlling hot flashes in women with or at high risk of developing breast cancer. *Breast Cancer Res Treat* 118(2):369-375, 2009 19495957
- Yonkers KA, Halbreich U, Freeman E, et al; Sertraline Premenstrual Dysphoric Collaborative Study Group: Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. *JAMA* 278(12): 983-988, 1997 9307345
- Zöger S, Svedlund J, Holgers KM: The effects of sertraline on severe tinnitus suffering—a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 26(1):32-39, 2006 16415703

# CHAPTER 12

## Paroxetine

Jonathon R. Howlett, M.D.

Murray B. Stein, M.D., M.P.H.

Charles B. Nemeroff, M.D., Ph.D.

**Paroxetine** (marketed as Paxil, Pexeva, and Brisdelle) is classified as one of the selective serotonin reuptake inhibitors (SSRIs) because of its potent inhibition of presynaptic serotonin (5-hydroxytryptamine [5-HT]) uptake. It is also a relatively potent norepinephrine reuptake inhibitor, particularly at higher dosages. Paroxetine has received U.S. Food and Drug Administration (FDA) approval for the treatment of depression, panic disorder, social anxiety disorder (social phobia), generalized anxiety disorder, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), and vasomotor symptoms (hot flashes) associated with menopause (the latter in a low-dosage formulation marketed as Brisdelle). Paroxetine also

has demonstrated efficacy in child and adolescent OCD and social anxiety disorder.

Paroxetine is available in 10-, 20-, 30-, and 40-mg tablets and in suspension form. A controlled-release (CR) formulation, available in 12.5-, 25-, and 37.5-mg tablets, exhibits equal or better efficacy than the paroxetine immediate-release (IR) formulation, as well as clear advantages in tolerability ([Golden et al. 2002](#)). Paroxetine is also available in 7.5-mg capsules in the Brisdelle formulation, approved for vasomotor symptoms associated with menopause.

---

## History and Discovery

---

The synthesis of the first SSRI, fluoxetine, in 1972 marked the inception of an exciting new era of scientific and clinical innovation in psychiatry ([Wong et al. 1995](#)). Prior to this discovery, psychiatrists had only a few classes of pharmacological treatments for managing depression and anxiety. These medication classes, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and benzodiazepines, were indeed efficacious; however, they were poorly tolerated and therefore quite limited in usefulness.

Shortly after the introduction of fluoxetine into the U.S. market in 1988, a marked increase in research led to the development of other SSRIs, which ultimately proved effective in a wide array of psychiatric disorders. In 1992, paroxetine became the third SSRI to be approved by the FDA for the treatment of depression. Since then, the FDA has also approved it for the treatment of panic disorder,

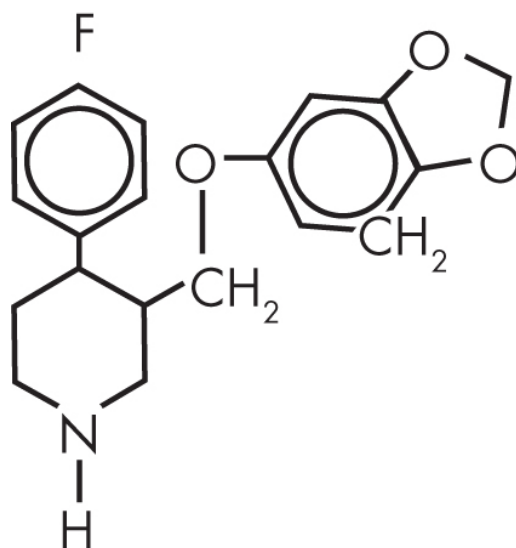
social anxiety disorder, generalized anxiety disorder, OCD, PTSD, PMDD, and hot flashes associated with menopause.

---

## Structure-Activity Relations and Pharmacological Profile

---

Paroxetine ([Figure 12-1](#)) is the most potent inhibitor of the serotonin transporter (5-HTT) among the SSRIs ([Frazer 2001](#)); 85%–100% of 5-HTT binding sites are occupied following 20- to 40-mg daily dosages of paroxetine ([Kent et al. 2002](#); [Meyer et al. 2001](#)), and transporter binding is maintained for up to 14 days after 4 weeks of treatment ([Magnussen et al. 1982](#); [Thomas et al. 1987](#)).



---

**FIGURE 12-1.** Chemical structure of paroxetine.

Paroxetine is also the most potent inhibitor of the norepinephrine transporter (NET) among drugs classified as SSRIs, although paroxetine's NET antagonism does not

approach the magnitude of its 5-HTT antagonism ([Finley 1994](#)). In an 8-week high-dosage forced-titration protocol comparing paroxetine CR dosages of 12.5 mg/day and 75 mg/day with venlafaxine extended release (XR) dosages of 75–375 mg/day, both paroxetine and venlafaxine produced dose-dependent inhibition of the 5-HTT and the NET ([Owens et al. 2008](#)); at 8 weeks, maximal 5-HTT inhibition for paroxetine and venlafaxine was 90% and 85%, respectively, and maximal NET inhibition was 33% and 61%. Substantial NET antagonism occurs at paroxetine IR dosages of 40 mg/day and higher ([Gilmor et al. 2002](#)).

Paroxetine has no appreciable affinity for the dopamine transporter (DAT) or for dopamine type 1 ( $D_1$ ), dopamine type 2 ( $D_2$ ), serotonin type 1A ( $5-HT_{1A}$ ), serotonin type 2A ( $5-HT_{2A}$ ),  $\alpha_1$ - and  $\alpha_2$ -adrenergic, and histamine type 1 ( $H_1$ ) receptors ([Hyttel 1994](#); [Owens et al. 1997](#)). It is distinguished from sertraline by its high affinity for the NET and low affinity for the DAT. Sertraline, by contrast, has a relatively high affinity for the DAT but no affinity for the NET ([Tulloch and Johnson 1992](#)). The affinity of paroxetine for the muscarinic cholinergic receptor is similar to that of desipramine, although paroxetine is used at lower dosages than desipramine and is therefore less anticholinergic than this tricyclic agent. However, this property may account for paroxetine's mild anticholinergic side effects, including dry mouth, blurry vision, and constipation ([Owens et al. 1997](#)).

---

## Pharmacokinetics and Disposition

---

Paroxetine is well absorbed from the alimentary tract, and absorption is not affected by the presence or absence of food ([Kaye et al. 1989](#)). Paroxetine is highly lipophilic and is readily distributed into peripheral tissues, with a high volume of distribution and 95% protein binding ([Kaye et al. 1989](#)). Oral bioavailability is affected by extensive first-pass metabolism ([Lane 1996](#)). With serial dosing, bioavailability increases as the hepatic metabolic system becomes saturated and a larger proportion of the parent compound enters systemic circulation ([Kaye et al. 1989](#)). Following oral dosing, steady-state concentrations of paroxetine exhibit wide intersubject variability ([Sindrup et al. 1992a](#)); however, there appears to be no relationship between paroxetine levels and clinical response or adverse outcomes ([Tasker et al. 1989](#)).

The rate-limiting step in the metabolism of paroxetine is the cytochrome P450 (CYP) 2D6 enzyme system ([Crewe et al. 1992](#); [Sindrup et al. 1992a](#)). Genetic studies have demonstrated up to 40 polymorphisms of the 2D6 enzyme, which in part may explain the differences in pharmacokinetic parameters observed among individuals ([Lane 1996](#)). Individuals can be categorized by CYP2D6 phenotype as being poor, intermediate, extensive, or ultrarapid metabolizers, denoting that they have very high, high, low, or very low serum paroxetine concentrations, respectively ([Charlier et al. 2003](#)). Ultrarapid metabolizers may be at greater risk of antidepressant nonresponse, although this has not been clearly demonstrated, and paroxetine's minimum therapeutic concentration is not well defined. Similarly, a putative increased risk of adverse events for poor metabolizers has not been confirmed ([Hicks et al. 2015](#)). Patients with negligible or diminished CYP2D6



activity are thought to use alternative enzyme systems (Gunasekara et al. 1998; Lane 1996).

Paroxetine is the most potent inhibitor of the CYP2D6 enzyme system among the SSRIs (Crewe et al. 1992; Nemeroff et al. 1996), and its inhibition of 2D6 can continue for up to 5 days after discontinuation (Liston et al. 2002). As both a substrate and an inhibitor of its own metabolism, paroxetine has a nonlinear pharmacokinetic profile, such that higher dosages produce disproportionately greater plasma drug concentrations as the enzyme becomes saturated (Preskorn 1993). With paroxetine IR, peak plasma concentration is attained in approximately 5 hours, and plasma steady-state concentration is achieved within 4–14 days (Kaye et al. 1989). The terminal half-life ( $t_{1/2}$ ) of the parent compound is approximately 1 day and increases at higher dosages, consequent to autoinhibition of CYP2D6 (Preskorn 1993). The pharmacokinetic properties of paroxetine appear to be affected by age. Bayer et al. (1989) reported a threefold increase in maximum plasma concentration in elderly subjects compared with younger subjects following a single dose of paroxetine. Furthermore, the  $t_{1/2}$  in the elderly subgroup was extended by nearly 100%.

In individuals with renal impairment, both half-life and maximum plasma levels of paroxetine have been shown to increase relative to the extent of renal disease (Doyle et al. 1989). In patients with severe liver disease, there are considerable elevations in the steady-state concentration and the  $t_{1/2}$  of paroxetine (Dalhoff et al. 1991). Patients with substantial renal or hepatic impairment should initially receive lower paroxetine dosages to avoid potential side effects.

Paroxetine CR is designed to slow absorption and delay the release of paroxetine until after the tablet has passed through the stomach. With this formulation, 20% of the drug is excreted unchanged from the gastrointestinal tract, such that 20% higher dosages of paroxetine CR are necessary to achieve the same bioavailability ([DeVane 2003](#)). Dissolution after single dosing takes 4–5 hours; otherwise paroxetine CR displays the same pharmacokinetic parameters as the IR formulation with regard to  $t_{1/2}$  and nonlinearity.

Paroxetine mesylate is a generic formulation. Although no studies have compared this formulation's efficacy against that of paroxetine hydrochloride and its bioequivalence has not been precisely established, case reports have indicated problems of decreased efficacy and poor tolerability in patients switched from paroxetine hydrochloride to paroxetine mesylate ([Borgheini 2003](#)).

---

## Pharmacogenomics

---

Paroxetine's primary mode of action is likely mediated by its binding to the 5-HTT. A well-known polymorphism (5-HT transporter gene-linked polymorphic region [5-HTTLPR]) has been located in the promoter region of the gene (*SLC6A4*) that encodes 5-HTT. This polymorphism may be a pharmacogenetic marker for antidepressant efficacy. The 5-HTTLPR polymorphism was first reported as two alleles, referred to as *long* (L) and *short* (S); a third allele (Lg) has also been identified but has not been studied in relation to SSRI response to any great extent. There exists some evidence that cells with the S allele express 50% less 5-HTT

than cells with the L allele, resulting in reduced efficacy of SSRI medications, including paroxetine (Lotrich et al. 2008; Zanardi et al. 2000). The S allele may influence tolerability of paroxetine as well (Murphy et al. 2004). Because patients with the S allele have less expression of 5-HTT, they require a higher serum paroxetine concentration to achieve an effect (Lotrich et al. 2008). It may be that patients with major depressive disorder who are L/L homozygotes have greater 5-HTT occupancy and improved clinical response (Ruhé et al. 2009b). However, the association of the L allele with improved clinical response to paroxetine has not been consistently observed (Kato et al. 2015; Seripa et al. 2015), and a meta-analysis found that this polymorphism does not usefully predict clinical response to SSRIs (Taylor et al. 2010).

Another possible genetic marker for antidepressant efficacy is the T102C single nucleotide polymorphism (rs6313) in the 5-HT<sub>2A</sub> gene (*5HTR2A*). Survival analysis has shown a more or less linear relationship between the number of C alleles and the odds of patients discontinuing paroxetine therapy because of untoward effects (Murphy et al. 2003).

Evidence that antidepressants exert their effects through brain-derived neurotrophic factor (BDNF) led to the hypothesis that polymorphisms in the *BDNF* gene may be associated with antidepressant response. However, studies testing this link have yielded mixed results (Notaras et al. 2015).

Another possible influence on antidepressant efficacy is the concentration of medication that reaches the brain. Evidence indicates that paroxetine, among other antidepressants such as sertraline, citalopram, amitriptyline, and venlafaxine, is actively transported across

the blood-brain barrier and out of the brain by the P-glycoprotein (P-gp) transporter ([Uhr et al. 2008](#)). P-gp is encoded by the adenosine triphosphate (ATP)-binding cassette, subfamily B, member 1 transporter (*ABCB1*) gene, also known as multidrug-resistance gene 1 (*MDR1*). Variable activity of P-gp may help explain why serum concentrations of SSRIs are poor predictors of efficacy ([Mitchell 2004](#)). A number of studies now indicate that polymorphisms of *ABCB1* may influence the efficacy of paroxetine ([Gex-Fabry et al. 2008](#); [Kato et al. 2008](#); [Ray et al. 2015](#); [Sarginson et al. 2010](#); [Uhr et al. 2008](#)).

In addition to the candidate gene studies mentioned here, several genomewide association studies have been conducted but have not identified any polymorphisms likely to exert a strong influence on SSRI response ([Biernacka et al. 2015](#)).

---

## Mechanism of Action

---

Paroxetine and all of the other SSRIs cause immediate elevations in extracellular 5-HT concentrations in serotonergic synapses, resulting from the decreased 5-HT clearance associated with 5-HTT inhibition ([Wagstaff et al. 2002](#)). Paroxetine initially causes a paradoxical *decrease* in 5-HT neurotransmission, likely due to activation of a negative feedback system mediated by increased 5-HT binding to the 5-HT<sub>1A</sub> autoreceptor and subsequent diminution in serotonergic neural activity ([Blier et al. 1990](#)). After 2 weeks of paroxetine treatment, the 5-HT<sub>1A</sub> autoreceptors are desensitized, and there is an associated increase in serotonergic neurotransmission ([Chaput et al.](#)

1991). The delayed changes in 5-HT<sub>1A</sub> receptor sensitivity and 5-HT neurotransmission seen after long-term daily paroxetine use are temporally associated with clinical improvement, hinting at a possible mechanistic link.

Pindolol, a nonselective  $\beta$ -adrenergic receptor antagonist/5-HT<sub>1A</sub> receptor antagonist, has been studied as a novel approach to accelerate the therapeutic response to SSRIs, as well as to convert SSRI nonresponders to responders. It was hypothesized that blockade of the presynaptic 5-HT<sub>1A</sub> autoreceptor might prevent the initial reduction in serotonergic transmission that occurs with SSRIs, leading to a more rapid and robust clinical response (Pérez et al. 1999).

This hypothesis was supported by results from open studies and from several double-blind, placebo-controlled trials indicating that the addition of pindolol (2.5–5.0 mg three times a day) to paroxetine in the early phase of treatment for major depressive disorder increased the rapidity of clinical improvement (Artigas et al. 1994; Blier and Bergeron 1995). However, data on augmentation of clinical efficacy with pindolol were not compelling, especially in individuals with depression refractory to paroxetine monotherapy (Bordet et al. 1998; Pérez et al. 1999; Tome et al. 1997; Zanardi et al. 1997). In another study, paroxetine with pindolol augmentation was found to be most efficacious in patients with depression who were drug naive and in patients with bipolar depression (Geretsegger et al. 2008). It may be that the dosages of pindolol previously studied were inadequate to obtain a response (Martinez et al. 2000).

Paroxetine has also been shown to have an effect on the hypothalamic-pituitary-adrenal (HPA) axis. It is well

established that many individuals with depression have HPA axis hyperactivity and hypersecretion of corticotropin-releasing factor (CRF) from the hypothalamic and extrahypothalamic circuits ([Heim and Nemeroff 1999](#)). Early life stress is associated with hyperactivity of the HPA axis and increased CRF messenger RNA (mRNA) expression ([Nemeroff 1996](#); [Newport et al. 2002](#)). In adult animals, these effects are reversed by chronic—but not acute—paroxetine treatment.

---

## Indications and Efficacy

---

### Major Depressive Disorder

#### Comparisons With Other Agents

The efficacy of paroxetine in major depressive disorder has been established in several randomized, placebo-controlled studies, as well as in studies comparing the effects of paroxetine with those of other antidepressants, including TCAs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and other SSRIs. Many studies have compared paroxetine with other SSRIs; however, many of these studies were sponsored by the pharmaceutical industry and therefore must be evaluated with caution. The earliest placebo-controlled trials used paroxetine dosages of 10–50 mg/day and were 6 weeks in duration. Outcome variables used were typically the Hamilton Rating Scale for Depression (Ham-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Clinical Global Impressions (CGI) Scale to assess improvement. A recent meta-analysis

of all published and unpublished industry-sponsored trials that included Ham-D change scores showed superiority of paroxetine over placebo, with a modest effect size of  $d=0.32$  ([Sugarman et al. 2014](#)).

There has been some debate regarding the use of such scales in the assessment of medication efficacy, as well as concerns that there exists a publication bias toward positive results. A minority of authors have suggested that “hard measures” of treatment effectiveness—namely, suicide attempts, treatment switching, hospital admission, job loss, or dropout from the trial ([Barbui et al. 2008](#))—be used instead, although such endpoints are not currently acceptable to the FDA. [Barbui et al. \(2008\)](#) undertook a systematic review of paroxetine, evaluating both published and unpublished data according to one specific hard measure—treatment discontinuation—by looking at the number of patients who left a study early for any reason. The authors found that when this measure was used as a primary outcome, paroxetine was not effective, whereas when rate of response (defined as  $\geq 50\%$  reduction in Ham-D score) was used, paroxetine was superior to placebo ([Barbui et al. 2008](#)).

**Tricyclic and tetracyclic antidepressants.** A meta-analysis by [Montgomery \(2001\)](#) compared the efficacy and tolerability of paroxetine with those of TCAs, including amitriptyline, imipramine, clomipramine, doxepin, and nortriptyline, as well as the tetracyclics mianserin and maprotiline. The data demonstrated no overall significant difference in antidepressant response rates between paroxetine and TCAs or tetracyclics. Paroxetine was better tolerated, had lower rates of discontinuation attributed to

adverse events, and had a greater effect on concomitant anxiety.

**Other SSRIs.** Many studies have found paroxetine and fluoxetine to be equally effective in the treatment of major depressive disorder and associated anxiety ([Chouinard et al. 1999](#); [De Wilde et al. 1993](#); [Fava et al. 1998, 2000](#); [Tignol 1993](#)). Similar results have been obtained from trials comparing paroxetine with sertraline or escitalopram. Equivalent efficacy has been demonstrated in comparisons of paroxetine against either sertraline or escitalopram; however, these studies tend to also show a greater dropout rate in paroxetine groups, likely due to adverse medication effects ([Aberg-Wistedt et al. 2000](#); [Baldwin et al. 2006](#); [Zanardi et al. 1996](#)). Some studies have suggested efficacy differences among the SSRIs, with a Cochrane review concluding that citalopram may be superior to paroxetine in the acute phase of treatment (6–12 weeks) ([Purgato et al. 2014](#)).

**Other agents.** Paroxetine has also been compared with a variety of other agents in the treatment of depression. Nefazodone and paroxetine were shown to possess similar efficacy and tolerability ([Baldwin et al. 1996](#)), and mirtazapine and paroxetine were found to be equivalent in terms of efficacy and tolerability ([Benkert et al. 2000](#)). However, a Cochrane review concluded that mirtazapine may be superior to paroxetine, whereas paroxetine may be superior to the norepinephrine reuptake inhibitor reboxetine in terms of early response to treatment (1–4 weeks) ([Purgato et al. 2014](#)). A post hoc analysis of a clinical trial determined that paroxetine CR was superior to bupropion extended release (XL) in reducing a “psychic



depression” symptom cluster that was correlated with suicidal ideation ([Grunebaum et al. 2013](#)).

In a meta-analysis of the venlafaxine worldwide database, the SNRI venlafaxine showed a slight statistically significant advantage in efficacy over SSRIs as a class, although no such advantage was demonstrated for venlafaxine over paroxetine ([Nemeroff et al. 2003](#)). A study comparing venlafaxine XR and paroxetine in the maintenance treatment of depression found higher rates of remission with venlafaxine ([Shelton et al. 2005](#)). In patients with treatment-resistant depression (defined as inadequate response to appropriate courses of at least two different antidepressants), venlafaxine (200–300 mg/day) was shown to be superior to paroxetine (30–40 mg/day) in bringing about remission ([Poirier and Boyer 1999](#)).

In contrast, a study in Chinese patients with treatment-resistant depression showed no significant differences among paroxetine, mirtazapine, and venlafaxine XR ([Fang et al. 2010](#)). A study comparing paroxetine with the SNRI duloxetine (40–80 mg/day) suggested a higher probability of remission with duloxetine 80 mg/day than with paroxetine ([Goldstein et al. 2004](#)). Another study in Chinese patients found a nonsignificantly higher remission rate with paroxetine compared with duloxetine 40–60 mg/day ([Wang et al. 2015](#)). A study comparing paroxetine with the SNRI milnacipran in Japanese patients showed no difference in efficacy ([Kamijima et al. 2013](#)). In evaluating studies comparing paroxetine with SNRI agents, it is important to take into account the dosages used for paroxetine, because paroxetine 20 mg/day is too low to exhibit any NET blockade.

Paroxetine has also been compared with investigational agents such as substance P (NK<sub>1</sub>) receptor antagonists. In

the Merck-sponsored NK<sub>1</sub> receptor antagonist trials in major depressive disorder, paroxetine 20 mg/day was superior to both placebo and the novel agent ([Cutler et al. 2000](#)).

## **Depression in the Elderly**

Following successful treatment for depression, elderly patients are more likely than nonelderly patients to experience early relapses ([Zis et al. 1980](#)). SSRIs are currently the treatment of choice in this population because of their demonstrated efficacy and their relative safety over TCAs and MAOIs. Whereas paroxetine, clomipramine, and amitriptyline are equally effective in geriatric patients ([Geretsegger et al. 1995](#); [Guillibert et al. 1989](#); [Hutchinson et al. 1992](#)), paroxetine and fluoxetine have both been shown to elicit improved depression response rates and improved cognitive functioning, and they are equally well tolerated ([Geretsegger et al. 1994](#); [Gunasekara et al. 1998](#); [Schöne and Ludwig 1993](#)). Paroxetine and bupropion sustained release (SR) also were shown to be equally effective in this population and to have low discontinuation rates ([Weihs et al. 2000](#)). Paroxetine CR at a daily dosage of 12.5 mg or 25 mg was found to be well tolerated by elderly patients and superior to placebo; at the higher dosage, patients showed numerically larger decreases in total Ham-D scores, and a greater number of patients achieved remission (Ham-D≤7) ([Rapaport et al. 2009](#)). A recent network meta-analysis determined that there is clear evidence for the effectiveness of paroxetine in depression in older adults, but paroxetine may have a greater risk of dizziness compared with placebo ([Thorlund et al. 2015](#)).

For maintenance treatment in elderly ( $\geq 65$  years old) patients with depression, paroxetine and nortriptyline are similarly effective in preventing relapse ([Bump et al. 2001](#)). In a maintenance study comparing continuation of combined treatment consisting of either interpersonal therapy plus paroxetine or interpersonal therapy plus placebo, patients who continued on paroxetine were significantly less likely to experience a recurrence, whereas therapy alone was not successful in preventing relapse ([Reynolds et al. 2006](#)).

One issue of concern in treating the elderly with paroxetine is the potential risk of anticholinergic side effects, leading to delirium. Fluoxetine has minimal anticholinergic activity, and in a study comparing the effects of fluoxetine and paroxetine in depressed elderly patients without dementia, both medications produced marked improvement in cognitive functioning and mood symptoms and were well tolerated ([Cassano et al. 2002](#)). A meta-analysis concluded that paroxetine was not significantly associated with risk of falls in older adults ([Ruxton et al. 2015](#)).

## **Maintenance Treatment of Depression**

Given that it is now well recognized that unipolar depression is a chronic and recurrent disorder, the prevention of recurrence should be a primary aim. Studies have demonstrated the effectiveness of paroxetine in maintaining remission over an extended period without adverse effects ([Duboff 1993](#)), particularly when compared with placebo ([Montgomery and Dunbar 1993](#)). However, studies comparing paroxetine with escitalopram reported that although both medications produced improvement in measures of depression, escitalopram appeared to be more

efficacious and to have better tolerability ([Baldwin et al. 2006](#); [Boulenger et al. 2006](#); [Kasper et al. 2009](#)). The paroxetine dosages used in the long-term studies were typically the same ones used in the acute studies (20–40 mg/day). Thus, for maintenance therapy for depression, the recommended dosage of paroxetine is the dosage that was effective during acute therapy.

In most patients with an acute major depressive episode, an initial daily dosage of 20 mg is sufficient for the duration of the illness episode, at least when response (defined as  $\geq 50\%$  reduction in symptoms) is used as an endpoint ([Dunner and Dunbar 1992](#)). One study demonstrated that in patients with major depressive disorder, dosage escalation of 20 mg/day and subsequent increased plasma levels were not associated with improved clinical outcomes ([Ruhé et al. 2009a](#)). However, to improve the likelihood of remission, we recommend increasing the dosage in 10-mg increments each week—up to 50 mg/day or more of the IR form and up to 75 mg/day of the CR form ([Nemeroff 1993](#)). For elderly patients and those with renal or hepatic dysfunction, paroxetine should be initiated at a lower dosage, with gradual dosage titration to therapeutic effect while monitoring for side effects.

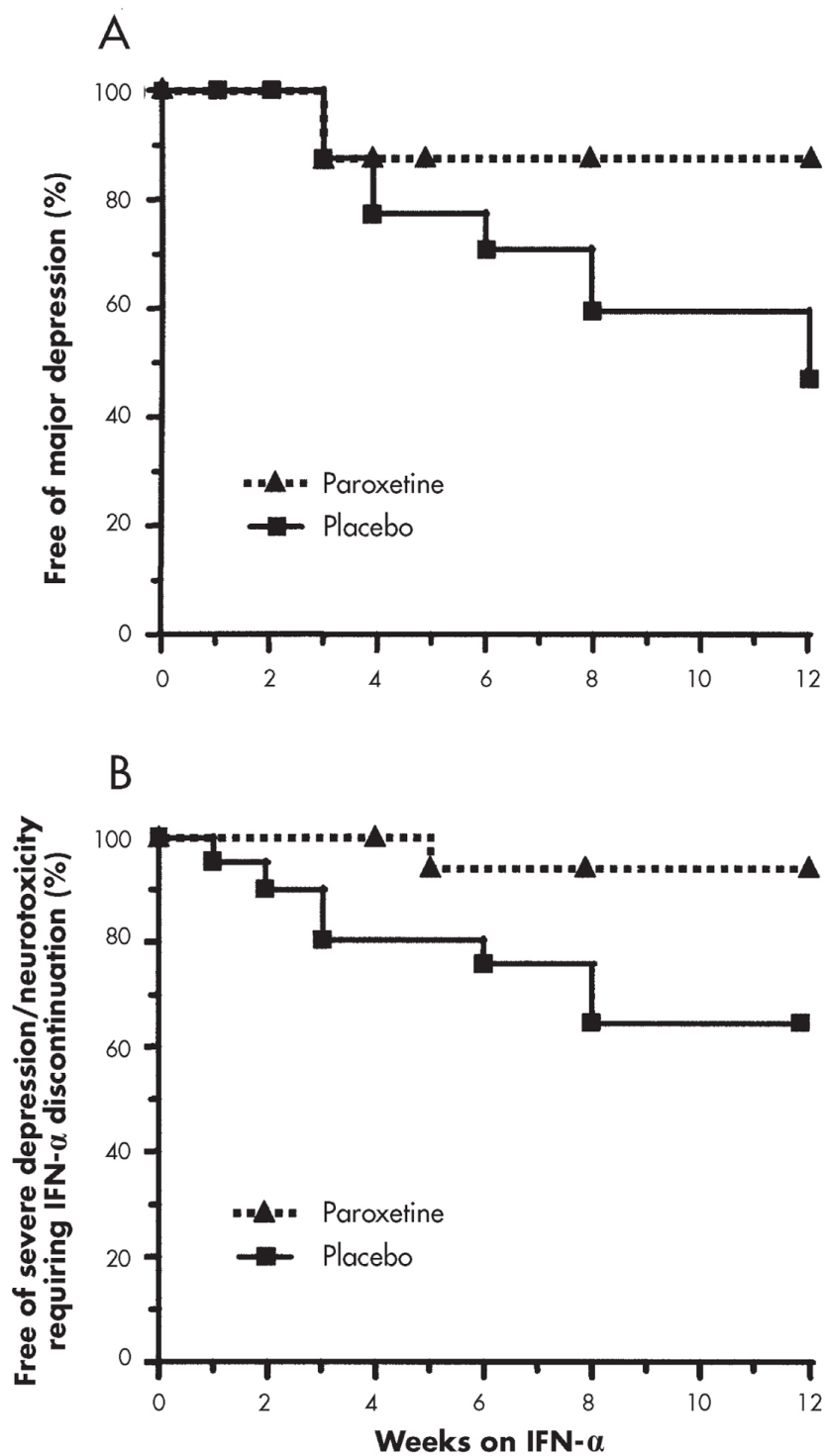
## **Adjunctive Treatment of Bipolar Depression**

Paroxetine has demonstrated efficacy and safety in the adjunctive treatment of bipolar depression, an often treatment-refractory disorder. In one study in lithium-treated patients, augmentation with paroxetine was shown to be superior to augmentation with amitriptyline ([Bauer et al. 1999](#)). In another study, paroxetine and imipramine were not significantly different from placebo in terms of overall efficacy, but both were superior to placebo among

patients with a low serum lithium level ([Nemeroff et al. 2001](#)). Another study evaluating antidepressant augmentation of a mood stabilizer showed no differences in efficacy among paroxetine, bupropion SR, and placebo ([Sachs et al. 2007](#)). Paroxetine was not associated with an increased rate of switch into mania or hypomania in any of these studies.

### **Depression Associated With Medical Illness**

Paroxetine has been found to be efficacious in the treatment of depression comorbid with several medical disorders, including rheumatoid arthritis, irritable bowel syndrome, cardiovascular disease, and Parkinson's disease ([Bird and Broggin 2000](#); [Masand et al. 2001](#); [Richard et al. 2012](#); [Roose et al. 1998](#)). Paroxetine also was demonstrated to be efficacious in the prevention of interferon- $\alpha$ -induced depression in patients with malignant melanoma ([Figure 12-2](#)) ([Musselman et al. 2001](#)).



**FIGURE 12-2.** Paroxetine effect on interferon- $\alpha$  (IFN- $\alpha$ )-induced depression.

Kaplan-Meier analysis of the percentage of patients in the placebo and paroxetine groups who were free of major depressive disorder **(A)** and of severe depression, requiring the discontinuation of IFN- $\alpha$  **(B)**.

*Source.* From Musselman DL, Lawson DH, Gumnick JF, et al.: "Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa." *The New England Journal of Medicine* 344(13):961-966, 2001. Copyright © 2001 Massachusetts Medical Society. Reprinted with permission.

## Depression in Children and Adolescents

In 2003, the FDA released a statement regarding a possible increased risk of suicidal thinking and suicide attempts in children and adolescents 18 years old and younger who are treated with paroxetine for major depressive disorder ([U.S. Food and Drug Administration 2004](#)). The statement was based on data from three well-controlled unpublished studies, each showing no benefit for paroxetine above placebo in the treatment of pediatric depression. The data also revealed an increased rate of suicidal ideation and suicide attempts with paroxetine treatment versus placebo (3.4% vs. 1.2%). Published data on paroxetine have also shown limited efficacy in this population ([Emslie et al. 2006](#); [Keller et al. 2001](#)). A recent reanalysis of Keller et al. found that the benefits of paroxetine were lower and the risks greater than had been reported in the initial publication. In particular, paroxetine did not show greater efficacy than placebo and was associated with increased risks, including suicidal ideation and behavior ([Le Noury et al. 2015](#)).

Differences in pharmacokinetics between children and adults may explain the observed age-related discrepancies in efficacy and suicide risk. In children, an increase in dosage from 10 mg to 20 mg results in a sixfold increase in

serum paroxetine levels ([Findling et al. 1999](#)). This dramatic increase in pediatric serum levels could conceivably trigger activation, akathisia, or disinhibition, potentially explaining the emergence of suicidal thinking or behavior ([Brent 2004](#)), and the effect would be even greater in children who are poor CYP2D6 metabolizers (roughly 10% of the Caucasian population) ([Riddle 2004](#)). Additionally, paroxetine has a relatively short half-life (11 hours vs. 5 days with fluoxetine), and limited treatment adherence—not uncommon in children and teens—could lead to SSRI discontinuation syndrome and dysphoria ([Brent 2004](#)).

Studies utilizing animal models have confirmed these observations. In a rat model, depressive symptoms appear with an increase in locus coeruleus (LC) activity, and effective antidepressant treatment decreases LC activity; however, in younger rats, administration of paroxetine initially increases LC activity, which then declines with prolonged administration ([West et al. 2010](#)). Furthermore, increased LC activity is also associated with low or decreasing serum paroxetine levels, further supporting the hypothesis that poor adherence to or faster metabolism of medication may contribute to the risk of suicidality ([West et al. 2010](#)).

The FDA's black box warning concerning antidepressant use and suicidality risk in children and adolescents has led to a decline in SSRI prescribing for the under-18 age group ([Nemeroff et al. 2007](#)). The [Centers for Disease Control and Prevention \(2007\)](#) reported that suicide rates in American children and adolescents increased 18% in 2004, after 10 years of steady decline. A cohort study of 20,906 adolescents (ages 10–18 years) prescribed SSRIs in British Columbia, Canada, demonstrated a risk of suicidal behavior



(attempted or completed suicide) five times higher than that in the general population; however, the authors noted that this increased rate likely reflects the risk associated with a diagnosis of depression ([Schneeweiss et al. 2010a](#)). Most of the suicidal events occurred during the first 6 months of SSRI treatment. Interestingly, the authors found no significant difference in risk of suicidal behavior among the specific SSRIs evaluated (fluoxetine, citalopram, fluvoxamine, paroxetine, and sertraline) ([Schneeweiss et al. 2010a](#)).

## Panic Disorder

Paroxetine was the first SSRI to be granted FDA approval for the treatment of panic disorder. Paroxetine and clomipramine have been shown to be equally efficacious in the treatment of panic attacks, and a faster onset of action was noted with paroxetine ([Lecrubier et al. 1997a](#)). Paroxetine's long-term efficacy and tolerability have also been demonstrated in patients with panic disorder ([Lecrubier et al. 1997b](#); [Nardi et al. 2012](#)). The combination of cognitive-behavioral therapy and paroxetine is more effective in the treatment of panic disorder than cognitive-behavioral therapy alone ([Bakker et al. 1999](#); [Oehrberg et al. 1995](#)).

In general, patients with panic disorder should be treated initially with a low dosage of paroxetine (e.g., 10 mg/day), with gradual increases in dosage as clinically indicated. The data that led to FDA approval suggested that 40 mg/day was the minimum effective dosage for this condition; however, clinical experience has shown that lower dosages may be sufficient in some patients and higher dosages may

be required in other patients ([Ballenger et al. 1998](#)). The standard duration of treatment ranges from 6 to 12 months; however, rates of relapse for panic disorder appear to be greater than those for major depressive disorder, suggesting that panic disorder may require an indefinite course of treatment ([Hirschfeld 1996](#)).

## Social Anxiety Disorder (Social Phobia)

Paroxetine, sertraline, fluvoxamine CR, and venlafaxine XR are the only medications with FDA approval for the treatment of social anxiety disorder (also called social phobia). Paroxetine's efficacy in the treatment of social anxiety disorder was first suggested by results from open clinical trials ([Mancini and Ameringen 1996](#); [Stein et al. 1996](#)) and was later confirmed by findings from double-blind, placebo-controlled studies ([Baldwin et al. 1999](#); [Stein et al. 1998](#)). Paroxetine and venlafaxine XR have been shown to be similarly effective and superior to placebo in the treatment of social anxiety disorder ([Liebowitz et al. 2005](#)).

In children and adolescents (ages 8–17 years) with social anxiety disorder, paroxetine was found to be superior to placebo ([Wagner et al. 2004](#)). It is important to note that a total of five patients in the paroxetine group ( $n=163$ ), versus none in the placebo group ( $n=156$ ), exhibited suicidal threats or gestures.

It appears that the optimal daily dosage of paroxetine for the treatment of social anxiety disorder is 20–40 mg, with no additional benefit seen for 60 mg ([Lydiard and Bobes 2000](#)). In patients who respond to paroxetine, it is also

advisable to continue treatment to prevent relapse ([Stein et al. 2002](#)).

## Generalized Anxiety Disorder

Venlafaxine XR, escitalopram, duloxetine, and paroxetine have all been approved by the FDA for treatment of generalized anxiety disorder. The first published study supporting the use of paroxetine in generalized anxiety disorder compared it with both imipramine and 2'-chlorodesmethyldiazepam, a benzodiazepine ([Rocca et al. 1997](#)). Not surprisingly, patients receiving the benzodiazepine showed the earliest improvement in symptoms; however, both paroxetine and imipramine produced significant reductions in Hamilton Anxiety Scale (Ham-A) total score, exceeding the reductions produced by the benzodiazepine by week 4 of the 8-week trial. Subsequent studies further confirmed the efficacy of paroxetine in treatment of generalized anxiety disorder ([Bielski et al. 2005](#); [Pollack et al. 2001](#); [Rickels et al. 2003](#)).

Long-term treatment of generalized anxiety disorder with paroxetine may be necessary ([Stocchi et al. 2003](#)). Clinical experience and investigative research indicate that the usual effective paroxetine dosage for treating generalized anxiety disorder is 20 mg/day (GlaxoSmithKline [2001](#)).

## Obsessive-Compulsive Disorder

Currently, the SSRIs fluvoxamine, fluoxetine, sertraline, and paroxetine are FDA approved for the treatment of OCD in adults. Although two meta-analyses assessing the efficacy and tolerability of the TCA clomipramine and SSRIs in OCD

seemed to favor clomipramine in terms of overall effectiveness ([Greist et al. 1995](#); [Piccinelli et al. 1995](#)), the only placebo-controlled multicenter study to compare clomipramine directly against an SSRI (paroxetine) revealed equal efficacy, with greater tolerability for paroxetine ([Zohar and Judge 1996](#)).

Paroxetine also has demonstrated efficacy in pediatric OCD. In a randomized, double-blind, placebo-controlled multicenter trial ([Geller et al. 2004](#)), paroxetine was found to be an effective and generally well-tolerated treatment for OCD in children and adolescents. Patients with comorbid major depressive disorder were excluded from this study, and only one incident of treatment-emergent suicidal behavior or ideation was reported.

In adults, paroxetine daily dosages of  $\geq 60$  mg are usually required for optimal efficacy in OCD. Although patients usually respond to treatment within 3–4 weeks, clinical improvement may not be discernible until 10–12 weeks; therefore, a standard trial of up to 12 weeks should be conducted before an alternative medication is considered ([Rasmussen et al. 1993](#)).

## Posttraumatic Stress Disorder

Among the SSRIs, sertraline and paroxetine have received FDA approval for the treatment of PTSD. Compared with placebo, paroxetine (20–40 mg/day) has been shown to produce significant improvements in the three symptom cluster groups of reexperiencing, avoiding/numbing, and hyperarousal and to reduce disability and depression ([Marshall et al. 1998, 2001](#)). OCD patients with comorbid major depressive disorder respond just as favorably as do

subjects without depression. Similar findings have been reported by other groups ([Tucker et al. 2001, 2004](#)), and paroxetine has also shown efficacy in combination with prolonged exposure therapy ([Schneier et al. 2012](#)) and in long-term treatment ([Kim et al. 2008](#); [Vermetten et al. 2003](#)). A recent study found that paroxetine was less effective than prolonged exposure in achieving symptom remission, and the combination of paroxetine and prolonged exposure was not superior to prolonged exposure alone ([Popiel et al. 2015](#)).

## Premenstrual Dysphoric Disorder

Fluoxetine, sertraline, and paroxetine are FDA approved for the treatment of PMDD. The somatic features of PMDD—bloating, weight gain, breast tenderness, poor concentration, and disturbed sleep and appetite—manifest in the luteal phase of ovulation and disappear with the onset of menstruation. These symptoms are cyclical, predictably appearing prior to each menses ([Dimmock et al. 2000](#)). The psychological symptoms of PMDD are more severe and prominent and include irritability, dysphoria, tension, and mood lability. Paroxetine has been shown to be significantly more effective than the tetracyclic maprotiline, a norepinephrine reuptake inhibitor, in reducing both psychological and somatic symptoms of PMDD ([Eriksson et al. 1995](#)). Two small open trials reported positive findings with paroxetine treatment ([Sundblad et al. 1997](#); [Yonkers et al. 1996](#)), and a double-blind, placebo-controlled study demonstrated that paroxetine CR (25 mg/day) was both well tolerated and effective in the treatment of PMDD ([Cohen et al. 2004](#)).

PMDD can be successfully managed with intermittent luteal-phase dosing, in which the medication is started 14 days before the estimated next menses and continued until the onset of menstruation ([Steiner et al. 2005](#)). It has been shown that paroxetine improves irritability within 14 hours of taking the first dose ([Landén et al. 2009](#)). Both luteal- and continuous-phase dosing of paroxetine (either the CR or the IR formulation) are superior to placebo in relieving the psychological symptoms of PMDD but not the somatic symptoms (food craving, breast tenderness) ([Steiner et al. 2005, 2008](#)). Somatic symptoms may be better addressed with continuous treatment ([Landén et al. 2007](#); [Wu et al. 2008](#)); however, with intermittent dosing, patients experience fewer adverse effects ([Steiner et al. 2008](#)).

## Menopausal Vasomotor Symptoms

In addition to its proven efficacy in PMDD, paroxetine has been found to be efficacious in treating perimenopausal hot flashes ([Simon et al. 2013](#); [Soares et al. 2008](#); [Stearns et al. 2003](#)). In 2013, a new formulation—paroxetine mesylate 7.5-mg capsules, marketed as Brisdelle—became the first nonhormonal medication to receive FDA approval for this indication. The mechanism of action may involve a paroxetine-induced increase in BDNF plasma levels ([Cubeddu et al. 2010](#)).

Earlier studies also demonstrated paroxetine (20 mg/day) to be effective in the treatment of postmenopausal hot flashes in breast cancer survivors with chemotherapy-induced ovarian failure ([Stearns et al. 2000, 2005](#); [Weitzner et al. 2002](#)). However, it is important to consider the risks of paroxetine in women with estrogen receptor-positive

breast cancer who are taking tamoxifen to decrease the risk of breast cancer relapse. Tamoxifen is a prodrug that requires CYP2D6 metabolism to create the more active metabolite endoxifen; however, as a potent inhibitor of CYP2D6, paroxetine blocks the conversion of tamoxifen to endoxifen ([Kelly et al. 2010](#)). An increased risk of death from breast cancer has been observed in women taking tamoxifen and paroxetine ([Kelly et al. 2010](#)).

---

## Side Effects and Toxicology

---

The popularity of SSRIs as a class in the treatment of psychiatric disorders is owed not to their superiority in efficacy over their predecessors but rather to their overall tolerability and safety. The most commonly cited adverse experiences in patients treated with paroxetine are, in order of frequency, nausea, headache, somnolence, dry mouth, asthenia, sweating, constipation, dizziness, and tremor ([Boyer and Blumhardt 1992](#)).

According to the worldwide preregistration clinical trial database, anticholinergic side effects, tremor, dizziness, postural hypotension, and somnolence were more common in comparison drugs (generally TCAs) ([Jenner 1992](#)). The most common side effect associated with early termination for paroxetine was nausea. Clinical experience demonstrates that this effect can be mitigated with a conservative starting dosage and administration with food, as well as with the use of the CR form of the compound ([Golden et al. 2002](#)). Furthermore, patients reported that nausea diminishes markedly with prolonged administration ([Jenner 1992](#)). As noted earlier, elderly patients do not

appear to be more susceptible than younger patients to the side effects of paroxetine, and cognitive function remains intact or improves during treatment ([Cassano et al. 2002](#); [Nebes et al. 1999](#)).

## Sexual Side Effects

All SSRIs and SNRIs have been associated with male and female sexual dysfunction. In a comparison study of 200 subjects, paroxetine treatment was associated with higher rates of anorgasmia in women and ejaculation difficulty or impotence in men compared with fluoxetine, fluvoxamine, and sertraline ([Montejo-González et al. 1997](#)). In a large cross-sectional observational study ([Clayton et al. 2002](#)), paroxetine was associated with the highest rates of sexual dysfunction among the antidepressants evaluated (mirtazapine, venlafaxine, sertraline, citalopram, fluoxetine, nefazodone, and bupropion).

On the other hand, the sexual side effects of paroxetine have been capitalized on in the treatment of premature ejaculation. Paroxetine produces a greater delay in time to ejaculation compared with fluoxetine, fluvoxamine, sertraline, dapoxetine (a short-acting SSRI awaiting FDA approval for the treatment of premature ejaculation), and mirtazapine ([Safarinejad 2006](#); [Waldinger et al. 1998, 2003](#)).

Sexual side effects emerge in a dose-dependent fashion and do not appear to diminish with prolonged administration; however, the effect is reversible, with most patients returning to normal functioning within 1 month of discontinuing the medication ([Tanrikut et al. 2010](#)). Strategies to lessen the impact of psychotropic medications



on sexual function include reducing the dosage, changing to a different antidepressant with less sexual side-effect liability, and adding an agent (e.g., sildenafil, yohimbine, buspirone, cyproheptadine, amantadine, methylphenidate, bupropion) to reverse the sexual side effects ([Rosen et al. 1999](#)). Ephedrine, an  $\alpha$ - and  $\beta$ -adrenergic receptor agonist previously shown to enhance genital blood flow in women, has been evaluated in women experiencing SSRI-induced sexual dysfunction from paroxetine, sertraline, or fluoxetine ([Meston 2004](#)). Both ephedrine and placebo improved self-reported scores of desire and orgasm intensity compared with baseline, although women taking sertraline or paroxetine fared better than did women taking fluoxetine, a finding the authors attributed to differences in the mechanism of action of these SSRIs ([Ahrold and Meston 2009](#)).

## Suicidality

As previously discussed (see “Depression in Children and Adolescents” subsection earlier in this chapter), in 2004 the FDA ordered pharmaceutical companies to place a black box warning on the package insert for all antidepressants, stating that suicidal behavior might increase in children and adolescents taking these medications. Concerns about a link between antidepressant usage and suicidal ideation led FDA regulators to request that antidepressant manufacturers examine their databases for similar findings in adults. GlaxoSmithKline conducted a meta-analysis of its clinical data comparing suicidality with paroxetine (Paxil/Seroxat) versus placebo. Among depressed patients taking paroxetine, 0.32% (11 of 3,455) attempted suicide,

compared with 0.05% (1 of 1,978) of depressed patients taking placebo, an odds ratio of 6.7 ([GlaxoSmithKline 2006](#)). Cases of completed suicide in both samples were exceedingly rare, with one reported in the paroxetine sample versus none reported with placebo. GlaxoSmithKline further examined the data to identify clinical features of those patients who developed suicidal behavior ([Kraus et al. 2010](#)). Common features among these patients included some improvement in depressive symptoms, younger age (<30 years old), psychosocial stressor preceding the attempt, and no identified suicidality at the prior study visit ([Kraus et al. 2010](#)).

Another analysis of both published and unpublished data on paroxetine in the treatment of depression evaluated suicidality as a secondary outcome ([Barbui et al. 2008](#)), finding an odds ratio of 2.55, with a number needed to harm of 142. The authors noted that whereas suicidality is exceedingly rare, the data are also variably recorded, making it difficult to track this outcome through retrospective reports ([Barbui et al. 2008](#)). As noted earlier, a recent reanalysis of a published GlaxoSmithKline study of paroxetine treatment of child and adolescent depression ([Keller et al. 2001](#)) concluded that the risk of suicidal ideation and suicidal behavior associated with paroxetine was greater than had initially been reported ([Le Noury et al. 2015](#)).

A retrospective cohort study of 36,842 children and adolescents ages 6–18 years initiating treatment with an antidepressant found no differences in risk of suicide attempts among commonly prescribed SNRIs and SSRIs, including paroxetine ([Cooper et al. 2014](#)). Another cohort study of 287,543 adult residents of British Columbia ages 18 years and older who were receiving antidepressants

([Schneeweiss et al. 2010b](#)) found no significant differences in suicidality risk among individual SSRIs (fluoxetine, citalopram, fluvoxamine, paroxetine, and sertraline). As in the study of children and adolescents mentioned earlier ([Schneeweiss et al. 2010a](#); see the subsection “Depression in Children and Adolescents”), most of the suicidal events occurred during the first 6 months of treatment ([Schneeweiss et al. 2010b](#)). A retrospective study of 502,179 U.S. Department of Veterans Affairs patients with depression diagnoses who initiated antidepressant treatment found evidence suggesting a lower risk of suicide death with fluoxetine and sertraline compared with paroxetine, although the authors noted that this finding differed according to which data analysis technique was used ([Valenstein et al. 2012](#)).

A limitation of findings regarding the link between paroxetine and suicidality is that the placebo-controlled studies included in meta-analyses did not have suicidal ideation and self-harming behaviors as main outcome measures. Procedures for assessing suicidality have not, until recently, been standardized and are based largely on unsolicited and unstructured reports and observations. Also, depression is a risk factor for suicidal behavior, and suicide is a potential complication of the disease. Transient suicidal thinking must be considered in the context of the overall risk-benefit analysis of paroxetine in the treatment of adults with major depressive disorder.

Nevertheless, in late 2006, an FDA advisory panel extended the black box warning to cover young adults up to their mid-20s ([U.S. Food and Drug Administration 2007](#)). The advisory panel reported that in patients 18–24 years of age, antidepressant use was associated with 4 cases of suicidal ideation per 1,000 patients treated, that there was

no evidence of increased risk in adults older than 24 years, and that antidepressant treatment was unequivocally protective against suicidality in patients 65 years and older.

Clinicians should inform their patients about the possible risks and should monitor depressed patients closely when paroxetine or any other antidepressant is prescribed, particularly during the early phase of treatment. The FDA advisory committee has made it clear that the black box warning should not dissuade physicians from prescribing antidepressants to patients in need ([U.S. Food and Drug Administration 2007](#)).

## Medical Safety

Paroxetine treatment in clinical trials has not been associated with any significant abnormalities in standard laboratory tests, including hematological indices and chemistry panels, electroencephalogram (EEG), or electrocardiogram (ECG). One possible concern regarding paroxetine had been its potential for decreasing heart rate variability, which is a significant risk factor for myocardial infarction and cardiovascular mortality ([Carney et al. 2005](#)). Other norepinephrine reuptake-inhibiting antidepressants have been shown to cause decreases in this electrophysiological variable ([Rechlin 1994](#)), and depressed patients have been shown to exhibit lower heart rate variability than nondepressed persons ([Gorman and Sloan 2000](#)); however, paroxetine does not exhibit this effect. A review of the literature also determined that paroxetine may have the lowest risk of QT prolongation among the SSRIs ([Funk and Bostwick 2013](#)).

Paroxetine and other SSRIs have been implicated in precipitation of the syndrome of inappropriate antidiuretic hormone (SIADH), particularly in elderly individuals; symptoms resolve on discontinuation of the medication ([Strachan and Shepherd 1998](#)). One study demonstrated that hyponatremia (defined as plasma sodium levels  $<135$  mEq/L) occurred in 12% (9 of 75) of subjects, typically within the first 10 days of paroxetine treatment ([Fabian et al. 2004](#)). Risk factors for developing hyponatremia were low body mass index and low baseline plasma sodium levels.

## Discontinuation Syndrome

With abrupt discontinuation or treatment interruption, patients may develop what has become known as the SSRI discontinuation syndrome. Symptoms (such as dizziness, paresthesias, agitation, anxiety, nausea, and sweating) occur as early as the second day after a missed dose and may persist for several days. A comparison of SSRI postmarketing safety data found that withdrawal-related events occurred more frequently in paroxetine-treated patients than in patients treated with sertraline, fluvoxamine, or fluoxetine and that these events had a mean duration of 10.2 days ([Price et al. 1996](#)); similar results were reported by other groups ([Michelson et al. 2000](#); [Montgomery et al. 2004](#); [Rosenbaum et al. 1998](#)). Studies examining the effect of shorter SSRI treatment interruptions (3–5 days)—similar to what a patient would experience if he or she missed just a few medication doses—found that whereas paroxetine-treated patients develop significant discontinuation-emergent effects, fluoxetine-treated patients do not, a disparity likely due to differences

in the half-lives of these medications ([Judge et al. 2002](#); [Michelson et al. 2000](#)).

To prevent the emergence of withdrawal symptoms, practitioners are advised to gradually taper the dosage when discontinuing paroxetine in their patients. Despite the potential for withdrawal reactions after abrupt discontinuation of paroxetine, there is no clinical evidence of dosage escalation, craving, or drug-seeking behavior associated with dependence or addiction ([Inman et al. 1993](#); [Johnson et al. 1998](#); [Sharma et al. 2000](#)).

## Overdose

Overdoses with paroxetine are rarely associated with morbidity or mortality, which is in sharp contrast to the situation with the TCAs or venlafaxine ([Cheeta et al. 2004](#); [Whyte et al. 2003](#)). In the clinical trials program prior to FDA registration of paroxetine, 16 patients had ingested an overdose (doses of up to 850 mg of paroxetine); all patients recovered uneventfully ([Jenner 1992](#)). An extensive review of the literature (including adverse events databases) revealed a total of 28 fatalities involving paroxetine overdoses; however, in nearly all cases, either coingestants were involved or causality could not be ascertained ([Barbey and Roose 1998](#)).

## Use During Pregnancy and Lactation

A more complete discussion of the use of psychotropic medications during pregnancy appears elsewhere in this volume (see [Chapter 57, “Psychopharmacology During Pregnancy and Lactation”](#)); however, because paroxetine is

the only SSRI to be allocated to FDA pregnancy category D (“There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”), it warrants specific discussion here.

Spontaneous abortion has been linked both to depression and to antidepressant use; the risk may be even greater for women who are treated with paroxetine or venlafaxine ([Nakhai-Pour et al. 2010](#)).

Compared with other SSRIs, paroxetine has lower transmission across the placenta, and cord blood concentrations do not correlate with maternal dosing ([Hendrick et al. 2003b](#)). Maternal CYP2D6 polymorphisms appear to affect the pharmacokinetics of paroxetine. Women characterized as extensive metabolizers show decreases in paroxetine plasma levels over the course of pregnancy, whereas women characterized as intermediate or poor metabolizers show increased paroxetine levels ([Ververs et al. 2009](#)). It is possible that this effect may translate to a greater risk of fetal teratogenicity for women who are poor or intermediate metabolizers ([Ververs et al. 2009](#)).

Teratogenicity is a major concern when prescribing medications to women of childbearing age. The results of an unpublished study by GlaxoSmithKline (Paxil) led the FDA to warn that paroxetine may increase the risk of major congenital malformations (GlaxoSmithKline [2005](#)). Several organ systems, including the gastrointestinal, genitourinary, and central nervous systems, were affected; the most common cardiovascular anomalies were ventricular septal defects. A meta-analysis, also completed by GlaxoSmithKline, found a prevalence odds ratio of 1.46 for

combined cardiac defects with exposure to paroxetine in the first trimester. Considering a background prevalence of cardiac defects in the unexposed population of 1%, this would represent a 50% increase for the paroxetine-exposed population (Wurst et al. 2010).

A cohort study comparing rates of major congenital malformations in infants born to women treated with paroxetine, fluvoxamine, or sertraline during pregnancy found no significant differences among the medication groups compared with the control group (Kulin et al. 1998). In another study comparing birth outcomes after prenatal exposure to paroxetine, fluoxetine, or sertraline, rates of neonatal complications and congenital malformations in antidepressant-exposed infants were lower (1.4%) than rates in the general population, with no significant differences among medications (Hendrick et al. 2003a). Whereas one prospective controlled observational study found no increased risk of cardiac defects with paroxetine exposure (Diav-Citrin et al. 2008), a case-control study of data from a population-based registry of birth defects in the Netherlands did find an increased risk of atrial septal defects with first-trimester paroxetine exposure (adjusted odds ratio=5.7, 95% confidence interval=1.4-23.7) (Bakker et al. 2010). A recent meta-analysis of 23 studies concluded that paroxetine exposure during the first trimester was associated with a significantly increased risk of major congenital malformations, particularly major cardiac malformations (Bérard et al. 2016). It is important to note that studies of teratogenicity are frequently complicated by the effects of depression itself or of polypharmacy (e.g., concurrent use of benzodiazepines) (Yonkers et al. 2009). Nevertheless, on the basis of the risk of malformations, the American College of Obstetricians and Gynecologists



(ACOG) has recommended that paroxetine be avoided, if possible, in pregnant women or women planning pregnancy ([ACOG Committee on Practice Bulletins—Obstetrics 2008](#)).

Clinical studies of paroxetine in the setting of pregnancy suggest that gestational exposure might have transient negative effects on the newborn infant, particularly if the mother is treated during the third trimester. Infants with third-trimester paroxetine exposure show significantly increased distress compared with infants not so exposed ([Costei et al. 2002](#)). Symptoms in neonates exposed to SSRIs in utero include tremor, hypertonicity, irritability, weak or absent cry, seizures, and poor feeding; these symptoms typically resolve within 2 weeks ([Knoppert et al. 2006](#); [Yonkers et al. 2009](#)). Debate continues among neonatologists as to whether this neonatal distress represents a manifestation of serotonin excess or serotonin withdrawal ([Laine et al. 2004](#); [Stiskal 2005, 2006](#)).

Although not specific to paroxetine, an issue that has received much media attention is the development of persistent pulmonary hypertension of the newborn (PPHN) in neonates exposed to SSRIs late (>20 weeks) in gestation. A rare condition associated with significant morbidity, PPHN has an estimated base rate in the United States of 1–2 per 1,000 births ([Andrade et al. 2009](#)). A large case-control epidemiological study found an odds ratio of developing PPHN of 6.1 for infants exposed to SSRIs after gestational week 20 ([Chambers et al. 2006](#)). However, a more recent retrospective review did not find a significant difference in risk of developing PPHN with exposure to SSRIs; in fact, the authors found a higher prevalence in the nonexposed group ([Andrade et al. 2009](#)).

If a woman opts to continue antidepressant treatment during pregnancy, the clinician is advised to monitor for

relapse, given that higher dosages are often needed, especially in the early third trimester, to achieve or maintain disease remission ([Hostetter et al. 2000](#)).

Paroxetine is secreted into breast milk, with greater concentrations found in hindmilk than foremilk ([Ohman et al. 1999](#); [Stowe et al. 2000](#)). However, in a study in which the sera of nursing infants were analyzed for the presence of paroxetine after 10 days of maternal treatment with paroxetine at a stable daily dosage of 10–50 mg, the drug was undetectable in all infants ([Stowe et al. 2000](#)). A literature review concluded that paroxetine and sertraline have a better safety profile in breast-feeding women compared with other SSRIs and SNRIs ([Orsolini and Bellantuono 2015](#)).

---

## Drug-Drug Interactions

---

As noted previously (see “Pharmacokinetics and Disposition” section earlier in chapter), paroxetine is dependent primarily on the CYP2D6 hepatic enzyme for conversion into its inactive metabolites ([Hiemke and Härter 2000](#)). Paroxetine is not only a substrate of this system but also an inhibitor; therefore, other drugs that are metabolized by CYP2D6 are potentially subject to decreased clearance and subsequent increased plasma concentrations ([Sindrup et al. 1992b](#)). Concern is greatest for potential drug-drug interactions when the medication in question has a low therapeutic index. ([Table 12-1](#) lists potentially important drug-drug interactions involving paroxetine.)

---

**TABLE 12-1. Clinical significance of potential drug-drug interactions involving paroxetine**

Monoamine oxidase inhibitors	Clinically significant
Tamoxifen	Clinically significant
Tricyclic antidepressants	Clinically significant
Antiepileptic agents	Probably significant
$\beta$ -Adrenergic receptor antagonists	Probably significant
Cimetidine	Probably significant
Type IC antiarrhythmics	Probably significant
Typical antipsychotics	Possibly significant
Warfarin	Possibly significant
Clozapine	Inconclusive
Digoxin	Not clinically significant
Lithium	Not clinically significant

Medications that are CYP2D6 dependent include many antipsychotics, TCAs, type Ic antiarrhythmics,  $\beta$ -adrenergic agents, trazodone, and dextromethorphan ([Nemeroff et al. 1996](#)). Most reports of interactions between these medications and paroxetine are published as case reports ([Lane 1996](#)). As discussed earlier (see the subsection “Menopausal Vasomotor Symptoms”), the breast cancer medication tamoxifen is converted to its active metabolite by CYP2D6, and there is evidence that paroxetine decreases the efficacy of tamoxifen and increases mortality in women with breast cancer who are taking tamoxifen ([Kelly et al. 2010](#)).

Paroxetine does not appear to potentiate the sedative effects of haloperidol ([Cooper et al. 1989](#)); however, dystonia has been reported with the combination ([Budman et al. 1995](#)). In one prospective study, clozapine serum levels increased by an average of 40% when clozapine was coadministered with SSRIs, including paroxetine at a mean dosage of 31.2 mg/day ([Centorrino et al. 1996](#)). In another study that used a lower dosage of paroxetine (20 mg/day), no significant increase in clozapine concentrations was noted ([Wetzel et al. 1998](#)). There is insufficient evidence to draw conclusions about the clinical significance of interactions between paroxetine and other second-generation antipsychotics ([Spina and de Leon 2014](#)). Case reports have described possible exaggeration of extrapyramidal side effects when paroxetine was coadministered with perphenazine ([Ozdemir et al. 1997](#)), molindone ([Malek-Ahmadi and Allen 1995](#)), or pimozide ([Horrigan and Barnhill 1994](#)).

Paroxetine was found to increase total exposure (i.e., area under the curve of plasma concentrations) to the  $\beta$ -adrenergic receptor antagonist nebivolol by a factor of 6.1 ([Briciu et al. 2014](#)). Paroxetine also increased plasma concentrations of the  $\beta$ -adrenergic receptor antagonist timolol (administered as eye drops) to a level that could cause systemic adverse events in at-risk patients ([Mäenpää et al. 2014](#)).

Paroxetine is highly protein bound and has the potential to increase free drug levels of other medications that are bound to plasma proteins, such as warfarin, lithium, and digoxin, although this effect is rarely clinically meaningful ([Bannister et al. 1989](#); [Haenen et al. 1995](#); [Preskorn 1993](#)).

In prospective studies involving valproate, carbamazepine, or phenytoin, coadministration with

paroxetine did not cause any significant changes in plasma levels of these drugs ([Andersen et al. 1991](#); [Kaye et al. 1989](#)). By contrast, both phenytoin and carbamazepine have been shown to decrease plasma paroxetine concentrations ([Hiemke and Härtter 2000](#); [Kaye et al. 1989](#)). Valproate also may increase plasma paroxetine concentrations ([Andersen et al. 1991](#)). Cimetidine, which is a potent inhibitor of the CYP2D6 isoenzyme, has been shown to result in a 50% elevation of paroxetine concentrations ([Bannister et al. 1989](#)). The clinical significance of these variations in paroxetine concentrations is minor because of the wide interindividual pharmacokinetic variability, high therapeutic index, and lack of a concentration–efficacy relationship with paroxetine ([Gunasekara et al. 1998](#)).

Paroxetine does not potentiate the psychomotor effects of amobarbital, oxazepam, diazepam, or alcohol ([Bannister et al. 1989](#); [Cooper et al. 1989](#)).

Combinations of medications that enhance serotonergic activity may result in serotonin toxicity (serotonin syndrome), manifesting as agitation, myoclonus, hyperreflexia, diarrhea, diaphoresis, delirium, fever, and possibly death ([Weiner et al. 1997](#)). Concomitant use of MAOIs with any of the SSRIs is absolutely contraindicated, and a washout period of 14 days is recommended when switching from one agent to another ([Gunasekara et al. 1998](#); [Weiner et al. 1997](#)). Evidence of serotonin toxicity has been documented in case reports describing coadministration of paroxetine with moclobemide ([Hawley et al. 1996](#)), nefazodone ([John et al. 1997](#)), dextromethorphan ([Skop et al. 1994](#)), imipramine ([Weiner et al. 1997](#)), trazodone ([Reeves and Bullen 1995](#)), or other agents. The combination of SSRIs and sumatriptan, a 5-

HT<sub>1D</sub> receptor agonist used in the treatment of migraine, was previously discouraged because of the theoretical risk of precipitation of serotonin toxicity; however, a series of six cases, one involving paroxetine, of concurrent sumatriptan and SSRI administration demonstrated no such adverse events ([Leung and Ong 1995](#)).

---

## Conclusion

---

Paroxetine has been demonstrated to be an effective treatment for several psychiatric disorders, including major depressive disorder and virtually all of the anxiety disorders, as well as OCD and PTSD. It is well tolerated, with convenient once-daily dosing, and it is available in both IR and CR formulations. Most patients can expect symptomatic relief within 4 weeks, and some patients respond as early as 2 weeks. With few exceptions, the potential for serious pharmacokinetic interactions with other drugs is low, although concomitant MAOI use is contraindicated and use with tamoxifen in women with breast cancer may increase mortality. Overdosage rarely results in significant toxicity. Along with other SSRIs, initiation of paroxetine has been linked to an increase in suicidal ideation and suicidal behavior, primarily in children and adolescents. Paroxetine should be used cautiously in the treatment of pediatric anxiety disorders. Other SSRIs should be considered over paroxetine in pregnancy because of evidence for an association with congenital malformations. In the postpartum setting, however, nursing very likely poses a negligible exposure risk to infants of mothers receiving treatment with paroxetine.

Paroxetine, with its wide application and favorable safety profile, represents an important member of the SSRI class. It continues to be evaluated for efficacy in the treatment of other psychiatric and nonpsychiatric disorders.

---

## References

---

- Aberg-Wistedt A, Agren H, Ekselius L, et al: Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. *J Clin Psychopharmacol* 20(6):645-652, 2000 11106136
- ACOG Committee on Practice Bulletins—Obstetrics: ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol* 111(4):1001-1020, 2008 18378767
- Ahrold TK, Meston CM: Effects of SNS activation on SSRI-induced sexual side effects differ by SSRI. *J Sex Marital Ther* 35(4):311-319, 2009 19466669
- Andersen BB, Mikkelsen M, Vesterager A, et al: No influence of the antidepressant paroxetine on carbamazepine, valproate and phenytoin. *Epilepsy Res* 10(2-3):201-204, 1991 1840138
- Andrade SE, McPhillips H, Loren D, et al: Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf* 18(3):246-252, 2009 19148882
- Artigas F, Perez V, Alvarez E: Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. *Arch Gen Psychiatry* 51(3): 248-251, 1994 8122960

- Bakker A, van Dyck R, Spinhoven P, et al: Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder. *J Clin Psychiatry* 60(12):831-838, 1999 10665629
- Bakker MK, Kerstjens-Frederikse WS, Buys CH, et al: First-trimester use of paroxetine and congenital heart defects: a population-based case-control study. *Birth Defects Res A Clin Mol Teratol* 88(2):94-100, 2010 19937603
- Baldwin DS, Hawley CJ, Abed RT, et al: A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. *J Clin Psychiatry* 57 (suppl 2):46-52, 1996 8626363
- Baldwin D, Bobes J, Stein DJ, et al; Paroxetine Study Group: Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 175:120-126, 1999 10627793
- Baldwin DS, Cooper JA, Huusom AK, et al: A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. *Int Clin Psychopharmacol* 21(3):159-169, 2006 16528138
- Ballenger JC, Wheadon DE, Steiner M, et al: Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. *Am J Psychiatry* 155(1):36-42, 1998 9433336
- Bannister SJ, Houser VP, Hulse JD, et al: Evaluation of the potential for interactions of paroxetine with diazepam, cimetidine, warfarin, and digoxin. *Acta Psychiatr Scand Suppl* 350:102-106, 1989 2530759
- Barbey JT, Roose SP: SSRI safety in overdose. *J Clin Psychiatry* 59 (suppl 15):42-48, 1998 9786310
- Barbui C, Furukawa TA, Cipriani A: Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and



- unpublished data from randomized trials. CMAJ 178(3):296-305, 2008 18227449
- Bauer M, Zaninelli R, Müller-Oerlinghausen B, et al: Paroxetine and amitriptyline augmentation of lithium in the treatment of major depression: a double-blind study. J Clin Psychopharmacol 19(2):164-171, 1999 10211918
- Bayer AJ, Roberts NA, Allen EA, et al: The pharmacokinetics of paroxetine in the elderly. Acta Psychiatr Scand Suppl 350:85-86, 1989 2530796
- Benkert O, Szegedi A, Kohnen R: Mirtazapine compared with paroxetine in major depression. J Clin Psychiatry 61(9):656-663, 2000 11030486
- Bérard A, Iessa N, Chaabane S, et al: The risk of major cardiac malformations associated with paroxetine use during the first trimester of pregnancy: a systematic review and meta-analysis. Br J Clin Pharmacol 81(4):589-604, 2016 26613360
- Bielski RJ, Bose A, Chang CC: A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychiatry 17(2):65-69, 2005 16075658
- Biernacka JM, Sangkuhl K, Jenkins G, et al: The International SSRI Pharmacogenomics Consortium (ISPC): a genome-wide association study of antidepressant treatment response. Transl Psychiatry 5:e553, 2015 25897834
- Bird H, Broggin M: Paroxetine versus amitriptyline for treatment of depression associated with rheumatoid arthritis: a randomized, double blind, parallel group study. J Rheumatol 27(12):2791-2797, 2000 11128665
- Blier P, Bergeron R: Effectiveness of pindolol with selected antidepressant drugs in the treatment of major depression. J Clin Psychopharmacol 15(3):217-222, 1995 7636000
- Blier P, de Montigny C, Chaput Y: A role for the serotonin system in the mechanism of action of antidepressant

- treatments: preclinical evidence. *J Clin Psychiatry* 51 (suppl):14-20, discussion 21, 1990 2157700
- Bordet R, Thomas P, Dupuis B: Effect of pindolol on onset of action of paroxetine in the treatment of major depression: intermediate analysis of a double-blind, placebo-controlled trial. *Réseau de Recherche et d'Expérimentation Psychopharmacologique. Am J Psychiatry* 155(10):1346-1351, 1998 9766765
- Borgheini G: The bioequivalence and therapeutic efficacy of generic versus brand-name psychoactive drugs. *Clin Ther* 25(6):1578-1592, 2003 12860486
- Boulenger JP, Huusom AK, Florea I, et al: A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. *Curr Med Res Opin* 22(7):1331-1341, 2006 16834832
- Boyer WF, Blumhardt CL: The safety profile of paroxetine. *J Clin Psychiatry* 53 (suppl): 61-66, 1992 1531828
- Brent DA: Paroxetine and the FDA (comment). *J Am Acad Child Adolesc Psychiatry* 43(2):127-128, 2004 14971062
- Briciu C, Neag M, Muntean D, et al: A pharmacokinetic drug interaction study between nebivolol and paroxetine in healthy volunteers. *J Clin Pharm Ther* 39(5):535-540, 2014 24845234
- Budman CL, Sherling M, Bruun RD: Combined pharmacotherapy risk. *J Am Acad Child Adolesc Psychiatry* 34(3):263-264, 1995 7896663
- Bump GM, Mulsant BH, Pollock BG, et al: Paroxetine versus nortriptyline in the continuation and maintenance treatment of depression in the elderly. *Depress Anxiety* 13(1):38-44, 2001 11233459
- Carney RM, Blumenthal JA, Freedland KE, et al: Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch Intern Med* 165(13):1486-1491, 2005 16009863

- Cassano GB, Puca F, Scapicchio PL, et al; Italian Study Group on Depression in Elderly Patients: Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. *J Clin Psychiatry* 63(5):396-402, 2002 12019663
- Centers for Disease Control and Prevention (CDC): Suicide trends among youths and young adults aged 10-24 years—United States, 1990-2004. *MMWR Morb Mortal Wkly Rep* 56(35):905-908, 2007 17805220
- Centorrino F, Baldessarini RJ, Frankenburg FR, et al: Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 153(6):820-822, 1996 8633698
- Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al: Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 354(6):579-587, 2006 16467545
- Chaput Y, de Montigny C, Blier P: Presynaptic and postsynaptic modifications of the serotonin system by long-term administration of antidepressant treatments. An in vivo electrophysiologic study in the rat. *Neuropsychopharmacology* 5(4):219-229, 1991 1839498
- Charlier C, Broly F, Lhermitte M, et al: Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. *Ther Drug Monit* 25(6):738-742, 2003 14639062
- Cheeta S, Schifano F, Oyefeso A, et al: Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998-2000. *Br J Psychiatry* 184:41-47, 2004 14702226
- Chouinard G, Saxena B, Bélanger MC, et al: A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder. *J Affect Disord* 54(1-2):39-48, 1999 10403145

- Clayton AH, Pradko JF, Croft HA, et al: Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 63(4):357-366, 2002 12000211
- Cohen LS, Soares CN, Yonkers KA, et al: Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. *Psychosom Med* 66(5):707-713, 2004 15385695
- Cooper SM, Jackson D, Loudon JM, et al: The psychomotor effects of paroxetine alone and in combination with haloperidol, amylobarbitone, oxazepam, or alcohol. *Acta Psychiatr Scand Suppl* 350:53-55, 1989 2530791
- Cooper WO, Callahan ST, Shintani A, et al: Antidepressants and suicide attempts in children. *Pediatrics* 133(2):204-210, 2014 24394688
- Costei AM, Kozer E, Ho T, et al: Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 156(11):1129-1132, 2002 12413342
- Crewe HK, Lennard MS, Tucker GT, et al: The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Clin Pharmacol* 34(3):262-265, 1992 1389951
- Cubeddu A, Giannini A, Bucci F, et al: Paroxetine increases brain-derived neurotrophic factor in postmenopausal women. *Menopause* 17(2):338-343, 2010 19934779
- Cutler NR, Kramer MS, Reines SA, et al: Single site results from a multicenter study of efficacy and safety of MK-869, an NK-1 antagonist, in patients with major depressive disorder (abstract S.05.4). *Int J Neuropsychopharmacol* 3 (suppl 1):S7, 2000
- Dalhoff K, Almdal TP, Bjerrum K, et al: Pharmacokinetics of paroxetine in patients with cirrhosis. *Eur J Clin Pharmacol* 41(4):351-354, 1991 1839532
- DeVane CL: Pharmacokinetics, drug interactions, and tolerability of paroxetine and paroxetine CR. *Psychopharmacol Bull* 37 (suppl 1):29-41, 2003 14566199

- De Wilde J, Spiers R, Mertens C, et al: A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. *Acta Psychiatr Scand* 87(2):141-145, 1993 8447241
- Diav-Citrin O, Shechtman S, Weinbaum D, et al: Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. *Br J Clin Pharmacol* 66(5):695-705, 2008 18754846
- Dimmock PW, Wyatt KM, Jones PW, et al: Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet* 356(9236):1131-1136, 2000 11030291
- Doyle GD, Laher M, Kelly JG, et al: The pharmacokinetics of paroxetine in renal impairment. *Acta Psychiatr Scand Suppl* 350:89-90, 1989 2530798
- Duboff EA: Long-term treatment of major depressive disorder with paroxetine. *J Clin Psychopharmacol* 13 (6 suppl 2):28S-33S, 1993 8106653
- Dunner DL, Dunbar GC: Optimal dose regimen for paroxetine. *J Clin Psychiatry* 53 (suppl):21-26, 1992 1531817
- Emslie GJ, Wagner KD, Kutcher S, et al: Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 45(6):709-719, 2006 16721321
- Eriksson E, Hedberg MA, Andersch B, et al: The serotonin reuptake inhibitor paroxetin is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. *Neuropsychopharmacology* 12(2):167-176, 1995 7779245
- Fabian TJ, Amico JA, Kroboth PD, et al: Paroxetine-induced hyponatremia in older adults: a 12-week prospective study. *Arch Intern Med* 164(3):327-332, 2004 14769630

- Fang Y, Yuan C, Xu Y, et al; OPERATION Study Team: Comparisons of the efficacy and tolerability of extended-release venlafaxine, mirtazapine, and paroxetine in treatment-resistant depression: a double-blind, randomized pilot study in a Chinese population. *J Clin Psychopharmacol* 30(4):357-364, 2010 20571433
- Fava M, Amsterdam JD, Deltito JA, et al: A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. *Ann Clin Psychiatry* 10(4):145-150, 1998 9988054
- Fava M, Rosenbaum JF, Hoog SL, et al: Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. *J Affect Disord* 59(2):119-126, 2000 10837880
- Findling RL, Reed MD, Myers C, et al: Paroxetine pharmacokinetics in depressed children and adolescents. *J Am Acad Child Adolesc Psychiatry* 38(8):952-959, 1999 10434486
- Finley PR: Selective serotonin reuptake inhibitors: pharmacologic profiles and potential therapeutic distinctions. *Ann Pharmacother* 28(12):1359-1369, 1994 7696728
- Frazer A: Serotonergic and noradrenergic reuptake inhibitors: prediction of clinical effects from in vitro potencies. *J Clin Psychiatry* 62 (suppl 12):16-23, 2001 11430614
- Funk KA, Bostwick JR: A comparison of the risk of QT prolongation among SSRIs. *Ann Pharmacother* 47(10):1330-1341, 2013 24259697
- Geller DA, Wagner KD, Emslie G, et al: Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 43(11):1387-1396, 2004 15502598
- Geretsegger C, Böhmer F, Ludwig M: Paroxetine in the elderly depressed patient: randomized comparison with

- fluoxetine of efficacy, cognitive and behavioural effects. *Int Clin Psychopharmacol* 9(1):25-29, 1994 8195578
- Geretsegger C, Stuppaeck CH, Mair M, et al: Multicenter double blind study of paroxetine and amitriptyline in elderly depressed inpatients. *Psychopharmacology (Berl)* 119(3):277-281, 1995 7675961
- Geretsegger C, Bitterlich W, Stelzig R, et al: Paroxetine with pindolol augmentation: a double-blind, randomized, placebo-controlled study in depressed in-patients. *Eur Neuropsychopharmacol* 18(2):141-146, 2008 18054209
- Gex-Fabry M, Eap CB, Oneda B, et al: CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. *Ther Drug Monit* 30(4):474-482, 2008 18641553
- Gilmor ML, Owens MJ, Nemeroff CB: Inhibition of norepinephrine uptake in patients with major depression treated with paroxetine. *Am J Psychiatry* 159(10):1702-1710, 2002 12359676
- GlaxoSmithKline: Paxil (package insert). Research Triangle Park, NC, GlaxoSmithKline, 2001
- GlaxoSmithKline: Important Prescribing Information. December 2005. Available at: <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164864.pdf>. Accessed June 6, 2016.
- GlaxoSmithKline: Paroxetine Adult Suicidality Analysis: Major Depressive Disorder and Non-Major Depressive Disorder. Briefing Document. Updated April 5, 2006. Available at: [http://www.gsk.com/media/388720/briefing\\_doc.pdf](http://www.gsk.com/media/388720/briefing_doc.pdf). Accessed June 6, 2016.
- Golden RN, Nemeroff CB, McSorley P, et al: Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J Clin Psychiatry* 63(7):577-584, 2002 12143913

- Goldstein DJ, Lu Y, Detke MJ, et al: Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 24(4):389-399, 2004 15232330
- Gorman JM, Sloan RP: Heart rate variability in depressive and anxiety disorders. *Am Heart J* 140 (4 suppl):77-83, 2000 11011352
- Greist JH, Jefferson JW, Kobak KA, et al: Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. *Arch Gen Psychiatry* 52(1):53-60, 1995 7811162
- Grunebaum MF, Keilp JG, Ellis SP, et al: SSRI versus bupropion effects on symptom clusters in suicidal depression: post hoc analysis of a randomized clinical trial. *J Clin Psychiatry* 74(9):872-879, 2013 24107760
- Guillibert E, Pelicier Y, Archambault JC, et al: A double-blind, multicentre study of paroxetine versus clomipramine in depressed elderly patients. *Acta Psychiatr Scand Suppl* 350:132-134, 1989 2530766
- Gunasekara NS, Noble S, Benfield P: Paroxetine. An update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. *Drugs* 55(1):85-120, 1998 9463792
- Haenen J, DeBleeker E, Mertens C, et al: An interaction study of paroxetine on lithium plasma levels in depressed patients stabilised on lithium therapy. *Eur J Clin Res* 7:161-167, 1995
- Hawley CJ, Quick SJ, Ratnam S, et al: Safety and tolerability of combined treatment with moclobemide and SSRIs: a systematic study of 50 patients. *Int Clin Psychopharmacol* 11(3):187-191, 1996 8923097
- Heim C, Nemeroff CB: The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry* 46(11):1509-1522, 1999 10599479



- Hendrick V, Smith LM, Suri R, et al: Birth outcomes after prenatal exposure to antidepressant medication. *Am J Obstet Gynecol* 188(3):812-815, 2003a 12634662
- Hendrick V, Stowe ZN, Altshuler LL, et al: Placental passage of antidepressant medications. *Am J Psychiatry* 160(5):993-996, 2003b 12727706
- Hicks JK, Bishop JR, Sangkuhl K, et al; Clinical Pharmacogenetics Implementation Consortium: Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther* 98(2):127-134, 2015 25974703
- Hiemke C, Härtter S: Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 85(1):11-28, 2000 10674711
- Hirschfeld RMA: Panic disorder: diagnosis, epidemiology, and clinical course. *J Clin Psychiatry* 57 (suppl 10):3-8, discussion 9-10, 1996 8917127
- Horrigan JP, Barnhill LJ: Paroxetine-pimozide drug interaction. *J Am Acad Child Adolesc Psychiatry* 33(7):1060-1061, 1994 7961347
- Hostetter A, Stowe ZN, Strader JR Jr, et al: Dose of selective serotonin uptake inhibitors across pregnancy: clinical implications. *Depress Anxiety* 11(2):51-57, 2000 10812529
- Hutchinson DR, Tong S, Moon CA, et al: Paroxetine in the treatment of elderly depressed patients in general practice: a double-blind comparison with amitriptyline. *Int Clin Psychopharmacol* 6 (suppl 4):43-51, 1992 1431010
- Hyttel J: Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). *Int Clin Psychopharmacol* 9 (suppl 1):19-26, 1994 8021435
- Inman W, Kubota K, Pearce G, Wilton L: PEM report number 6: paroxetine. *Pharmacoepidemiol Drug Saf* 2(4-5):393-422, 1993 doi: 10.1002/pds.2630020409

- Jenner PN: Paroxetine: an overview of dosage, tolerability, and safety. *Int Clin Psychopharmacol* 6 (suppl 4):69–80, 1992 1431015
- John L, Perreault MM, Tao T, et al: Serotonin syndrome associated with nefazodone and paroxetine. *Ann Emerg Med* 29(2): 287–289, 1997 9018197
- Johnson H, Bouman WP, Lawton J: Withdrawal reaction associated with venlafaxine. *BMJ* 317(7161):787, 1998 9740568
- Judge R, Parry MG, Quail D, et al: Discontinuation symptoms: comparison of brief interruption in fluoxetine and paroxetine treatment. *Int Clin Psychopharmacol* 17(5):217–225, 2002 12177584
- Kamijima K, Hashimoto S, Nagayoshi E, et al: Double-blind, comparative study of milnacipran and paroxetine in Japanese patients with major depression. *Neuropsychiatr Dis Treat* 9:555–565, 2013 23650446
- Kasper S, Baldwin DS, Larsson Lönn S, et al: Superiority of escitalopram to paroxetine in the treatment of depression. *Eur Neuropsychopharmacol* 19(4):229–237, 2009 19185467
- Kato M, Fukuda T, Serretti A, et al: ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 32(2):398–404, 2008 17913323
- Kato M, Serretti A, Nonen S, et al: Genetic variants in combination with early partial improvement as a clinical utility predictor of treatment outcome in major depressive disorder: the result of two pooled RCTs. *Transl Psychiatry* 5:e513, 2015 25710119
- Kaye CM, Haddock RE, Langley PF, et al: A review of the metabolism and pharmacokinetics of paroxetine in man. *Acta Psychiatr Scand Suppl* 350:60–75, 1989 2530793
- Keller MB, Ryan ND, Strober M, et al: Efficacy of paroxetine in the treatment of adolescent major depression: a

- randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 40(7):762-772, 2001 11437014
- Kelly CM, Juurlink DN, Gomes T, et al: Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ* 340:c693, 2010 20142325
- Kent JM, Coplan JD, Lombardo I, et al: Occupancy of brain serotonin transporters during treatment with paroxetine in patients with social phobia: a positron emission tomography study with  $^{11}\text{C}$  McN 5652. *Psychopharmacology (Berl)* 164(4):341-348, 2002 12457263
- Kim Y, Asukai N, Konishi T, et al: Clinical evaluation of paroxetine in post-traumatic stress disorder (PTSD): 52-week, non-comparative open-label study for clinical use experience. *Psychiatry Clin Neurosci* 62(6):646-652, 2008 19068000
- Knoppert DC, Nimkar R, Principi T, et al: Paroxetine toxicity in a newborn after in utero exposure: clinical symptoms correlate with serum levels. *Ther Drug Monit* 28(1):5-7, 2006 16418684
- Kraus JE, Horrigan JP, Carpenter DJ, et al: Clinical features of patients with treatment-emergent suicidal behavior following initiation of paroxetine therapy. *J Affect Disord* 120(1-3):40-47, 2010 19439363
- Kulin NA, Pastuszak A, Sage SR, et al: Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 279(8):609-610, 1998 9486756
- Laine K, Kytölä J, Bertilsson L: Severe adverse effects in a newborn with two defective CYP2D6 alleles after exposure to paroxetine during late pregnancy. *Ther Drug Monit* 26(6):685-687, 2004 15570195
- Landén M, Nissbrandt H, Allgulander C, et al: Placebo-controlled trial comparing intermittent and continuous paroxetine in premenstrual dysphoric disorder.

- Neuropsychopharmacology 32(1):153-161, 2007  
17035933
- Landén M, Erlandsson H, Bengtsson F, et al: Short onset of action of a serotonin reuptake inhibitor when used to reduce premenstrual irritability. Neuropsychopharmacology 34(3):585-592, 2009  
18596686
- Lane RM: Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 11 (suppl 5):31-61, 1996 9032002
- Lecrubier Y, Bakker A, Dunbar G, et al; Collaborative Paroxetine Panic Study Investigators: A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Acta Psychiatr Scand 95(2):145-152, 1997a 9065680
- Lecrubier Y, Judge R; Collaborative Paroxetine Panic Study Investigators: Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Acta Psychiatr Scand 95(2):153-160, 1997b 9065681
- Le Noury J, Nardo JM, Healy D, et al: Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ 351:h4320, 2015 26376805
- Leung M, Ong M: Lack of an interaction between sumatriptan and selective serotonin reuptake inhibitors. Headache 35(8):488-489, 1995 7591744
- Liebowitz MR, Gelenberg AJ, Munjack D: Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. Arch Gen Psychiatry 62(2):190-198, 2005 15699296
- Liston HL, DeVane CL, Boulton DW, et al: Differential time course of cytochrome P450 2D6 enzyme inhibition by fluoxetine, sertraline, and paroxetine in healthy volunteers. J Clin Psychopharmacol 22(2):169-173, 2002  
11910262

- Lotrich FE, Pollock BG, Kirshner M, et al: Serotonin transporter genotype interacts with paroxetine plasma levels to influence depression treatment response in geriatric patients. *J Psychiatry Neurosci* 33(2):123-130, 2008 18330458
- Lydiard RB, Bobes J: Therapeutic advances: paroxetine for the treatment of social anxiety disorder. *Depress Anxiety* 11(3):99-104, 2000 10875050
- Mäenpää J, Volotinen-Maja M, Kautiainen H, et al: Paroxetine markedly increases plasma concentrations of ophthalmic timolol; CYP2D6 inhibitors may increase the risk of cardiovascular adverse effects of 0.5% timolol eye drops. *Drug Metab Dispos* 42(12):2068-2076, 2014 25261563
- Magnussen I, Tønder K, Engbaek F: Paroxetine, a potent selective long-acting inhibitor of synaptosomal 5-HT uptake in mice. *J Neural Transm* 55(3):217-226, 1982 doi: 10.1007/BF01276577
- Malek-Ahmadi P, Allen SA: Paroxetine-molindone interaction. *J Clin Psychiatry* 56(2):82-83, 1995 7852260
- Mancini C, Ameringen MV: Paroxetine in social phobia. *J Clin Psychiatry* 57(11):519-522, 1996 8968300
- Marshall RD, Schneier FR, Fallon BA, et al: An open trial of paroxetine in patients with noncombat-related, chronic posttraumatic stress disorder. *J Clin Psychopharmacol* 18(1):10-18, 1998 9472837
- Marshall RD, Beebe KL, Oldham M, et al: Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry* 158(12):1982-1988, 2001 11729013
- Martinez D, Broft A, Laruelle M: Pindolol augmentation of antidepressant treatment: recent contributions from brain imaging studies. *Biol Psychiatry* 48(8):844-853, 2000 11063979
- Masand PS, Gupta S, Schwartz T, et al: Paroxetine in patients with irritable bowel syndrome (IBS): a pilot

- open-label study. Paper presented at the New Clinical Drug Evaluation Unit (NCDEU), Phoenix, AZ, May 2001
- Meston CM: A randomized, placebo-controlled, crossover study of ephedrine for SSRI-induced female sexual dysfunction. *J Sex Marital Ther* 30(2):57-68, 2004 14742097
- Meyer JH, Wilson AA, Ginovart N, et al: Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: a [(11)C]DASB PET imaging study. *Am J Psychiatry* 158(11):1843-1849, 2001 11691690
- Michelson D, Fava M, Amsterdam J, et al: Interruption of selective serotonin reuptake inhibitor treatment. Double-blind, placebo-controlled trial. *Br J Psychiatry* 176:363-368, 2000 10827885
- Mitchell PB: Therapeutic drug monitoring of non-tricyclic antidepressant drugs. *Clin Chem Lab Med* 42(11):1212-1218, 2004 15576285
- Montejo-González AL, Llorca G, Izquierdo JA, et al: SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* 23(3):176-194, 1997 9292833
- Montgomery SA: A meta-analysis of the efficacy and tolerability of paroxetine versus tricyclic antidepressants in the treatment of major depression. *Int Clin Psychopharmacol* 16(3):169-178, 2001 11354239
- Montgomery SA, Dunbar G: Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. *Int Clin Psychopharmacol* 8(3):189-195, 1993 8263317
- Montgomery SA, Kennedy SH, Burrows GD, et al: Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-

- controlled discontinuation study. *Int Clin Psychopharmacol* 19(5):271-280, 2004 15289700
- Murphy GM Jr, Kremer C, Rodrigues HE, et al: Pharmacogenetics of antidepressant medication intolerance. *Am J Psychiatry* 160(10):1830-1835, 2003 14514498
- Murphy GM Jr, Hollander SB, Rodrigues HE, et al: Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry* 61(11):1163-1169, 2004 15520364
- Musselman DL, Lawson DH, Gumnick JF, et al: Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 344(13):961-966, 2001 11274622
- Nakhai-Pour HR, Broy P, Bérard A: Use of antidepressants during pregnancy and the risk of spontaneous abortion. *CMAJ* 182(10):1031-1037, 2010 20513781
- Nardi AE, Freire RC, Mochcovitch MD, et al: A randomized, naturalistic, parallel-group study for the long-term treatment of panic disorder with clonazepam or paroxetine. *J Clin Psychopharmacol* 32(1):120-126, 2012 22198456
- Nebes RD, Pollock BG, Mulsant BH, et al: Cognitive effects of paroxetine in older depressed patients. *J Clin Psychiatry* 60 (suppl 20):26-29, 1999 10513855
- Nemeroff CB: Paroxetine: an overview of the efficacy and safety of a new selective serotonin reuptake inhibitor in the treatment of depression. *J Clin Psychopharmacol* 13(6) (suppl 2):10S-17S, 1993 8106649
- Nemeroff CB: The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol Psychiatry* 1(4):336-342, 1996 9118360
- Nemeroff CB, DeVane CL, Pollock BG: Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 153(3):311-320, 1996 8610817

- Nemeroff CB, Evans DL, Gyulai L, et al: Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry* 158(6):906-912, 2001 11384898
- Nemeroff CB, Etsuah AR, Willard LB, et al: Venlafaxine and SSRIs: pooled remission analysis (New Research Abstract NR263). Program and abstracts of the American Psychiatric Association 156th Annual Meeting, San Francisco, CA, May 17-22, 2003
- Nemeroff CB, Kalali A, Keller MB, et al: Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. *Arch Gen Psychiatry* 64(4):466-472, 2007 17404123
- Newport DJ, Stowe ZN, Nemeroff CB: Parental depression: animal models of an adverse life event. *Am J Psychiatry* 159(8): 1265-1283, 2002 12153816
- Notaras M, Hill R, van den Buuse M: The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: progress and controversy. *Mol Psychiatry* 20(8):916-930, 2015 25824305
- Oehrberg S, Christiansen PE, Behnke K, et al: Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 167(3):374-379, 1995 7496647
- Ohman R, Hägg S, Carleborg L, Spigset O: Excretion of paroxetine into breast milk. *J Clin Psychiatry* 60(8):519-523, 1999 10485633
- Orsolini L, Bellantuono C: Serotonin reuptake inhibitors and breastfeeding: a systematic review. *Hum Psychopharmacol* 30(1):4-20, 2015 25572308
- Owens MJ, Morgan WN, Plott SJ, et al: Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Ther* 283(3):1305-1322, 1997 9400006
- Owens MJ, Krulewicz S, Simon JS, et al: Estimates of serotonin and norepinephrine transporter inhibition in



depressed patients treated with paroxetine or venlafaxine. *Neuropsychopharmacology* 33(13):3201-3212, 2008 18418363

Ozdemir V, Naranjo CA, Herrmann N, et al: Paroxetine potentiates the central nervous system side effects of perphenazine: contribution of cytochrome P4502D6 inhibition in vivo. *Clin Pharmacol Ther* 62(3):334-347, 1997 9333110

Pérez V, Soler J, Puigdemont D, et al: A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Grup de Recerca en Trastorns Afectius. Arch Gen Psychiatry* 56(4):375-379, 1999 10197835

Piccinelli M, Pini S, Bellantuono C, Wilkinson G: Efficacy of drug treatment in obsessive-compulsive disorder. A meta-analytic review. *Br J Psychiatry* 166(4):424-443, 1995 7795913

Poirier MF, Boyer P: Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *Br J Psychiatry* 175:12-16, 1999 10621762

Pollack MH, Zaninelli R, Goddard A, et al: Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 62(5):350-357, 2001 11411817

Popiel A, Zawadzki B, Pragłowska E, et al: Prolonged exposure, paroxetine and the combination in the treatment of PTSD following a motor vehicle accident. A randomized clinical trial—The “TRAKT” study. *J Behav Ther Exp Psychiatry* 48:17-26, 2015 25677254

Preskorn SH: Pharmacokinetics of antidepressants: why and how they are relevant to treatment. *J Clin Psychiatry* 54 (suppl):14-34, discussion 55-56, 1993 8407856

Price JS, Waller PC, Wood SM, et al: A comparison of the post-marketing safety of four selective serotonin re-

- uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 42(6):757-763, 1996 8971432
- Purgato M, Papola D, Gastaldon C, et al: Paroxetine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev* 4:CD006531, 2014 24696195
- Rapaport MH, Lydiard RB, Pitts CD, et al: Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial. *J Clin Psychiatry* 70(1):46-57, 2009 19026248
- Rasmussen SA, Eisen JL, Pato MT: Current issues in the pharmacologic management of obsessive compulsive disorder. *J Clin Psychiatry* 54 (suppl):4-9, 1993 8101187
- Ray A, Tennakoon L, Keller J, et al: ABCB1 (MDR1) predicts remission on P-gp substrates in chronic depression. *Pharmacogenomics J* 15(4):332-339, 2015 25487678
- Rechlin T: The effect of amitriptyline, doxepin, fluvoxamine, and paroxetine treatment on heart rate variability. *J Clin Psychopharmacol* 14(6):392-395, 1994 7884019
- Reeves RR, Bullen JA: Serotonin syndrome produced by paroxetine and low-dose trazodone. *Psychosomatics* 36(2):159-160, 1995 7724720
- Reynolds CF 3rd, Dew MA, Pollock BG, et al: Maintenance treatment of major depression in old age. *N Engl J Med* 354(11): 1130-1138, 2006 16540613
- Richard IH, McDermott MP, Kurlan R, et al; SAD-PD Study Group: A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology* 78(16):1229-1236, 2012 22496199
- Rickels K, Zaninelli R, McCafferty J, et al: Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* 160(4):749-756, 2003 12668365
- Riddle MA: Paroxetine and the FDA (comment). *J Am Acad Child Adolesc Psychiatry* 43(2):128-130, 2004 14964296

- Rocca P, Fonzo V, Scotta M, et al: Paroxetine efficacy in the treatment of generalized anxiety disorder. *Acta Psychiatr Scand* 95(5):444-450, 1997 9197912
- Roose SP, Laghrissi-Thode F, Kennedy JS, et al: Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 279(4):287-291, 1998 9450712
- Rosen RC, Lane RM, Menza M: Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol* 19(1):67-85, 1999 9934946
- Rosenbaum JF, Fava M, Hoog SL, et al: Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry* 44(2):77-87, 1998 9646889
- Ruhé HG, Booij J, v Weert HC, et al: Evidence why paroxetine dose escalation is not effective in major depressive disorder: a randomized controlled trial with assessment of serotonin transporter occupancy. *Neuropsychopharmacology* 34(4):999-1010, 2009a 18830236
- Ruhé HG, Ooteman W, Booij J, et al: Serotonin transporter gene promoter polymorphisms modify the association between paroxetine serotonin transporter occupancy and clinical response in major depressive disorder. *Pharmacogenet Genomics* 19(1):67-76, 2009b 18987562
- Ruxton K, Woodman RJ, Mangoni AA: Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. *Br J Clin Pharmacol* 80(2):209-220, 2015 25735839
- Sachs GS, Nierenberg AA, Calabrese JR, et al: Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 356(17):1711-1722, 2007 17392295

- Safarinejad MR: Comparison of dapoxetine versus paroxetine in patients with premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. *Clin Neuropharmacol* 29(5):243-252, 2006 16960468
- Sarginson JE, Lazzeroni LC, Ryan HS, et al: ABCB1 (MDR1) polymorphisms and antidepressant response in geriatric depression. *Pharmacogenet Genomics* 20(8):467-475, 2010 20555295
- Schneeweiss S, Patrick AR, Solomon DH, et al: Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics* 125(5): 876-888, 2010a 20385637
- Schneeweiss S, Patrick AR, Solomon DH, et al: Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults: a propensity score-adjusted analysis of 9 years' data. *Arch Gen Psychiatry* 67(5):497-506, 2010b 20439831
- Schneier FR, Neria Y, Pavlicova M, et al: Combined prolonged exposure therapy and paroxetine for PTSD related to the World Trade Center attack: a randomized controlled trial. *Am J Psychiatry* 169(1):80-88, 2012 21908494
- Schöne W, Ludwig M: A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression. *J Clin Psychopharmacol* 13 (6 suppl 2):34S-39S, 1993 8106654
- Seripa D, Pilotto A, Paroni G, et al: Role of the serotonin transporter gene locus in the response to SSRI treatment of major depressive disorder in late life. *J Psychopharmacol* 29(5):623-633, 2015 25827644
- Sharma A, Goldberg MJ, Cerimele BJ: Pharmacokinetics and safety of duloxetine, a dual-serotonin and norepinephrine reuptake inhibitor. *J Clin Pharmacol* 40(2):161-167, 2000 10664922

- Shelton C, Entsuah R, Padmanabhan SK, Vinall PE: Venlafaxine XR demonstrates higher rates of sustained remission compared to fluoxetine, paroxetine or placebo. *Int Clin Psychopharmacol* 20(4): 233-238, 2005 15933485
- Simon JA, Portman DJ, Kaunitz AM, et al: Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause* 20(10):1027-1035, 2013 24045678
- Sindrup SH, Brøsen K, Gram LF: Pharmacokinetics of the selective serotonin reuptake inhibitor paroxetine: nonlinearity and relation to the sparteine oxidation polymorphism. *Clin Pharmacol Ther* 51(3):288-295, 1992a 1531951
- Sindrup SH, Brøsen K, Gram LF, et al: The relationship between paroxetine and the sparteine oxidation polymorphism. *Clin Pharmacol Ther* 51(3):278-287, 1992b 1531950
- Skop BP, Finkelstein JA, Mareth TR, et al: The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. *Am J Emerg Med* 12(6):642-644, 1994 7945606
- Soares CN, Joffe H, Viguera AC, et al: Paroxetine versus placebo for women in midlife after hormone therapy discontinuation. *Am J Med* 121(2):159-162.e1, 2008 18261506
- Spina E, de Leon J: Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol* 10(5):721-746, 2014 24494611
- Stearns V, Isaacs C, Rowland J, et al: A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. *Ann Oncol* 11(1):17-22, 2000 10690382
- Stearns V, Beebe KL, Iyengar M, Dube E: Paroxetine controlled release in the treatment of menopausal hot

- flashes: a randomized controlled trial. JAMA 289(21):2827-2834, 2003 12783913
- Stearns V, Slack R, Greep N, et al: Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. J Clin Oncol 23(28):6919-6930, 2005 16192581
- Stein DJ, Versiani M, Hair T, Kumar R: Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. Arch Gen Psychiatry 59(12):1111-1118, 2002 12470127
- Stein MB, Chartier MJ, Hazen AL, et al: Paroxetine in the treatment of generalized social phobia: open-label treatment and double-blind placebo-controlled discontinuation. J Clin Psychopharmacol 16(3): 218-222, 1996 8784653
- Stein MB, Liebowitz MR, Lydiard RB, et al: Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. JAMA 280(8): 708-713, 1998 9728642
- Steiner M, Hirschberg AL, Bergeron R, et al: Luteal phase dosing with paroxetine controlled release (CR) in the treatment of premenstrual dysphoric disorder. Am J Obstet Gynecol 193(2):352-360, 2005 16098854
- Steiner M, Ravindran AV, LeMelledo JM, et al: Luteal phase administration of paroxetine for the treatment of premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled trial in Canadian women. J Clin Psychiatry 69(6):991-998, 2008 18517289
- Stiskal JA: Defective alleles may not have contributed to adverse effects. Ther Drug Monit 27(5):683, 2005 16175145
- Stiskal JA: Defective alleles may not have contributed to adverse effects (comment). Ther Drug Monit 28(1):142, author reply 143, 2006 16418712
- Stocchi F, Nordera G, Jokinen RH, et al; Paroxetine Generalized Anxiety Disorder Study Team: Efficacy and

- tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry* 64(3):250-258, 2003 12716265
- Stowe ZN, Cohen LS, Hostetter A, et al: Paroxetine in human breast milk and nursing infants. *Am J Psychiatry* 157(2):185-189, 2000 10671385
- Strachan J, Shepherd J: Hyponatraemia associated with the use of selective serotonin re-uptake inhibitors. *Aust N Z J Psychiatry* 32(2):295-298, 1998 9588311
- Sugarman MA, Loree AM, Baltes BB, et al: The efficacy of paroxetine and placebo in treating anxiety and depression: a meta-analysis of change on the Hamilton Rating Scales. *PLoS One* 9(8):e106337, 2014 25162656
- Sundblad C, Wikander I, Andersch B, Eriksson E: A naturalistic study of paroxetine in premenstrual syndrome: efficacy and side-effects during ten cycles of treatment. *Eur Neuropsychopharmacol* 7(3): 201-206, 1997 9213079
- Tanrikut C, Feldman AS, Altemus M, et al: Adverse effect of paroxetine on sperm. *Fertil Steril* 94(3):1021-1026, 2010 19515367
- Tasker TCG, Kaye CM, Zussman BD, Link CG: Paroxetine plasma levels: lack of correlation with efficacy or adverse events. *Acta Psychiatr Scand Suppl* 350:152-155, 1989 2530776
- Taylor MJ, Sen S, Bhagwagar Z: Antidepressant response and the serotonin transporter gene-linked polymorphic region. *Biol Psychiatry* 68(6):536-543, 2010 20615496
- Thomas DR, Nelson DR, Johnson AM: Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxytryptamine uptake inhibitor. *Psychopharmacology (Berl)* 93(2):193-200, 1987 2962217
- Thorlund K, Druyts E, Wu P, et al: Comparative efficacy and safety of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in older

- adults: a network meta-analysis. *J Am Geriatr Soc* 63(5):1002-1009, 2015 25945410
- Tignol J: A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression. *J Clin Psychopharmacol* 13 (6 suppl 2): 18S-22S, 1993 8106650
- Tome MB, Isaac MT, Harte R, Holland C: Paroxetine and pindolol: a randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. *Int Clin Psychopharmacol* 12(2):81-89, 1997 9219043
- Tucker P, Zaninelli R, Yehuda R, et al: Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 62(11):860-868, 2001 11775045
- Tucker P, Beebe KL, Burgin C, et al: Paroxetine treatment of depression with posttraumatic stress disorder: effects on autonomic reactivity and cortisol secretion. *J Clin Psychopharmacol* 24(2):131-140, 2004 15206659
- Tulloch IF, Johnson AM: The pharmacologic profile of paroxetine, a new selective serotonin reuptake inhibitor. *J Clin Psychiatry* 53 (suppl):7-12, 1992 1531829
- Uhr M, Tontsch A, Namendorf C, et al: Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. *Neuron* 57(2): 203-209, 2008 18215618
- U.S. Food and Drug Administration: Worsening Depression and Suicidality in Patients Being Treated With Antidepressants. March 22, 2004. Available at: <http://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm161696.htm>. Accessed November 2016.
- U.S. Food and Drug Administration: New Warnings Proposed for Antidepressants. May 2, 2007. (FDA Consumer Health Information, Consumer Updates archive) Available at: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048950.htm>. Accessed June 6, 2016.



- Valenstein M, Kim HM, Ganoczy D, et al: Antidepressant agents and suicide death among US Department of Veterans Affairs patients in depression treatment. *J Clin Psychopharmacol* 32(3):346-353, 2012 22544011
- Vermetten E, Vythilingam M, Southwick SM, et al: Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry* 54(7):693-702, 2003 14512209
- Ververs FF, Voorbij HA, Zwartz P, et al: Effect of cytochrome P450 2D6 genotype on maternal paroxetine plasma concentrations during pregnancy. *Clin Pharmacokinet* 48(10):677-683, 2009 19743889
- Wagner KD, Berard R, Stein MB, et al: A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry* 61(11):1153-1162, 2004 15520363
- Wagstaff AJ, Cheer SM, Matheson AJ, et al: Paroxetine: an update of its use in psychiatric disorders in adults. *Drugs* 62(4):655-703, 2002 11893234
- Waldinger MD, Hengeveld MW, Zwinderman AH, et al: Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol* 18(4):274-281, 1998 9690692
- Waldinger MD, Zwinderman AH, Olivier B: Antidepressants and ejaculation: a double-blind, randomized, fixed-dose study with mirtazapine and paroxetine. *J Clin Psychopharmacol* 23(5):467-470, 2003 14520123
- Wang Z, Xu X, Tan Q, et al: Treatment of major depressive disorders with generic duloxetine and paroxetine: a multi-centered, double-blind, double-dummy, randomized controlled clinical trial. *Shanghai Arch Psychiatry* 27(4):228-236, 2015 26549959

- Weihs KL, Settle EC Jr, Batey SR, et al: Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psychiatry* 61(3):196-202, 2000 10817105
- Weiner AL, Tilden FF Jr, McKay CA Jr: Serotonin syndrome: case report and review of the literature. *Conn Med* 61(11):717-721, 1997 9419960
- Weitzner MA, Moncello J, Jacobsen PB, et al: A pilot trial of paroxetine for the treatment of hot flashes and associated symptoms in women with breast cancer. *J Pain Symptom Manage* 23(4):337-345, 2002 11997203
- West CHK, Ritchie JC, Weiss JM: Paroxetine-induced increase in activity of locus coeruleus neurons in adolescent rats: implication of a countertherapeutic effect of an antidepressant. *Neuropsychopharmacology* 35(8):1653-1663, 2010 20357759
- Wetzel H, Anghelescu I, Szegedi A, et al: Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. *J Clin Psychopharmacol* 18(1):2-9, 1998 9472836
- Whyte IM, Dawson AH, Buckley NA: Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *QJM* 96(5):369-374, 2003 12702786
- Wong DT, Bymaster FP, Engleman EA: Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication. *Life Sci* 57(5):411-441, 1995 7623609
- Wu KY, Liu CY, Hsiao MC: Six-month paroxetine treatment of premenstrual dysphoric disorder: continuous versus intermittent treatment protocols. *Psychiatry Clin Neurosci* 62(1):109-114, 2008 18289149
- Wurst KE, Poole C, Ephross SA, et al: First trimester paroxetine use and the prevalence of congenital,

specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res A Clin Mol Teratol* 88(3):159-170, 2010 19739149

Yonkers KA, Gullion C, Williams A, et al: Paroxetine as a treatment for premenstrual dysphoric disorder. *J Clin Psychopharmacol* 16(1):3-8, 1996 8834412

Yonkers KA, Wisner KL, Stewart DE, et al: The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry* 31(5):403-413, 2009 19703633

Zanardi R, Franchini L, Gasperini M, et al: Double-blind controlled trial of sertraline versus paroxetine in the treatment of delusional depression. *Am J Psychiatry* 153(12):1631-1633, 1996 8942464

Zanardi R, Artigas F, Franchini L, et al: How long should pindolol be associated with paroxetine to improve the antidepressant response? *J Clin Psychopharmacol* 17(6):446-450, 1997 9408806

Zanardi R, Benedetti F, Di Bella D, et al: Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *J Clin Psychopharmacol* 20(1):105-107, 2000 10653220

Zis AP, Grof P, Webster M, et al: Prediction of relapse in recurrent affective disorder. *Psychopharmacol Bull* 16(1):47-49, 1980 7360839

Zohar J, Judge R; OCD Paroxetine Study Investigators: Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry* 169(4):468-474, 1996 8894198

# CHAPTER 13

## Fluvoxamine

Elias Aboujaoude, M.D.

Lorin M. Koran, M.D.

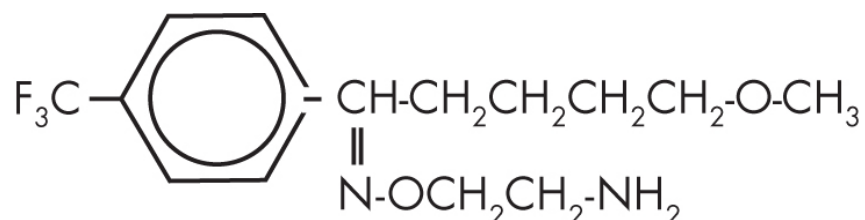
Fluvoxamine is a member of the selective serotonin reuptake inhibitor (SSRI) family of drugs. Initially manufactured by Duphar Laboratories in the United Kingdom in 1971, fluvoxamine was registered as an antidepressant in Switzerland in 1983, becoming the first drug in the now hugely popular SSRI class to reach the market. Since its introduction, fluvoxamine has undergone a wide range of trials to assess its therapeutic potential in depression, several anxiety disorders, and obsessive-compulsive disorder (OCD). Fluvoxamine has been available in the United States since 1994, when it received U.S. Food and Drug Administration (FDA) approval for the treatment of OCD ([Ware 1997](#)). More than 28 million people worldwide have been treated with fluvoxamine ([Buchberger and Wagner 2002](#)).

---

## Structure-Activity Relations

---

Fluvoxamine belongs to the 2-aminoethyl oxime ethers of the aralkyl ketones ([Figure 13-1](#)) and is chemically identified as 5-methoxy-4'-(trifluoromethyl) valerophenone-(E)-O-(2-aminoethyl) oxime maleate (1:1). Fluvoxamine's empirical formula is  $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$ , and it does not have a chiral center or exist in stereoisomers. Because of local irritant properties, fluvoxamine cannot be administered parenterally ([Physicians' Desk Reference 2015](#)).



---

**FIGURE 13-1.** Chemical structure of fluvoxamine.

---

## Mechanism of Action

---

Like other SSRIs, fluvoxamine binds to the presynaptic serotonin transporter (SERT) and prevents it from reabsorbing serotonin into the presynaptic terminals. This increases the amount of serotonin in the synaptic cleft. How this increase translates into efficacy remains unclear, but it has been hypothesized to involve downstream effects, including serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) autoreceptor desensitization ([Stahl 1998](#)); increased sensitivity of dopamine<sub>2</sub> (D<sub>2</sub>)-like receptors in the nucleus accumbens ([Gershon et al. 2007](#));

enhanced neurogenesis ([Dranovsky and Hen 2006](#)); changes in mitochondrial production of cerebral adenosine triphosphate (ATP) ([Ferreira et al. 2014](#)); and individual pharmacogenomics factors involving SERT and catechol-*O*-methyltransferase (COMT) gene variants ([Fukui et al. 2014](#); [Mancama and Kerwin 2003](#)). Furthermore, sigma-1 receptors appear to modulate several neurotransmitter pathways, and evidence suggests that fluvoxamine's affinity for the sigma-1 receptor exceeds that of all other SSRIs ([Ishikawa et al. 2007](#)).

---

## Pharmacological Profile

---

Fluvoxamine is a more potent inhibitor of serotonin reuptake than the tricyclic antidepressants, including clomipramine, but is less potent than the other SSRIs. It is highly selective for the serotonin transporter ( $K_i=2.3$  nmol/L) and has minimal affinity for the norepinephrine and dopamine transporters, or the muscarinic,  $\alpha_1$ -adrenergic, histaminic, and 5-HT<sub>2C</sub> receptors. It possesses no monoamine oxidase-inhibiting properties ([Lapierre et al. 1983](#); [Owens et al. 2001](#); [Palmer and Benfield 1994](#); [Ware 1997](#)).

---

## Pharmacokinetics and Disposition

---

Fluvoxamine is almost entirely absorbed from the gastrointestinal tract, regardless of the presence of food

([van Harten 1995](#)). Still, first-pass metabolism limits oral bioavailability to 53% ([DeVane 2003](#); [DeVane and Gill 1997](#)). Peak plasma concentrations occur within 2–8 hours, and steady-state concentration is achieved within 10 days ([van Harten 1995](#)). Plasma concentration shows no consistent correlation with efficacy or side effects, thus limiting the value of monitoring concentration.

The mean half-life of fluvoxamine is 15 hours, making twice-daily dosing preferable. Despite fluvoxamine's relatively short half-life, a discontinuation syndrome is rare ([Buchberger and Wagner 2002](#)), possibly because of the drug's slower elimination from the brain ([Strauss et al. 1998](#)).

Because fluvoxamine is widely distributed and reaches higher concentrations in the brain and other organs than in plasma ([Benfield and Ward 1986](#)), patients receiving hemodialysis do not require replacement doses; re-equilibration should occur ([DeVane and Gill 1997](#)).

Compared with other SSRIs, fluvoxamine's rate of protein binding is relatively low (77%) ([DeVane and Gill 1997](#)), which implies less risk of interactions from drug displacement.

At least 11 products of fluvoxamine metabolism are known, but none seems pharmacologically active ([DeVane and Gill 1997](#); [Palmer and Benfield 1994](#)). Metabolism is thought to occur primarily through oxidative demethylation. Only minimal amounts of fluvoxamine (3%) are excreted unchanged by the kidneys, suggesting that renal impairment should not significantly alter fluvoxamine's pharmacokinetics ([van Harten 1995](#)).

Because hepatic clearance is decreased in patients with liver disease and in elderly patients, dosage adjustments are sometimes necessary ([DeVane and Gill 1997](#); [van](#)

[Harten et al. 1993](#)). No gender-based differences in concentration seem to exist in adults ([DeVane and Gill 1997](#)). Pharmacokinetics studies in children report a higher area under the curve (AUC) than in adolescents, with the difference being more pronounced in females, suggesting lower dosages may be sufficient in children. No appreciable pharmacokinetic differences were observed between adolescents and adults ([Physicians' Desk Reference 2015](#)).

In the United States, fluvoxamine is available in both immediate-release and controlled-release formulations.

---

## Indications and Efficacy

---

### Depression

The first trial of fluvoxamine treatment of depression dates to 1976. Since then, several randomized, single- or double-blind studies conducted have tested fluvoxamine's antidepressant efficacy against placebo, SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, tetracyclic antidepressants, and a reversible inhibitor of monoamine oxidase. The trials vary in design but, taken together, support the efficacy and safety of fluvoxamine in treating depression—including psychotic depression—across all age groups ([Fukuchi and Kanemoto 2002](#); [Haffmans et al. 1996](#); [Kiev and Feiger 1997](#); [Otsubo et al. 2005](#); [Rapaport et al. 1996](#); [Rossini et al. 2005](#); [Ware 1997](#); [Zanardi et al. 2000](#); [Zohar et al. 2003](#)). Study durations ranged from 4 to 7 weeks, and dosages ranged from 50 to 300 mg/day. Further, benefits from fluvoxamine



seem to be sustained over at least 1 year ([Terra and Montgomery 1998](#)).

In a well-designed recent analysis of 54 randomized controlled trials ( $N=5,122$ ), no strong evidence was found to indicate that fluvoxamine was either superior or inferior to other antidepressants regarding response and remission ([Omori et al. 2010](#)). However, differing side-effect profiles were evident, especially in regard to more frequent reports of nausea and vomiting for fluvoxamine compared with some other antidepressants.

Finally, because of fluvoxamine's potent sigma-1 agonist action and the putative antipsychotic property such action might confer, some authors have suggested that fluvoxamine monotherapy might be a useful alternative to combined treatment with an antidepressant and an antipsychotic in cases of psychotic depression ([Furuse and Hashimoto 2009](#)).

## Panic Disorder

The largest randomized, double-blind, placebo-controlled study to test fluvoxamine in the treatment of panic disorder involved 188 subjects who were assigned to 8 weeks of fluvoxamine 100–300 mg/day or placebo. At study end, significantly more subjects in the fluvoxamine group were free from panic attacks (69% vs. 46%,  $P=0.002$ ) ([Figgitt and McClellan 2000](#)).

Limited data suggest similar efficacy for fluvoxamine and the tricyclic antidepressant imipramine, as well as a possible potentiating effect of fluvoxamine when combined with cognitive or exposure therapy ([Figgitt and McClellan 2000](#)).

# Social Anxiety Disorder (Social Phobia)

The largest double-blind, placebo-controlled study to assess the effectiveness of fluvoxamine (50–300 mg/day) in social anxiety disorder recruited 92 subjects with social phobia ([Stein et al. 1999](#)). Significantly more subjects assigned to fluvoxamine responded (43% vs. 23%,  $P=0.04$ ), as determined by a rating of much or very much improved on the global improvement item of the Clinical Global Impressions Scale. More recently, a controlled-release formulation of fluvoxamine showed similarly good results in two randomized, double-blind studies ([Davidson et al. 2004](#); [Westenberg et al. 2004](#)). This formulation was approved in the United States in 2008 for the treatment of social anxiety disorder and OCD.

## Obsessive-Compulsive and Related Disorders

### **Obsessive-Compulsive Disorder in Adults**

The first formal test of fluvoxamine in the treatment of OCD took place in 1987 ([Price et al. 1987](#)). Since then, multiple randomized studies have established fluvoxamine's efficacy and safety in treating OCD. These trials have compared fluvoxamine with placebo, clomipramine, and other SSRIs.

In randomized, double-blind comparisons with placebo, subjects were given fluvoxamine 100–300 mg/day for 6–10 weeks. Significant improvements in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores were observed, and

response rates ranged from 38% to 52% (vs. 0% to 18% for placebo) ([Figgitt and McClellan 2000](#)).

We identified five published double-blind comparisons of fluvoxamine and clomipramine, both dosed at  $\leq 300$  mg/day, involving a total of 531 subjects and lasting 9–10 weeks ([Figgitt and McClellan 2000](#); [Freeman et al. 1994](#); [Koran et al. 1996](#); [Milanfranchi et al. 1997](#); [Mundo et al. 2000, 2001](#)). All studies demonstrated equal efficacy for the two agents (range of response rates: 56%–85% for fluvoxamine and 53%–83% for clomipramine). One small published study compared fluvoxamine with other SSRIs. This 10-week single-blind study of 30 subjects randomly assigned to fluvoxamine, paroxetine, or citalopram suggested similar efficacy ([Mundo et al. 1997](#)).

Long-term maintenance treatment with fluvoxamine seems to protect against relapse. A 2-year open-label follow-up study enrolling 130 subjects who had responded to fluvoxamine 300 mg/day, clomipramine 150 mg/day, or fluoxetine 40 mg/day showed that maintenance treatment at full or half dosages was significantly superior to treatment discontinuation in preventing relapse ([Ravizza et al. 1996](#)).

Predictors of response to fluvoxamine in OCD were evaluated in a recent functional magnetic resonance imaging (fMRI) study involving 17 subjects who underwent fMRI at baseline and after 12 weeks of treatment (final dose=200 mg/day). Pretreatment hyperactivation of the right cerebellum and left superior temporal gyrus was associated with reduced posttreatment Y-BOCS scores ([Sanematsu et al. 2010](#)).

Another study investigated treatment compliance with fluvoxamine and cognitive therapy. Forty-eight subjects with OCD who had failed to respond to behavioral therapy were

randomly assigned to 12 weeks of either fluvoxamine ( $n=26$ ) or cognitive therapy ( $n=22$ ). Although a higher baseline Y-BOCS score and assignment to cognitive therapy were associated with better compliance, fluvoxamine demonstrated statistically superior improvement compared with cognitive therapy ([Landsheer et al. 2015](#)).

## **Obsessive-Compulsive Disorder in Children and Adolescents**

Fluvoxamine 50–200 mg/day was tested in a 10-week double-blind, placebo-controlled study involving 120 subjects ages 8–17 years with OCD. Response was defined as a reduction of at least 25% in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score. Mean scores were significantly lower in the fluvoxamine group as early as week 1 ( $P < 0.05$ ). End-of-study response rates were 42% for the fluvoxamine group versus 26% for the placebo group ( $P=0.065$ ). The most common side effects were insomnia and asthenia ([Riddle et al. 2001](#)).

## **Other Obsessive-Compulsive and Related Disorders**

Three open-label trials of fluvoxamine involving a total of 75 subjects with body dysmorphic disorder reported response rates of 63%–67% ([Perugi et al. 1996](#); [Phillips et al. 1998, 2001](#)).

A 12-week open-label study of fluvoxamine in 21 subjects with trichotillomania produced only minor improvement ([Stanley et al. 1997](#)).

## **Other Addictive or Impulse-Control Disorders**

Like other SSRIs, fluvoxamine has produced inconsistent results when tested in impulse-control disorders or behavioral addictions that are sometimes considered part of the obsessive-compulsive spectrum. Despite encouraging open-label data in compulsive buying disorder ([Black et al. 1997](#)), two double-blind, placebo-controlled studies failed to show benefit over placebo ([Black et al. 2000](#); [Ninan et al. 2000](#)).

Similarly, two small studies in DSM-IV (American Psychiatric Association 1994) pathological gambling suggested that fluvoxamine might be beneficial ([Hollander et al. 1998, 2000](#)). However, a larger 6-month double-blind, placebo-controlled study failed to show separation from placebo ([Blanco et al. 2002](#)).

## Posttraumatic Stress Disorder

Small open-label studies suggest a role for fluvoxamine in treating posttraumatic stress disorder (PTSD) ([Davidson et al. 1998](#); [Figgitt and McClellan 2000](#); [Marmar et al. 1996](#); [Tucker et al. 2000](#)). Twenty-four Dutch veterans of World War II with chronic PTSD showed significant improvement on a PTSD self-rating scale after a 12-week course of fluvoxamine at  $\leq 300$  mg/day ( $P=0.04$ ) ([De Boer et al. 1992](#)). More recently, a 14-week open-label trial of fluvoxamine (100–300 mg/day) in 15 U.S. veterans with combat-related PTSD reported a statistically significant decrease in the Clinician-Administered PTSD Scale (CAPS) total score ( $P<0.001$ ) ([Escalona et al. 2002](#)).

## Eating Disorders

In another study, 72 subjects with bulimia nervosa who had been treated successfully with psychotherapy were randomly assigned to receive fluvoxamine (100–300 mg/day) or placebo and were followed for 12 weeks. Fluvoxamine was significantly superior in preventing relapse ( $P < 0.05$ ) ([Fichter et al. 1996](#)). A small 12-week double-blind, placebo-controlled study in 12 subjects with acute bulimia nervosa suggested that fluvoxamine 200 mg/day was superior to placebo ([Milano et al. 2005](#)).

A 9-week double-blind, placebo-controlled study in 85 subjects with binge-eating disorder found that fluvoxamine (50–300 mg/day) was significantly more effective than placebo in reducing binge frequency ([Hudson et al. 1998](#)).

## Delirium

Delirium, especially in hospitalized older patients, is associated with increased morbidity and mortality, prolonged hospital stays, and cognitive deterioration. Antipsychotic drugs have been widely used for treating delirium but are associated with sedation, extrapyramidal side effects, and cardiac arrhythmias. Furthermore, there is an elevated risk of mortality in older patients treated with atypical antipsychotics. The endoplasmic reticulum protein sigma-1 receptors are thought to play a key role in calcium signaling and cell survival and may regulate a number of neurotransmitter systems implicated in the pathophysiology of delirium. Several recent case reports have suggested that fluvoxamine, because of its potent sigma-1 receptor agonism, may be effective in the treatment of delirium ([Furuse and Hashimoto 2010a, 2010b, 2010c](#)).

# Pain

Preliminary research has explored the potential anti-pain properties of fluvoxamine. An animal study investigated fluvoxamine in the treatment of neuropathic pain in diabetic rats. Experimental animals were given intraperitoneal streptozotocin to induce neuropathic pain, followed by daily oral fluvoxamine. Using the hind paw withdrawal threshold to assess hyperalgesia, researchers concluded that fluvoxamine was associated with decreased pain ([Kato et al. 2013](#)).

More recently, a randomized controlled trial in 120 subjects with cancer accompanied by moderate to severe pain assigned participants to receive flexibly dosed extended-release oxycodone either alone ( $n=60$ ) or in combination with fluvoxamine dosages of 150 mg/day or greater ( $n=60$ ). Individuals in the oxycodone-only group required maximum dosages of extended-release oxycodone of 54 mg/day and 132 mg/day for moderate and severe pain, respectively, compared with 44.7 mg/day and 110 mg/day in the combination group. Subjects who received fluvoxamine augmentation required lower doses of oxycodone, but the difference was statistically significant only for severe pain. Additionally, treatment with fluvoxamine was associated with improved overall quality of life ([Xiao et al. 2014](#)).

---

## Side Effects and Toxicology

---

Data from 34,587 patients enrolled in postmarketing fluvoxamine studies were combined in a database to assess

safety. Dosages ranged from 50 to 300 mg/day taken over 4–52 weeks ([Wagner et al. 1994](#)). Overall, 14% of participants discontinued treatment because of side effects, most frequently nausea and vomiting (4.6% and 1.7%, respectively). The adverse events reported at greater than 5% incidence were nausea, somnolence, and asthenia (15.7%, 6.4%, and 5.1%, respectively). The rate of weight gain was only 1%. Sexual side effects were not mentioned in the analysis (only side effects with >1% incidence were listed), although a separate open-label study designed to assess SSRI-induced sexual dysfunction in men and women showed statistically similar rates for fluvoxamine, fluoxetine, sertraline, and paroxetine (range: 54.4%–64.7%) ([Montejo-González et al. 1997](#)).

Another postmarketing surveillance review covering 17 years ([Buchberger and Wagner 2002](#)) analyzed 6,658 individual reports, including 16,110 adverse drug reactions. The frequency of death was calculated at 0.9 per 100,000 patients. Suicide, mostly by overdose, was the cause of death in nearly half, but only 1.2% of overdoses involved fluvoxamine alone. The rate of suicidality (ideation, attempts, and completed suicides) was estimated at 2.81 events per 100,000 patients. Drug interactions were reported at a rate of 0.85 cases per 100,000 patients, most commonly with clozapine. Cases of switch to mania and discontinuation syndrome were also rare, occurring at rates of 0.47 and 0.38 events per 100,000 patients, respectively. Serotonin syndrome was even less frequent.

A more recent study assessed the cardiac effects of fluvoxamine in beagle dogs ( $n=4$ ). Dogs were administered 0.1 mg/kg of fluvoxamine intravenously, corresponding to the recommended daily oral dose, followed by a second and third dose of 1 mg/kg and 10 mg/kg, respectively. Both



supratherapeutic doses were associated with QT interval prolongation ([Yamazaki-Hashimoto et al. 2015](#)).

Two studies found no consistent treatment-related changes in laboratory values or vital signs in fluvoxamine-exposed subjects ([Wagner et al. 1994](#)).

---

## Drug-Drug Interactions

---

Fluvoxamine is a potent inhibitor of cytochrome P450 (CYP) 1A2. Drugs partially metabolized by CYP1A2 whose levels may rise as a result of fluvoxamine's inhibition of this isozyme include tizanidine, tertiary-amine tricyclic antidepressants (imipramine, amitriptyline, clomipramine), clozapine, tacrine, theophylline, propranolol, and caffeine. Doses of theophylline and clozapine should be reduced if co-administered with fluvoxamine ([DeVane and Gill 1997](#)).

Fluvoxamine also inhibits CYP2C19 and CYP3A4. CYP2C19 metabolizes warfarin, and elevations in warfarin concentration have been reported in patients taking fluvoxamine. As a result, closer monitoring of anticoagulation status is indicated in these patients. Alprazolam and diazepam are metabolized in part through CYP3A4, and fluvoxamine has been shown to prolong their elimination ([DeVane and Gill 1997](#)). Carbamazepine is partially metabolized through CYP3A4, and elevated carbamazepine levels have been documented in patients concomitantly taking fluvoxamine ([Palmer and Benfield 1994](#)). Other drugs whose metabolism through CYP3A4 may be affected by fluvoxamine include pimozide, methadone, and thioridazine. Also, because of the serious QT interval prolongation that can occur when terfenadine

or astemizole is combined with the potent CYP3A4 inhibitor ketoconazole, it is recommended that fluvoxamine be avoided in patients who require these antihistamines ([DeVane and Gill 1997](#)). Fluvoxamine is contraindicated for use with thioridazine, tizanidine, pimozide, alosetron, ramelteon, and monoamine oxidase inhibitors (MAOIs) ([Jazz Pharmaceuticals 2011](#)).

---

## Use in Pregnancy and Lactation

---

Limited data are available to guide clinicians and patients on the use of fluvoxamine in pregnancy. One study tried to assess teratogenic or perinatal effects relating to fluvoxamine exposure in utero in 92 pregnant women, 37 of whom were taking concomitant medications. No significant difference in adverse events was seen in the treatment group compared with the control group ([Gentile 2005](#)). The FDA lists fluvoxamine in Category C.

Very limited information is available on infants exposed to fluvoxamine during lactation ([Gentile 2005](#)). In the eight cases published, no adverse events were reported.

---

## Conclusion

---

More than three decades of research and clinical experience with fluvoxamine have established it as a generally well-tolerated SSRI with potential efficacy across a broad range of disorders. While millions of patients have taken fluvoxamine and benefited from it worldwide, two factors may have prevented even more widespread use:

drug-drug interactions, which make fluvoxamine a less attractive choice in patients on complex drug regimens; and a perception, especially in the United States, that it is primarily an anti-OCD drug.

---

## References

---

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Benfield P, Ward A: Fluvoxamine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs* 32(4):313-334, 1986 3096686
- Black DW, Monahan P, Gabel J: Fluvoxamine in the treatment of compulsive buying. *J Clin Psychiatry* 58(4):159-163, 1997 9164426
- Black DW, Gabel J, Hansen J, et al: A double-blind comparison of fluvoxamine versus placebo in the treatment of compulsive buying disorder. *Ann Clin Psychiatry* 12(4):205-211, 2000 11140921
- Blanco C, Petkova E, Ibáñez A, et al: A pilot placebo-controlled study of fluvoxamine for pathological gambling. *Ann Clin Psychiatry* 14(1):9-15, 2002 12046642
- Buchberger R, Wagner W: Fluvoxamine: safety profile in extensive post-marketing surveillance. *Pharmacopsychiatry* 35(3):101-108, 2002 12107854
- Davidson JR, Weisler RH, Malik M, et al: Fluvoxamine in civilians with posttraumatic stress disorder. *J Clin Psychopharmacol* 18(1):93-95, 1998 9472854
- Davidson J, Yaryura-Tobias J, DuPont R, et al: Fluvoxamine-controlled release formulation for the treatment of

- generalized social anxiety disorder. *J Clin Psychopharmacol* 24(2):118-125, 2004 15206657
- De Boer M, Op den Velde W, Falger PJ, et al: Fluvoxamine treatment for chronic PTSD: a pilot study. *Psychother Psychosom* 57(4):158-163, 1992 1410191
- DeVane CL: Pharmacokinetics, drug interactions, and tolerability of paroxetine and paroxetine CR. *Psychopharmacol Bull* 37 (suppl 1):29-41, 2003 14566199
- DeVane CL, Gill HS: Clinical pharmacokinetics of fluvoxamine: applications to dosage regimen design. *J Clin Psychiatry* 58 (suppl 5):7-14, 1997 9184622
- Dranovsky A, Hen R: Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol Psychiatry* 59(12):1136-1143, 2006 16797263
- Escalona R, Canive JM, Calais LA, et al: Fluvoxamine treatment in veterans with combat-related post-traumatic stress disorder. *Depress Anxiety* 15(1):29-33, 2002 11816050
- Ferreira GK, Cardoso MR, Jeremias IC, et al: Fluvoxamine alters the activity of energy metabolism enzymes in the brain. *Rev Bras Psiquiatr* 36(3):220-226, 2014 24676049
- Fichter MM, Krüger R, Rief W, et al: Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. *J Clin Psychopharmacol* 16(1):9-18, 1996 8834413
- Figgitt DP, McClellan KJ: Fluvoxamine. An updated review of its use in the management of adults with anxiety disorders. *Drugs* 60(4):925-954, 2000 11085201
- Freeman CP, Trimble MR, Deakin JF, et al: Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. *J Clin Psychiatry* 55(7):301-305, 1994 8071291

- Fukuchi T, Kanemoto K: Differential effects of milnacipran and fluvoxamine, especially in patients with severe depression and agitated depression: a case-control study. *Int Clin Psychopharmacol* 17(2):53–58, 2002 11890186
- Fukui N, Suzuki Y, Sugai T, et al: Promoter variation in the catechol-O-methyltransferase gene is associated with remission of symptoms during fluvoxamine treatment for major depression. *Psychiatry Res* 218(3):353–355, 2014 24814141
- Furuse T, Hashimoto K: Fluvoxamine monotherapy for psychotic depression: the potential role of sigma-1 receptors. *Ann Gen Psychiatry* 8:26, 2009 20025739
- Furuse T, Hashimoto K: Sigma-1 receptor agonist fluvoxamine for delirium in intensive care units: report of five cases. *Ann Gen Psychiatry* 9:18, 2010a 20416097
- Furuse T, Hashimoto K: Sigma-1 receptor agonist fluvoxamine for delirium in patients with Alzheimer's disease. *Ann Gen Psychiatry* 9:6, 2010b 20148109
- Furuse T, Hashimoto K: Sigma-1 receptor agonist fluvoxamine for postoperative delirium in older adults: report of three cases. *Ann Gen Psychiatry* 9:28, 2010c 20573265
- Gentile S: The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Saf* 28(2):137–152, 2005 15691224
- Gershon AA, Vishne T, Grunhaus L: Dopamine D2-like receptors and the antidepressant response. *Biol Psychiatry* 61(2): 145–153, 2007 16934770
- Haffmans PM, Timmerman L, Hoogduin CA; The LUCIFER Group: Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: a double-blind, multicentre study. *Int Clin Psychopharmacol* 11(3):157–164, 1996 8923094
- Hollander E, DeCaria CM, Mari E, et al: Short-term single-blind fluvoxamine treatment of pathological gambling.

- Am J Psychiatry 155(12):1781-1783, 1998 9842795
- Hollander E, DeCaria CM, Finkell JN, et al: A randomized double-blind fluvoxamine/placebo crossover trial in pathologic gambling. Biol Psychiatry 47(9):813-817, 2000 10812040
- Hudson JI, McElroy SL, Raymond NC, et al: Fluvoxamine in the treatment of binge-eating disorder: a multicenter placebo-controlled, double-blind trial. Am J Psychiatry 155(12):1756-1762, 1998 9842788
- Ishikawa M, Ishiwata K, Ishii K, et al: High occupancy of sigma-1 receptors in the human brain after single oral administration of fluvoxamine: a positron emission tomography study using [11C]SA4503. Biol Psychiatry 62(8):878-883, 2007 17662961
- Jazz Pharmaceuticals: Luvox CR (fluvoxamine maleate) extended-release capsules for oral administration (package insert). Palo Alto, CA, Jazz Pharmaceuticals Inc., May 2011. Available at: <http://www.luvoxcr.com/LUVOX-CR-PI.pdf>. Accessed June 29, 2015.
- Kato T, Kajiyama S, Hamada H, et al: Long-term administration of fluvoxamine attenuates neuropathic pain and involvement of spinal serotonin receptors in diabetic model rats. Hiroshima J Med Sci 62(4):83-89, 2013 24597211
- Kiev A, Feiger A: A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. J Clin Psychiatry 58(4):146-152, 1997 9164424
- Koran LM, McElroy SL, Davidson JR, et al: Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol 16(2):121-129, 1996 8690827
- Landsheer JA, Smit JH, van Oppen P, et al: Assignment refusal and its relation to outcome in a randomized controlled trial comparing cognitive therapy and

- fluvoxamine in treatment-resistant patients with obsessive compulsive disorder. *Psychiatry Res* 226(1):198–203, 2015 25618476
- Lapierre YD, Rastogi RB, Singhal RL: Fluvoxamine influences serotonergic system in the brain: neurochemical evidence. *Neuropsychobiology* 10(4):213–216, 1983 6427651
- Mancama D, Kerwin RW: Role of pharmacogenomics in individualising treatment with SSRIs. *CNS Drugs* 17(3):143–151, 2003 12617694
- Marmar CR, Schoenfeld F, Weiss DS, et al: Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder. *J Clin Psychiatry* 57 (suppl 8):66–70, discussion 71–72, 1996 8698684
- Milanfranchi A, Ravagli S, Lensi P, et al: A double-blind study of fluvoxamine and clomipramine in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol* 12(3):131–136, 1997 9248868
- Milano W, Siano C, Putrella C, et al: Treatment of bulimia nervosa with fluvoxamine: a randomized controlled trial. *Adv Ther* 22(3):278–283, 2005 16236688
- Montejo-González AL, Llorca G, Izquierdo JA, et al: SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* 23(3):176–194, 1997 9292833
- Mundo E, Bianchi L, Bellodi L: Efficacy of fluvoxamine, paroxetine, and citalopram in the treatment of obsessive-compulsive disorder: a single-blind study. *J Clin Psychopharmacol* 17(4):267–271, 1997 9241005
- Mundo E, Maina G, Uslenghi C: Multicentre, double-blind, comparison of fluvoxamine and clomipramine in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol* 15(2):69–76, 2000 10759337
- Mundo E, Rouillon F, Figuera ML, et al: Fluvoxamine in obsessive-compulsive disorder: similar efficacy but

- superior tolerability in comparison with clomipramine. *Hum Psychopharmacol* 16(6):461–468, 2001 12404554
- Ninan PT, McElroy SL, Kane CP, et al: Placebo-controlled study of fluvoxamine in the treatment of patients with compulsive buying. *J Clin Psychopharmacol* 20(3):362–366, 2000 10831025
- Omori IM, Watanabe N, Nakagawa A, et al: Fluvoxamine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev* (3):CD006114, 2010 20238342
- Otsubo T, Akimoto Y, Yamada H, et al: A comparative study of the efficacy and safety profiles between fluvoxamine and nortriptyline in Japanese patients with major depression. *Pharmacopsychiatry* 38(1):30–35, 2005 15706464
- Owens MJ, Knight DL, Nemeroff CB: Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. *Biol Psychiatry* 50(5):345–350, 2001 11543737
- Palmer KJ, Benfield P: Fluvoxamine. *CNS Drugs* 1(1):57–87, 1994. Available at: <http://link.springer.com/article/10.2165/00023210-199401010-00006>. Accessed July 24, 2015.
- Perugi G, Giannotti D, Di Vaio S, et al: Fluvoxamine in the treatment of body dysmorphic disorder (dysmorphophobia). *Int Clin Psychopharmacol* 11(4):247–254, 1996 9031991
- Phillips KA, Dwight MM, McElroy SL: Efficacy and safety of fluvoxamine in body dysmorphic disorder. *J Clin Psychiatry* 59(4):165–171, 1998 9590666
- Phillips KA, McElroy SL, Dwight MM, et al: Delusionality and response to open-label fluvoxamine in body dysmorphic disorder. *J Clin Psychiatry* 62(2):87–91, 2001 11247107
- Physicians' Desk Reference, 69th Edition. Montvale, NJ, PDR Network, 2015



- Price LH, Goodman WK, Charney DS, et al: Treatment of severe obsessive-compulsive disorder with fluvoxamine. *Am J Psychiatry* 144(8):1059-1061, 1987 3111279
- Rapaport M, Coccaro E, Sheline Y, et al: A comparison of fluvoxamine and fluoxetine in the treatment of major depression. *J Clin Psychopharmacol* 16(5):373-378, 1996 8889909
- Ravizza L, Barzega G, Bellino S, et al: Drug treatment of obsessive-compulsive disorder (OCD): long-term trial with clomipramine and selective serotonin reuptake inhibitors (SSRIs). *Psychopharmacol Bull* 32(1):167-173, 1996 8927668
- Riddle MA, Reeve EA, Yaryura-Tobias JA, et al: Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry* 40(2):222-229, 2001 11211371
- Rossini D, Serretti A, Franchini L, et al: Sertraline versus fluvoxamine in the treatment of elderly patients with major depression: a double-blind, randomized trial. *J Clin Psychopharmacol* 25(5):471-475, 2005 16160624
- Sanematsu H, Nakao T, Yoshiura T, et al: Predictors of treatment response to fluvoxamine in obsessive-compulsive disorder: an fMRI study. *J Psychiatr Res* 44(4):193-200, 2010 19758599
- Stahl SM: Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord* 51(3):215-235, 1998 10333979
- Stanley MA, Breckenridge JK, Swann AC, et al: Fluvoxamine treatment of trichotillomania. *J Clin Psychopharmacol* 17(4):278-283, 1997 9241007
- Stein MB, Fyer AJ, Davidson JR, et al: Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. *Am J Psychiatry* 156(5):756-760, 1999 10327910

- Strauss WL, Layton ME, Dager SR: Brain elimination half-life of fluvoxamine measured by <sup>19</sup>F magnetic resonance spectroscopy. *Am J Psychiatry* 155(3):380–384, 1998 9501749
- Terra JL, Montgomery SA: Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. *Int Clin Psychopharmacol* 13(2):55–62, 1998 9669185
- Tucker P, Smith KL, Marx B, et al: Fluvoxamine reduces physiologic reactivity to trauma scripts in posttraumatic stress disorder. *J Clin Psychopharmacol* 20(3):367–372, 2000 10831026
- van Harten J: Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 29 (suppl 1):1–9, 1995 8846617
- van Harten J, Duchier J, Devissaguet JP, et al: Pharmacokinetics of fluvoxamine maleate in patients with liver cirrhosis after single-dose oral administration. *Clin Pharmacokinet* 24(2):177–182, 1993 8453824
- Wagner W, Zaborny BA, Gray TE: Fluvoxamine. A review of its safety profile in world-wide studies. *Int Clin Psychopharmacol* 9(4):223–227, 1994 7868844
- Ware MR: Fluvoxamine: a review of the controlled trials in depression. *J Clin Psychiatry* 58 (suppl 5):15–23, 1997 9184623
- Westenberg HG, Stein DJ, Yang H, et al: A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol* 24(1): 49–55, 2004 14709947
- Xiao Y, Liu J, Huang XE, et al: Clinical study on fluvoxamine combined with oxycodone prolonged-release tablets in treating patients with moderate to severe cancer pain. *Asian Pac J Cancer Prev* 15(23):10445–10449, 2014 25556490

- Yamazaki-Hashimoto Y, Nakamura Y, Ohara H, et al: Fluvoxamine by itself has potential to directly induce long QT syndrome at supra-therapeutic concentrations. J Toxicol Sci 40(1):33-42, 2015 25560394
- Zanardi R, Franchini L, Serretti A, et al: Venlafaxine versus fluvoxamine in the treatment of delusional depression: a pilot double-blind controlled study. J Clin Psychiatry 61(1):26-29, 2000 10695642
- Zohar J, Keegstra H, Barrelet L: Fluvoxamine as effective as clomipramine against symptoms of severe depression: results from a multicentre, double-blind study. Hum Psychopharmacol 18(2):113-119, 2003 12590404

## CHAPTER 14

# Citalopram and Escitalopram

Patrick H. Roseboom, Ph.D.

Ned H. Kalin, M.D.

Citalopram (Celexa) and its pharmacologically active enantiomer, escitalopram (Lexapro), are among the most selective serotonin reuptake inhibitors available. Both drugs are widely prescribed and have been shown in large-scale controlled trials to be effective in the treatment of depression; escitalopram has also been shown to be effective in the treatment of anxiety disorders. Generic formulations of both drugs are now available. Both drugs are well tolerated in patients and show a low potential for pharmacokinetic drug-drug interactions. Citalopram and escitalopram have similar effectiveness in the treatment of depression, although some studies suggest a modest superiority of escitalopram over citalopram on some measures of efficacy, including a possibly faster onset of

therapeutic effect for escitalopram. Antagonism of the effects of escitalopram by *R*-citalopram has been invoked to explain the purported therapeutic differences between the two drugs. Also, the affinity of citalopram for histamine receptors appears to reside in the *R*-enantiomer, suggesting that escitalopram has a decreased potential for antihistaminergic side effects. Finally, in terms of cardiac safety, citalopram has a greater potential to prolong the electrocardiogram (ECG) QT interval and produce potentially serious arrhythmias.

---

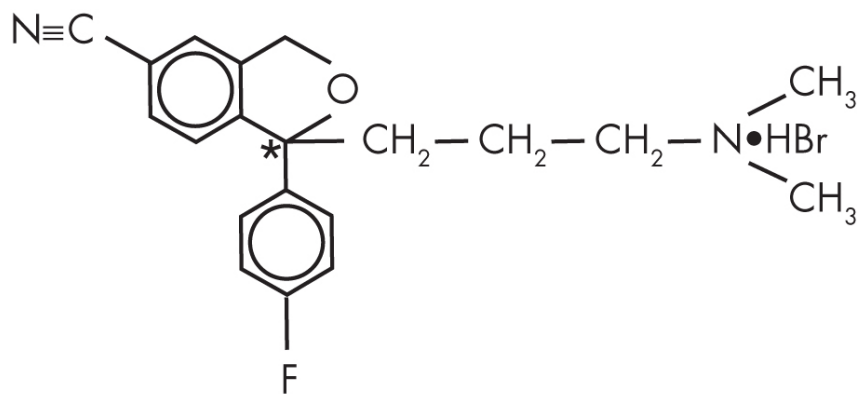
## History and Discovery

---

The pharmacology of citalopram was first described in 1977 ([Christensen et al. 1977](#); [Hyttel 1977](#)). Citalopram was shown to be a very potent inhibitor of serotonin (5-HT) reuptake in both in vitro and in vivo models ([Hyttel 1977, 1978](#)). It was subsequently discovered that all of the inhibitory activity of citalopram on 5-HT reuptake resides in the *S*-(+)-enantiomer (escitalopram) ([Hyttel et al. 1992](#)). Originally introduced in Denmark in 1989, citalopram was approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression in July 1998. Escitalopram received FDA approval for the treatment of major depressive disorder in August 2002 and for the treatment of generalized anxiety disorder (GAD) in December 2003. Escitalopram also received FDA approval in March 2009 for the treatment of major depressive disorder in adolescents ages 12–17 years.

# Structure-Activity Relations

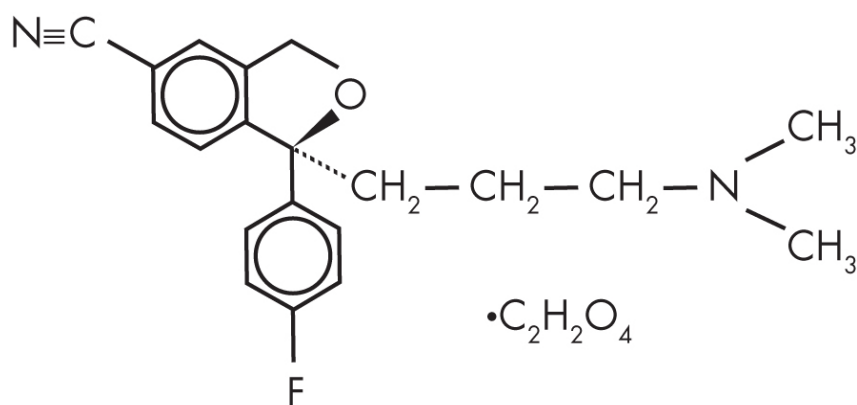
Citalopram has a single chiral center ([Figure 14-1](#)). A chiral center is an atom surrounded by an asymmetrical arrangement of atoms such that the three-dimensional configuration is not superimposable on its mirror image. At this chiral center, there are two possible stereoisomers. Often, drugs are produced as a mixture of both stereoisomers, referred to as the *racemate*. However, because desired pharmacological activity or unwanted toxicity may reside in only one of the stereoisomers, a stereoisomer-selective formulation may be superior ([Agranat et al. 2002](#)). Citalopram was originally characterized and marketed as the racemate, but subsequently the single stereoisomer of citalopram, escitalopram ([Figure 14-2](#)), was developed for the treatment of depression and other psychiatric disorders. Preclinical studies indicate that inhibition of 5-HT transporter activity resides in the *S*-enantiomer ([Hyttel et al. 1992](#)), with escitalopram being 30 times more potent than *R*-citalopram at inhibiting 5-HT transport ([Owens et al. 2001](#)).



---

**FIGURE 14-1.** Chemical structure of citalopram hydrobromide.

\*Indicates chiral center.



---

**FIGURE 14-2.** Chemical structure of escitalopram oxalate.

A possible explanation for the postulated modest superiority of escitalopram over citalopram in some measures of antidepressant efficacy is provided by the evidence that the *R*-enantiomer of citalopram may interfere with the activity of the *S*-enantiomer, as evidenced in several behavioral and physiological assays (for a review, see [Sánchez 2006](#)). This antagonism has been hypothesized to result from a kinetic interaction at the level of the 5-HT transporter ([Stórustovu et al. 2004](#)).

---

## Pharmacological Profile

---

### Citalopram

Of the selective serotonin reuptake inhibitors (SSRIs) approved to date, citalopram is one of the most selective, with a 524-fold lower potency for inhibiting the human norepinephrine (NE) transporter and a >10,000-fold lower potency for inhibiting the human dopamine transporter (Owens et al. 2001). In addition, citalopram has low affinity for a wide variety of neurotransmitter receptors (for a review, see Hyttel et al. 1995). Citalopram has been reported to have submicromolar affinity for the histamine type 1 (H<sub>1</sub>) receptor (Hyttel 1994; Richelson and Nelson 1984), but this appears to be true only for the *R*-enantiomer (Owens et al. 2001). Citalopram does not show significant inhibition of monoamine oxidase (MAO) (Hyttel 1977). Behavioral studies in rats and mice have shown citalopram to be a potent and selective inhibitor of 5-HT reuptake (Christensen et al. 1977; Hyttel 1994). In contrast, citalopram is ineffective in models that reflect in vivo inhibition of dopamine and NE reuptake (Hyttel 1994). Citalopram is active in various behavioral models related to antidepressant activity (Martin et al. 1990; Sánchez and Meier 1997) and anxiolytic activity (Inoue 1993; Sánchez 1995).

## Escitalopram

Escitalopram is also a highly potent inhibitor of 5-HT reuptake, with a K<sub>i</sub> for binding to the human 5-HT transporter of 1.1 nM compared with a K<sub>i</sub> of 1.9 nM for citalopram and 36 nM for *R*-citalopram (Owens et al. 2001). Escitalopram is the most selective SSRI approved for clinical use, with a 2,600-fold lower potency for inhibiting the human NE transporter and a >45,000-fold lower



potency for inhibiting the human dopamine transporter. Escitalopram has no appreciable binding affinity for a large number of other neurotransmitter receptors ([Owens et al. 2001](#); [Sánchez et al. 2003](#)). Escitalopram shows potent activity in various in vivo paradigms, including a model of 5-HT reuptake inhibition and behavioral models of antidepressant, antiaggressive, and anxiolytic activity (for a review, see [Sánchez et al. 2003](#)). In these in vivo paradigms, escitalopram's potency ranges from being similar to that of citalopram to being approximately twofold greater than that of citalopram. In contrast, in the majority of these paradigms, *R*-citalopram is severalfold less potent than either escitalopram or citalopram.

---

## Pharmacokinetics and Disposition

---

### Citalopram

Citalopram is well absorbed after oral administration, with an absolute bioavailability of 80% for citalopram tablets ([Joffe et al. 1998](#)). The peak plasma concentration is normally observed 2–4 hours following an oral dose ([Kragh-Sørensen et al. 1981](#)). The bioavailability of citalopram is not affected by food ([Baumann 1992](#)), and it is subject to very little first-pass metabolism ([Kragh-Sørensen et al. 1981](#)). The apparent volume of distribution is 12–16 L/kg ([Fredricson Overø 1982](#); [Kragh-Sørensen et al. 1981](#)), which indicates that the drug distributes widely. There is a linear relationship between steady-state plasma

concentration and dose ([Bjerkenstedt et al. 1985](#)), and plasma protein binding is approximately 80% ([Baumann 1992](#)). Systemic clearance of citalopram is 0.3–0.4 L/minute ([Baumann 1992](#)), and renal clearance of citalopram is approximately 0.05–0.08 L/minute ([Sindrup et al. 1993](#)).

Racemic citalopram undergoes *N*-demethylation by the hepatic cytochrome P450 (CYP) system to the major metabolite monodesmethylecitalopram (DCT). CYP enzymes 2C19, 3A4, and 2D6 all contribute approximately equally to the formation of DCT ([Kobayashi et al. 1997](#); [Rochat et al. 1997](#); [von Moltke et al. 1999](#)). DCT also undergoes *N*-demethylation to the minor metabolite didesmylecitalopram (DDCT) by the actions of CYP2D6 ([Sindrup et al. 1993](#); [von Moltke et al. 2001](#)). Clinical studies indicate that the half-lives for citalopram, DCT, and DDCT are approximately 36 hours, 50 hours, and 100 hours, respectively ([Dalgaard and Larsen 1999](#); [Fredricson Overø 1982](#); [Kragh-Sørensen et al. 1981](#)). Citalopram is metabolized by human cytochromes that display genetic polymorphisms, and metabolism of citalopram and DCT is impaired in subjects who show poor metabolism via the CYP2C19 and CYP2D6 pathways ([Baumann et al. 1996](#); [Sindrup et al. 1993](#); [Yu et al. 2003](#)).

## Escitalopram

The clinical pharmacokinetics of escitalopram, reviewed by [Rao \(2007\)](#), are similar to those described for citalopram. The pharmacokinetic characteristics of escitalopram are essentially the same regardless of whether patients are given a single oral dose of 20 mg of escitalopram or 40 mg of racemic citalopram (which contains 20 mg of

escitalopram); this indicates that there is no pharmacokinetic interaction or interconversion between *R*-citalopram and escitalopram ([Rao 2007](#)).

---

## Mechanism of Action

---

The majority of studies on mechanism of action have focused on citalopram, with a relatively limited number of studies using escitalopram. Because the antidepressant activity of citalopram results from escitalopram, the majority of the conclusions from these studies pertain to both citalopram and escitalopram.

Citalopram is a potent and selective inhibitor of 5-HT reuptake and acts by binding directly to the 5-HT transporter. Citalopram selectively inhibits radioligand binding to the 5-HT transporter ( $K_i=0.75$  nM) versus the NE transporter ( $K_i=3,042$  nM) in rat cortical membranes. A similar selectivity was found for inhibiting the binding of the same radioligands to the cloned human 5-HT and NE transporters expressed in transfected cells and for inhibiting [ $^3$ H]5-HT ( $K_i=8.9$  nM) and [ $^3$ H]NE ( $K_i=30,285$  nM) reuptake into these transfected cells ([Owens et al. 1997](#)).

Several studies have described how repeated dosing alters the effects of citalopram on serotonergic neuronal function. As with other SSRIs, the ability of citalopram to inhibit the firing of 5-HT neurons in the dorsal raphe nucleus is greatly reduced after 14 days of repeated administration ([Chaput et al. 1986](#)). This change is associated with an increase in the ability of citalopram to elevate the extracellular levels of 5-HT in the cortex

([Invernizzi et al. 1994](#)). These two effects appear to result from a desensitization of 5-HT<sub>1A</sub> autoreceptors ([Chaput et al. 1986](#); [Cremers et al. 2000](#); [Invernizzi et al. 1994](#)). This adaptive change of 5-HT<sub>1A</sub> receptors following repeated administration of citalopram, or other SSRIs, has been postulated to underlie the slow onset of antidepressant efficacy that is observed clinically ([Blier and de Montigny 1994](#)).

Evidence suggests that a variety of antidepressants, including those that block monoamine reuptake or metabolism, produce their therapeutic response in part by overcoming depression-associated decreases in neurogenesis and synaptogenesis, possibly through effects on brain-derived neurotrophic factor (BDNF) expression. Citalopram, like several other antidepressants, has been shown to increase the levels of BDNF messenger RNA (mRNA) in various subregions of the rat ventral hippocampus ([Russo-Neustadt et al. 2004](#)) and to induce signaling through the BDNF receptor tyrosine kinase receptor B (TrkB) ([Rantamäki et al. 2007](#)). Interestingly, this effect of antidepressants on TrkB appears to be independent of BDNF release and 5-HT transporter blockade and does not involve a direct binding of the antidepressant to TrkB ([Rantamäki et al. 2011](#)). Escitalopram treatment has been demonstrated to affect circulating BDNF levels. A study in depressed subjects ( $n=18$ ) showed elevated plasma levels of BDNF and decreased platelet levels of BDNF compared with healthy control subjects ( $n=14$ ), and these differences were normalized with 24 weeks of escitalopram (10–40 mg/day) treatment ([Serra-Millàs et al. 2011](#)). Additionally, there are preliminary clinical data suggesting that a polymorphism

within the coding region for BDNF (Val66Met) is associated with therapeutic response to citalopram ([Choi et al. 2006](#)).

A number of studies have implicated the 5-HT<sub>2A</sub> receptor in a variety of neuropsychiatric disorders ([Norton and Owen 2005](#)), and there is evidence implicating the 5-HT<sub>2A</sub> receptor in the mechanism of action of antidepressants, including citalopram ([Chen and Lawrence 2003](#); [Peremans et al. 2005](#)). Also, a large-scale clinical study involving 1,953 patients who participated in the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial identified a significant association between a polymorphism contained in the second intron of the gene for the 5-HT<sub>2A</sub> receptor (rs7997012) and treatment response to citalopram ([McMahon et al. 2006](#)). While perhaps relevant to clinical work, the functional significance of this intronic polymorphism on the 5-HT<sub>2A</sub> receptor has yet to be determined.

Several cellular and in vivo animal model studies have shown that antidepressants can increase glucocorticoid receptor (GR) translocation, induce GR downregulation, and decrease GR agonist-mediated effects ([Anacker et al. 2011](#); [Carvalho and Pariante 2008](#)), and there is evidence suggesting that similar effects occur in vivo in humans. In a double-blind, placebo-controlled, crossover study in healthy men, treatment for 4 days with citalopram 20 mg/day was associated with a diminished ability of cortisol to increase electroencephalogram alpha power and to impair working memory ([Pariante et al. 2012](#)). These results suggest that GR activation by antidepressants does occur in the human brain.

Corticotropin-releasing factor (CRF) mediates many of the effects of psychological stress and is postulated to play a

role in the pathophysiology of depression and anxiety disorders ([Arborelius et al. 1999](#)). In rats, lentiviral-mediated chronic elevation of amygdala CRF reproduces many of the behavioral and endocrine consequences of chronic stress that are consistent with a depressive or anxious phenotype ([Flandreau et al. 2012](#)). Interestingly, chronic escitalopram treatment of these CRF-overexpressing rats for 4 weeks reversed some but not all of the CRF-induced anxiety-like and depressive-like behavioral alterations ([Flandreau et al. 2013](#)).

---

## Indications and Efficacy

---

### Depression

#### Citalopram

The efficacy of citalopram (dosage range 20–80 mg/day) in the treatment of depression has been shown in at least 11 placebo-controlled clinical trials (for a review, see [Keller 2000](#)). In addition, meta-analyses of multiple placebo-controlled studies reported similar findings ([Bech and Cialdella 1992](#); [Montgomery et al. 1994](#)). In the United States, three large multicenter clinical trials have demonstrated citalopram's efficacy in the treatment of major depression ([Feighner and Overø 1999](#); [Mendels et al. 1999](#); [Stahl 2000](#)). More recently, primary care patients in the United Kingdom were given citalopram 20 mg/day ( $n=274$ ) or the NE reuptake inhibitor reboxetine 4 mg twice daily ( $n=272$ ), which were found to be equally effective in the treatment of severe depression (defined as

scores  $\geq 15$  on the Beck Depression Inventory) ([Wiles et al. 2012](#)).

**STAR\*D trial.** The effectiveness of citalopram has also been demonstrated in a study designed to simulate real-world conditions for the treatment of depression. The STAR\*D trial was a large-scale multicenter study that enrolled 4,041 patients with nonpsychotic major depression in a test of various antidepressant therapies ([Rush et al. 2004](#)). The mean daily dose of citalopram at study exit was 41.8 mg, the remission rates were 28% (when remission was defined as a score of  $\leq 7$  on the 17-item version of the Hamilton Rating Scale for Depression [Ham-D]) and 33% (when defined as a score of  $\leq 5$  on the 16-item Quick Inventory of Depressive Symptomatology, Self-Report [QIDS-SR]), and the response rate was 47% (when response was defined as a  $\geq 50\%$  reduction in QIDS-SR score) ([Trivedi et al. 2006](#)). These response and remission rates are comparable to those found in 8-week controlled clinical trials examining the efficacy of acute antidepressant treatment.

**Long-term treatment with citalopram.** Two placebo-controlled studies indicate that citalopram may be effective in continuation therapy to prevent depression relapse. Both studies showed that for patients with an acute therapeutic response to citalopram, continuation of citalopram therapy at the same dosage (20, 40, or 60 mg/day) for an additional 24 weeks significantly decreased the relapse rate compared with placebo ([Montgomery et al. 1993](#); [Robert and Montgomery 1995](#)). Two additional studies suggest that citalopram may be beneficial in patients with a history of recurrent depression. Long-term

(at least 48 weeks) administration of citalopram at the same fixed dosage at which patients initially showed therapeutic response (20–60 mg/day) can significantly increase the time before depression recurs in adult patients (ages 18–64 years) and in elderly patients (ages 65 years and older) ([Hochstrasser et al. 2001](#); [Klysner et al. 2002](#)).

## **Escitalopram**

A number of placebo-controlled clinical trials and retrospective analyses have demonstrated the efficacy of escitalopram (dosage range 10–20 mg/day) in the treatment of major depression ([Burke et al. 2002](#); [Lepola et al. 2003](#); [Montgomery et al. 2001b](#); [Wade et al. 2002](#)). Also, a large number of retrospective pooled analyses have compared escitalopram with other SSRIs ([Einarson 2004](#); [Kennedy et al. 2006](#); [Llorca et al. 2005](#)). In general, escitalopram was at least as effective as other widely used antidepressants, and in some clinical trials it has been suggested to be superior to other antidepressants based on modestly greater score changes on various depression rating scales, especially in patients with severe depression. In addition, escitalopram has been suggested in a few clinical trials to possibly have a faster onset of therapeutic effect (based on changes in depression rating scale scores), occurring as early as week 1. It remains to be demonstrated whether the modest differences between escitalopram and other antidepressants in controlled clinical trials translate into a therapeutically meaningful difference in the treatment of depression in psychiatric practice.

**Major depressive disorder with severe asthma.** Major depressive disorder is often seen in



asthmatic individuals, and depression may be a risk factor for asthma-related morbidity. In a placebo-controlled, randomized, double-blind proof-of-concept trial ([Brown et al. 2012](#)), escitalopram 10–20 mg/day was evaluated for the treatment of depression in patients ( $n=25$ ) with asthma. Improvement in depression symptoms was seen in both placebo and escitalopram groups from week 1 to study exit at week 12, with a trend favoring escitalopram for depression remission based on changes in the Ham-D score ([Brown et al. 2012](#)).

**Long-term treatment with escitalopram.** In a 36-week placebo-controlled clinical trial, subjects given escitalopram 10–20 mg/day ( $n=181$ ) were less likely to experience relapse following resolution of a depressive episode than were those given placebo ( $n=93$ ) ([Rapaport et al. 2004](#)). Additionally, the effectiveness of long-term escitalopram therapy in the prevention of recurrence of depression was also demonstrated in a group of patients who had been diagnosed with recurrent major depressive disorder ([Kornstein et al. 2006](#)). Patients given escitalopram 10 or 20 mg/day ( $n=73$ ) in this 52-week study had significantly prolonged time to recurrence compared with those given placebo ( $n=66$ ).

**iSPOT-D trial.** Treatment of depression will be significantly improved with the discovery of biomarkers that can identify which patients will respond best to which treatments. For example, depression is associated with impairments in a wide range of cognitive and emotional functioning ([Snyder 2013](#)). The focus of the International Study to Predict Optimized Treatment in Depression (iSPOT-D) trial was to determine whether laboratory

measures of impaired functioning can be used to predict antidepressant treatment outcomes. In one report, medication-free outpatients with nonpsychotic major depression ( $n=665$  completers) were assessed before treatment with 13 computerized tests of cognitive and emotional functioning, and their performance was compared with that of healthy controls ( $n=336$ ). Patients were then randomly assigned to receive 8 weeks of treatment with escitalopram, sertraline, or extended-release venlafaxine ([Etkin et al. 2015](#)). Approximately one-quarter of the patients had significant impairment across most cognitive tests relative to the healthy controls, and these patients had poorer treatment outcomes. For this subset of patients, better task performance predicted remission (based on scores on the 16-item QIDS-SR) with 72% accuracy for treatment with escitalopram but not for treatment with the other antidepressants. Among the patients predicted to be nonresponders, the greatest impairments were on tests of attention, decision speed, working memory, and speed of emotion identification.

Neuroimaging studies have also focused on identifying patterns of brain activation that may be predictive of antidepressant treatment outcomes. Previous functional magnetic resonance imaging (fMRI) studies demonstrated that activation of the right lateral and medial prefrontal cortices and limbic regions during inhibitory responses on the go/no-go task predicted a greater treatment response to escitalopram ([Langenecker et al. 2007](#)). A similar approach was described in a study from the iSPOT-D trial that involved 80 medication-free outpatients with major depression and 34 matched healthy controls ([Gyurak et al. 2016](#)). During the fMRI scans, subjects completed three tasks to assess core domains of cognitive function. Subjects

then received 8 weeks of antidepressant treatment, fMRI scans were repeated, and depression remission was assessed with the Ham-D. Intact activation of the frontoparietal network during inhibitory “no-go” responses predicted remission, particularly for subjects given the SSRIs escitalopram and sertraline. During the “no-go” responses, remitters showed the same pretreatment dorsolateral prefrontal cortex activation as control subjects, and nonremitters showed hypoactivation relative to control subjects. These study findings hold promise for identifying biomarkers that can help predict which patients are most likely to respond to citalopram and escitalopram treatment.

**GENDEP study.** A genome-based approach to identifying genes associated with therapeutic response to escitalopram has also yielded interesting findings. As part of the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, genomewide association analysis examined 539,391 single-nucleotide polymorphisms (SNPs) to identify genes that underlie individual differences in antidepressant treatment response. The partially randomized, single-blind study examined DNA from unrelated patients of European ancestry who were assigned to receive 12 weeks of treatment with either escitalopram 10–30 mg/day ( $n=394$ ) or nortriptyline 50–150 mg/day ( $n=312$ ). Although no marker was associated at a genomewide level of significance, escitalopram response was predicted at a suggestive level of significance ( $P=0.00049$ ) by a synonymous SNP (rs1126757) in the gene for interleukin 11 (*IL11*) ([Uher et al. 2010](#)). In addition, a targeted analysis of 72 a priori selected candidate genes identified an association between escitalopram response and a SNP (rs7801617) in the gene encoding interleukin 6 (*IL6*), a

close homolog of *IL11*. A follow-up epigenetic study examined variations in DNA methylation of *IL11* as a predictor of antidepressant treatment response using a subset of subjects who were randomly selected from the GENDEP study and received either escitalopram ( $n=80$ ) or nortriptyline ( $n=33$ ) ([Powell et al. 2013b](#)). This study found that DNA methylation levels on some CpG islands predicted antidepressant treatment response and that an interaction between CpG island methylation and genotype at rs1126757 could also predict treatment response. These studies are some of the first to provide evidence that a genomic approach may be fruitful for identifying molecular biomarkers that can predict which patients will best respond to specific antidepressants.

Another investigation from the GENDEP study sought to identify gene expression differences present prior to treatment that could predict treatment response. This study examined leukocyte mRNA expression in healthy controls ( $n=34$ ) and depressed patients ( $n=74$ ) before and after 8 weeks of treatment with escitalopram or nortriptyline ([Cattaneo et al. 2013](#)). The analysis was limited to 15 candidate genes that belonged to one of three groups previously implicated in the pathogenesis of depression or putative mechanisms of action of antidepressants (glucocorticoid receptor function, inflammation, and neuroplasticity). In regard to predictors present prior to treatment, nonresponders had higher mRNA levels for interleukin 1 $\beta$  (*IL1 $\beta$* ; +33%), macrophage inhibiting factor (*MIF*; +48%), and tumor necrosis factor (*TNF*; +39%). A similar study using a nonoverlapping set of GENDEP subjects and focusing only on escitalopram treatment also found higher mRNA levels for *TNF* (+20%) in nonresponders ([Powell et al. 2013a](#)).

A second aim of the [Cattaneo et al. \(2013\)](#) study was to identify changes in gene expression occurring during the course of successful treatment that could point to potential targets of drug action. Successful antidepressant treatment was associated with modest reductions in mRNA levels for *IL6* (−9%) and FK506 binding protein 5 (*FKBP5*) (−11%), as well as increases in mRNA levels for *BDNF* (+48%) and VGF nerve growth factor inducible (*VGF*) (+20%). Taken together, these data indicate that the genes thought to serve as predictors of antidepressant response may be separate from the genes hypothesized to be altered by successful treatment. The authors also noted that with the exception of *IL6*, all gene expression differences were in the same direction for both escitalopram and nortriptyline despite their different mechanisms of action, suggesting that these gene expression changes reflect alterations in pathways common to the two antidepressants and not pathways selective to serotonergic or adrenergic neurotransmission ([Cattaneo et al. 2013](#)).

## Depression in Children and Adolescents

Fluoxetine is currently the only FDA-approved medication for the treatment of depression in both children and adolescents (ages 8 years and older). Escitalopram was approved in 2009 for the treatment of depression in adolescents (ages 12-17 years) but not in younger children. In addition, the FDA has mandated the placement of black box warnings on product labels to indicate the potential for increased suicidality associated with the use of SSRIs in patients younger than 25 years. Importantly, a meta-

analysis of pediatric trials conducted between 1988 and 2006 indicated that the benefits of antidepressant treatment of the young outweigh the risks ([Bridge et al. 2007](#)).

## **Citalopram**

Only a limited number of clinical studies have examined the effectiveness of citalopram in the treatment of depression in youth. In one double-blind trial involving 174 children and adolescents (ages 7–17 years), citalopram (20 mg/day) showed a modest superiority over placebo in the treatment of depression ([Wagner et al. 2004](#)). Conversely, citalopram (10–40 mg/day) was not superior to placebo in a clinical trial involving 244 adolescents (ages 13–18 years) receiving treatment for 12 weeks ([von Knorring et al. 2006](#)). Clearly, additional clinical trials are required to establish the efficacy and safety of citalopram in the treatment of childhood depression.

## **Escitalopram**

Three studies have addressed the effectiveness of escitalopram in the pediatric population. Escitalopram was shown to be effective in the treatment of depression in adolescents (ages 12–17 years) in a randomized, double-blind, placebo-controlled multicenter clinical trial ([Emslie et al. 2009](#)). In this study, the group given escitalopram 10–20 mg/day ( $n=155$ ), compared with the group given placebo ( $n=157$ ), had greater improvement based on change from baseline to week 8 in scores on the Children's Depression Rating Scale—Revised (CDRS-R). In another randomized, double-blind trial investigating treatment of major depressive disorder in children and adolescents (ages 6–17

years), those given escitalopram 10–20 mg/day ( $n=131$ ) did not improve significantly more than those given placebo ( $n=133$ ). However, in a post hoc analysis of just the adolescents (ages 12–17 years), those given escitalopram ( $n=80$ ), compared with those given placebo ( $n=77$ ), had significantly improved CDRS-R scores from baseline to week 8 ([Wagner et al. 2006](#)). Finally, the long-term benefits of escitalopram treatment for depression in adolescents were demonstrated in an extension trial that enrolled a subset of the sample participating in the aforementioned [Emslie et al. \(2009\)](#) study. This double-blind 16- to 24-week trial ([Findling et al. 2013](#)) showed that in comparison with subjects given placebo ( $n=40$ ), those given escitalopram 10–20 mg/day ( $n=37$ ) had a modest but statistically significantly greater improvement in CDRS-R score from baseline of the lead-in study to treatment week 24 (8-week lead-in study plus 16-week extension) ( $P=0.005$ ).

## Generalized Anxiety Disorder

### Citalopram

No large-scale randomized, double-blind clinical trials have examined the effectiveness of citalopram in the treatment of GAD. As described in the next subsection, all large-scale trials have focused on the use of escitalopram in the treatment of GAD.

### Escitalopram

The efficacy of escitalopram in the treatment of GAD has been established in several randomized controlled clinical trials ([Baldwin and Nair 2005](#)). Escitalopram's effectiveness

in acute treatment of GAD was shown in three double-blind, placebo-controlled clinical trials that were also subjected to pooled analysis. These studies demonstrated that escitalopram (10–20 mg/day administered for 8–12 weeks) was superior to placebo ([Davidson et al. 2004](#); [Goodman et al. 2005](#); [Stein et al. 2005](#)). The efficacy of escitalopram (10–20 mg/day) in the long-term treatment of GAD was demonstrated in two 24-week controlled clinical trials, one open label ([Davidson et al. 2005](#)) and the other double blind ([Bielski et al. 2005](#)). Escitalopram also showed efficacy in the prevention of GAD relapse for an additional 24–76 weeks ([Allgulander et al. 2006](#)).

## Panic Disorder

### Citalopram

Few well-controlled studies have evaluated the effectiveness of citalopram in the treatment of panic disorder. In a 1-year placebo-controlled, double-blind study of 279 patients who agreed to continue treatment after an acute treatment period during which they had been randomly assigned to receive citalopram (20 or 30 mg/day, or 40 or 60 mg/day), clomipramine (60 or 90 mg/day), or placebo, all drug-treated groups showed significantly greater improvement compared with placebo on a variety of anxiety rating instruments, including the Clinical Anxiety Scale (CAS) panic attack item. The authors concluded that citalopram at a dosage range of 20–60 mg/day was an effective long-term therapy for the management of panic disorder ([Lepola et al. 1998](#)).

### Escitalopram



Escitalopram 5–10 mg/day was shown to be effective in the treatment of panic disorder in a 10-week randomized, double-blind, placebo-controlled, flexible-dosage study in patients with a diagnosis of panic disorder with or without agoraphobia ([Stahl et al. 2003](#)). The relative panic attack frequency was significantly lower in the escitalopram group ( $n=125$ ) than in the placebo group ( $n=114$ ), and at the end of the study, a greater proportion of patients had zero panic attacks in the escitalopram group (50%) than in the placebo group (38%) ( $P=0.051$ ).

## Social Anxiety Disorder (Social Phobia)

### Citalopram

A large-scale, double-blind, placebo-controlled study demonstrated that paroxetine is effective in the treatment of social anxiety disorder, suggesting that some SSRIs may be effective in the treatment of this disorder ([Stein et al. 1998](#)). Despite the lack of large-scale, placebo-controlled studies using citalopram, case reports indicate that citalopram may have effectiveness in the treatment of social anxiety disorder ([Bouwer and Stein 1998](#); [Lepola et al. 1994, 1996](#); [Simon et al. 2001](#)). In addition, one 12-week small-scale ( $n=21$ ), flexible-dose, open-label study demonstrated the effectiveness of citalopram (20–60 mg/day) in relieving the symptoms of social anxiety disorder in patients with comorbid depression ([Schneier et al. 2003](#)).

### Escitalopram

Two large-scale, multinational, multicenter clinical trials have demonstrated the effectiveness of escitalopram in the treatment of social anxiety disorder. In a 24-week fixed-dosage trial in patients with a diagnosis of social anxiety disorder, escitalopram at three dosages—5 mg/day ( $n=167$ ), 10 mg/day ( $n=167$ ), or 20 mg/day ( $n=170$ )—and paroxetine 20 mg/day ( $n=169$ ) each showed a statistically superior therapeutic effect compared with placebo ( $n=166$ ) by week 12 ([Lader et al. 2004](#)). Further improvement was seen by week 24 for all dosages of escitalopram and for paroxetine, and escitalopram 20 mg/day was superior to paroxetine 20 mg/day. In a 12-week study, escitalopram 10–20 mg/day ( $n=181$ ) produced a superior therapeutic response compared with placebo ( $n=177$ ) based on mean change from baseline in the Liebowitz Social Anxiety Scale score ([Kasper et al. 2005](#)). In a long-term study, escitalopram treatment at dosages of 10 or 20 mg/day for up to 24 weeks was shown to be effective in preventing relapse of social anxiety disorder following successful short-term therapy, with relapse being 2.8 times more likely with placebo treatment ( $n=181$ ) than with escitalopram treatment ( $n=190$ ) ([Montgomery et al. 2005](#)).

## Anxiety Associated With Major Depressive Disorder

### Citalopram

A retrospective study of 2,000 depressed patients enrolled in eight double-blind, placebo-controlled clinical trials revealed that citalopram was effective in relieving the symptoms of anxiety in depressed patients based on a

greater decrease in the anxiety factor of the Ham-D ([Flicker et al. 1998](#)). Another double-blind, placebo-controlled study in 323 patients with a diagnosis of major depression revealed a significant antianxiety effect of citalopram 20–60 mg/day compared with placebo based on decreases in the Hamilton Anxiety Scale (Ham-A) score ([Stahl 2000](#)).

## **Escitalopram**

The effectiveness of escitalopram in the treatment of anxiety symptoms associated with major depressive disorder was evaluated in a pooled analysis of five clinical trials ([Bandelow et al. 2007](#)). These placebo-controlled trials were originally designed to examine the effectiveness of escitalopram in treating major depression. In the pooled analysis, escitalopram 10–20 mg/day ( $n=850$ ) was consistently superior to placebo ( $n=737$ ) in relieving the anxious symptoms associated with depression, as evaluated with several different assessments of anxiousness. The analyses presented in this pooled study indicate that escitalopram is effective in relieving anxiety symptoms in depressed patients.

# **Obsessive-Compulsive Disorder**

## **Citalopram**

To date, a limited number of clinical studies have evaluated the effectiveness of citalopram in the treatment of obsessive-compulsive disorder (OCD). In the only published large-scale ( $N=401$ ) double-blind, placebo-controlled study of citalopram in the treatment of OCD, all three dosages of citalopram (20, 40, and 60 mg/day) given for 12 weeks

were significantly more effective than placebo in relieving the symptoms of OCD ([Montgomery et al. 2001a](#)). Citalopram appears to be effective in treating both obsessions and compulsions.

## **Escitalopram**

The effectiveness of escitalopram in the treatment of OCD was demonstrated in a 24-week double-blind, placebo-controlled multicenter clinical trial ([Stein et al. 2007](#)). In this study, escitalopram 20 mg/day ( $n=116$ ) and paroxetine 40 mg/day ( $n=119$ ) produced significant improvement compared with placebo, and by week 24, all treatments, including escitalopram at 10 mg/day ( $n=116$ ), were superior to placebo ( $n=115$ ). Long-term treatment with escitalopram was shown in one large-scale study to prevent relapse of OCD in patients who had responded to initial treatment ([Fineberg et al. 2007](#)). Patients treated with escitalopram 10 or 20 mg/day ( $n=163$ ) showed a significantly greater time to relapse compared with those receiving placebo ( $n=157$ ).

---

## **Investigational Uses**

---

### **Stress-Induced Myocardial Ischemia**

#### **Escitalopram**

Substantial evidence implicates emotional stress as a trigger of acute coronary syndromes, and this effect can be reproduced in laboratory settings; studies show that up to 70% of patients with stable coronary heart disease display

mental stress-induced myocardial ischemia (MSIMI) ([Strike and Steptoe 2003](#)). The Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment (REMIT) study was designed to determine whether SSRI treatment could improve heart function following mental stress in patients with laboratory-diagnosed MSIMI. At the end of this 6-week randomized, double-blind, placebo-controlled study, significantly more of the patients receiving escitalopram treatment ( $n=56$ ; 5 mg/day titrated to 20 mg/day over 3 weeks) than of those receiving placebo ( $n=56$ ) (odds ratio, 2.62 [95% confidence interval, 1.06–6.44];  $P=0.04$ ) showed no MSIMI during three mental stressor tasks ([Jiang et al. 2013](#)). There was no statistically significant effect for exercise-induced ischemia. These results offer a preliminary indication of the potential utility of SSRIs in preventing mental stress-induced acute coronary syndromes.

## Alzheimer's Disease

### Citalopram

Brain accumulation of amyloid plaques formed by the aggregation of the amyloid- $\beta$  peptide ( $A\beta$ ) is thought to be central to the pathophysiology of Alzheimer's disease (AD) ([Holtzman et al. 2011](#)). The aggregation of  $A\beta$  into plaques is concentration dependent ([Bero et al. 2011](#); [Lomakin et al. 1997](#)); therefore, methods to decrease  $A\beta$  levels may be therapeutic. Previous studies have shown that serotonin signaling suppresses the generation of  $A\beta$  in vitro and in animal models of AD ([Cirrito et al. 2011](#); [Nitsch et al. 1996](#)). In an aged transgenic AD mouse model (APP/PS1 plaque-bearing mice), acute citalopram treatment led to a dose-

dependent decrease in brain interstitial fluid A $\beta$  levels, and chronic citalopram treatment arrested the growth of preexisting plaques and reduced the appearance of new plaques by 78% ([Sheline et al. 2014](#)). In addition, in a double-blind study, acute administration of citalopram (60 mg/day) in 23 healthy humans (ages 18–50 years, 11 females) resulted in lower cerebrospinal fluid A $\beta$  production (37%) and concentration (38%) compared with placebo ([Sheline et al. 2014](#)). To the extent that AD involves the accumulation of A $\beta$ , these results suggest a potential role for SSRI treatment in the prevention of AD, and future studies should be aimed at defining the mechanism by which citalopram treatment lowers A $\beta$  levels.

---

## Side Effects and Toxicology

---

### Citalopram

In a meta-analysis of 746 depressed patients involved in several short-term clinical trials, the most common adverse events associated with citalopram were nausea and vomiting (20%), increased sweating (18%), and dry mouth and headache (17%) ([Baldwin and Johnson 1995](#)). Analysis of an integrated safety database, which includes data from 3,107 patients enrolled in 24 clinical trials, indicated that in placebo-controlled trials, nausea, dry mouth, somnolence, increased sweating, tremor, diarrhea, and ejaculatory failure of mild to moderate severity occurred with significantly greater frequency in patients given citalopram than in those given placebo ([Muldoon 1996](#)). The incidences of these adverse events with citalopram were less than 10%

above those seen with placebo and were comparable to those reported with other SSRIs. Citalopram had a tolerability that was superior to that of the tricyclic antidepressants, with the exception that nausea and ejaculatory failure occurred with a 5% greater frequency in patients given citalopram ([Keller 2000](#)).

## Escitalopram

In general, the side effects associated with escitalopram are similar to those observed with citalopram. In three placebo-controlled clinical trials performed with escitalopram, rates of discontinuation due to adverse events did not differ for patients given a dosage of 10 mg/day versus patients in the placebo group ([Burke et al. 2002](#); [Montgomery et al. 2001b](#); [Wade et al. 2002](#)). In the trial that included an escitalopram dosage of 20 mg/day, the rate of discontinuation was 10.4% for the group given escitalopram versus 2.5% for the group given placebo ([Burke et al. 2002](#)). In addition, the rate of adverse events overall in the group receiving escitalopram 20 mg/day (85.6%) was significantly greater than the rate in the placebo group (70.5%). Regardless of dosage, the adverse events that have been reported to occur more frequently with escitalopram compared with placebo are nausea, diarrhea, insomnia, dry mouth, and ejaculatory disorder, with nausea being reported most frequently, at a rate of 15% ([McRae 2002](#)). No published studies have reported clinically significant findings in laboratory test values, vital signs, weight gain or loss, or ECG values.

# Specific Effects and Syndromes

## QT Interval Prolongation

Citalopram has been shown to be associated with a dose-dependent prolongation of the corrected QT (QTc) interval in the ECG, which can increase the risk of a potentially fatal abnormal heart rhythm called torsades de pointes. As a result, the FDA recommends that citalopram not be prescribed at dosages greater than 40 mg/day ([The Medical Letter on Drugs and Therapeutics 2013](#); [U.S. Food and Drug Administration 2013](#)). In addition, citalopram use should be avoided in populations at increased risk of QTc interval prolongation, such as patients with congenital long QT syndrome. For at-risk patients for whom no satisfactory alternatives to citalopram are available, a low dosage of citalopram should be used, and ECG and/or electrolytes should be monitored. Citalopram should be discontinued in patients with a QTc interval greater than 500 msec. Finally, for patients older than 60 years, dosages greater than 20 mg/day are not recommended. As in any clinical situation, the clinician must weigh the risk-benefit ratio for the treatment, and in some cases it may be reasonable to use dosages that exceed the FDA guidelines. Importantly, escitalopram at dosages therapeutically equivalent to those of citalopram has not been demonstrated to significantly impact the QTc interval.

## Hyponatremia

Citalopram and escitalopram have been shown to produce hyponatremia in case reports involving elderly patients, and this information has been reviewed elsewhere ([Jacob and Spinler 2006](#)). In addition to advanced age, other factors



that may increase the likelihood of hyponatremia include female gender, concurrent diuretic use, low body weight, and recent pneumonia. Treatment of SSRI-induced hyponatremia usually involves fluid restriction and/or administration of a loop diuretic such as furosemide and may include discontinuation of the SSRI.

## **Discontinuation Syndrome**

The abrupt cessation of antidepressant therapy can result in a discontinuation syndrome characterized by dizziness, nausea and vomiting, lethargy, and flu-like symptoms. This syndrome is more common with short-half-life SSRIs such as paroxetine and less common with long-half-life SSRIs such as fluoxetine. The data obtained from clinical trials suggest that the adverse events associated with discontinuation of citalopram or escitalopram tend to be mild and transient ([Baldwin et al. 2007](#); [Markowitz et al. 2000](#); [Montgomery et al. 1993](#)). Dose tapering is recommended for patients discontinuing treatment.

## **Treatment-Emergent Suicidal Ideation and Suicide**

Considerable attention has been focused in recent years on the possibility that antidepressant drugs, especially SSRIs, may lead to treatment-emergent suicidal ideation (TESI) and an increased risk of suicide in some patients, particularly at the onset of therapy ([Jick et al. 2004](#)). This issue is of great concern in young patients and was described earlier in the chapter (see earlier section “Depression in Children and Adolescents”). In the case of citalopram, analyses of data obtained from 17 controlled clinical trials involving 5,000 patients indicate that the

group of patients receiving citalopram had the lowest rate of suicide compared with the groups receiving placebo, tricyclic antidepressants, or other SSRIs ([Nemeroff 2003](#)). The risk of suicide associated with escitalopram was evaluated from data contained in the Summary Basis of Approval reports obtained from the FDA ([Khan and Schwartz 2007](#)). This study did not detect a significantly greater rate of suicide in the escitalopram group compared with either the citalopram or the placebo group. A meta-analysis of the escitalopram clinical trials database—consisting of 2,277 escitalopram-treated patients and 1,814 placebo-treated patients—also yielded no indication that escitalopram increased suicidal behavior in major depressive disorder and anxiety disorders ([Pedersen 2005](#)).

Although the data do not indicate a significantly greater risk of suicide for patients receiving either citalopram or escitalopram compared with those receiving placebo, most antidepressant studies show that a limited number of patients will exhibit TESI on initiation of therapy. Family and twin studies provide some evidence of a genetic influence on suicidal behavior, and it has been postulated that TESI may also be genetically influenced. Interestingly, a study in patients participating in the STAR\*D trial demonstrated a significant association between citalopram-induced TESI in men and polymorphisms near the gene encoding the transcription factor cyclic adenosine monophosphate (cAMP) response-element binding (*CREB*) protein ([Perlis et al. 2007](#)). This protein is of great interest because it mediates the effects of second messengers on new gene transcription and has been implicated in antidepressant action and suicide ([Dowlathshahi et al. 1998](#); [Dwivedi et al. 2003a](#)). An analysis of nine candidate genes in patients from the GENDEP study who received either

escitalopram or nortriptyline identified polymorphisms in *BDNF* as being associated with TESI, and there was also a significant interaction between variants in *BDNF* and *TRKB*, the gene encoding the BDNF receptor (Perroud et al. 2009). A proposed role for the BDNF pathway in TESI is consistent with previous reports of lower levels of BDNF mRNA and protein in the hippocampus and prefrontal cortex of suicide victims and lower levels of BDNF protein in the plasma of suicide attempters (Dwivedi et al. 2003b; Karege et al. 2005; Kim et al. 2007). In addition, CREB is thought to control *BDNF* gene transcription, providing a functional link between these two genetic associations and TESI (Dwivedi et al. 2003a; Finkbeiner 2000).

Finally, in a genomewide association study also using subjects from the GENDEP study, the strongest association with TESI was with a single-nucleotide polymorphism located 30 kilobytes downstream of the gene encoding guanine deaminase (*GDA*). This study also found two suggestive escitalopram-specific associations with TESI that were contained in the gene for Kv channel-interacting protein 4 (*KCNIP4*) and near the gene for elongation protein 3 homolog (*ELP3*) (Perroud et al. 2012). Although no definitive conclusions can be drawn from this study or other genetic studies until they are replicated with larger samples, the findings point to the possibility that in the future, genetic markers may be used to predict not only treatment response but also vulnerabilities to the adverse effects of specific drugs.

---

## Drug-Drug Interactions

---

Even though the majority of a dose of citalopram is metabolized in the liver (75%), because multiple P450 enzymes (CYP2C19, CYP3A4, and CYP2D6) contribute equally to the metabolism of citalopram and escitalopram, inhibition of any one of these enzymes by another drug is unlikely to significantly impact the overall metabolism of citalopram or escitalopram. Consistent with this, there are relatively few reports in the literature of drug-drug interactions involving citalopram or escitalopram. Because of the possibility of a potentially fatal pharmacodynamic interaction resulting in the serotonin syndrome, neither citalopram nor escitalopram should be administered with an MAO inhibitor or within 14 days of discontinuing an MAO inhibitor.

---

## Conclusion

---

Citalopram and escitalopram are highly selective 5-HT reuptake inhibitors that are well tolerated and effective for the treatment of depression, with escitalopram also having proven efficacy in large-scale clinical trials in the treatment of GAD. Although the use of citalopram and escitalopram in the treatment of other psychiatric conditions has not been as thoroughly studied, the few well-controlled trials that have been completed suggest that both drugs may have a significant role in treating a wide range of psychiatric illnesses, including panic disorder, social anxiety disorder, anxiety associated with depression, and OCD. An advantage of citalopram and escitalopram compared with some other common SSRIs is a relatively weak inhibition of liver CYP450 enzymes, which reduces the potential for adverse

pharmacokinetic drug-drug interactions. In addition, because escitalopram does not share with citalopram a modest affinity for the histamine H<sub>1</sub> receptor, it may have a lower potential for antihistaminergic side effects compared with citalopram, a difference that has yet to be demonstrated in a clinical trial. In terms of effects on cardiac function, escitalopram's risk of producing QT interval prolongation appears to be lower than that of citalopram, and careful monitoring must accompany use of citalopram in patients at risk for QT prolongation. There are a number of clinical trials comparing escitalopram with a variety of other antidepressants, including citalopram and venlafaxine, that suggest that escitalopram may have a faster onset of antidepressant efficacy and modest superiority in the treatment of individuals who are severely depressed. However, a clinically significant superiority of escitalopram over citalopram in the "real world" of psychiatric practice remains to be definitely established.

---

## References

---

- Agranat I, Caner H, Caldwell J: Putting chirality to work: the strategy of chiral switches. *Nat Rev Drug Discov* 1(10):753-768, 2002 12360254
- Allgulander C, Florea I, Huusom AK: Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *Int J Neuropsychopharmacol* 9(5):495-505, 2006 16316482
- Anacker C, Zunszain PA, Cattaneo A, et al: Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. *Mol Psychiatry* 16(7):738-750, 2011 21483429

- Arborelius L, Owens MJ, Plotsky PM, et al: The role of corticotropin-releasing factor in depression and anxiety disorders. *J Endocrinol* 160(1):1-12, 1999 9854171
- Baldwin D, Johnson FN: Tolerability and safety of citalopram. *Rev Contemp Pharmacother* 6:315-325, 1995
- Baldwin DS, Nair RV: Escitalopram in the treatment of generalized anxiety disorder. *Expert Rev Neurother* 5(4):443-449, 2005 16026227
- Baldwin DS, Montgomery SA, Nil R, et al: Discontinuation symptoms in depression and anxiety disorders. *Int J Neuropsychopharmacol* 10(1):73-84, 2007 16359583
- Bandelow B, Andersen HF, Dolberg OT: Escitalopram in the treatment of anxiety symptoms associated with depression. *Depress Anxiety* 24(1):53-61, 2007 16937393
- Baumann P: Clinical pharmacokinetics of citalopram and other selective serotonergic reuptake inhibitors (SSRI). *Int Clin Psychopharmacol* 6 (suppl 5):13-20, 1992 1431018
- Baumann P, Nil R, Souche A, et al: A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol* 16(4):307-314, 1996 8835706
- Bech P, Cialdella P: Citalopram in depression—meta-analysis of intended and unintended effects. *Int Clin Psychopharmacol* 6 (suppl 5):45-54, 1992 1431021
- Bero AW, Yan P, Roh JH, et al: Neuronal activity regulates the regional vulnerability to amyloid-beta deposition. *Nat Neurosci* 14(6):750-756, 2011 21532579
- Bielski RJ, Bose A, Chang CC: A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. *Ann Clin Psychiatry* 17(2):65-69, 2005 16075658

- Bjerkenstedt L, Flyckt L, Overø KF, et al: Relationship between clinical effects, serum drug concentration and serotonin uptake inhibition in depressed patients treated with citalopram. A double-blind comparison of three dose levels. *Eur J Clin Pharmacol* 28(5):553-557, 1985 3899675
- Blier P, de Montigny C: Current advances and trends in the treatment of depression. *Trends Pharmacol Sci* 15(7):220-226, 1994 7940983
- Bouwer C, Stein DJ: Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia. *J Affect Disord* 49(1):79-82, 1998 9574863
- Bridge JA, Iyengar S, Salary CB, et al: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 297(15):1683-1696, 2007 17440145
- Brown ES, Howard C, Khan DA, et al: Escitalopram for severe asthma and major depressive disorder: a randomized, double-blind, placebo-controlled proof-of-concept study. *Psychosomatics* 53(1):75-80, 2012 22221724
- Burke WJ, Gergel I, Bose A: Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 63(4):331-336, 2002 12000207
- Carvalho LA, Pariante CM: In vitro modulation of the glucocorticoid receptor by antidepressants. *Stress* 11(6):411-424, 2008 19065455
- Cattaneo A, Gennarelli M, Uher R, et al: Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology* 38(3):377-385, 2013 22990943
- Chaput Y, de Montigny C, Blier P: Effects of a selective 5-HT reuptake blocker, citalopram, on the sensitivity of 5-HT

autoreceptors: electrophysiological studies in the rat brain. Naunyn Schmiedebergs Arch Pharmacol 333(4):342-348, 1986 3022157

Chen F, Lawrence AJ: The effects of antidepressant treatment on serotonergic and dopaminergic systems in Fawn-Hooded rats: a quantitative autoradiography study. Brain Res 976(1):22-29, 2003 12763618

Choi MJ, Kang RH, Lim SW, et al: Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder. Brain Res 1118(1):176-182, 2006 16979146

Christensen AV, Fjalland B, Pedersen V, et al: Pharmacology of a new phthalane (Lu 10-171), with specific 5-HT uptake inhibiting properties. Eur J Pharmacol 41(2):153-162, 1977 12988

Cirrito JR, Disabato BM, Restivo JL, et al: Serotonin signaling is associated with lower amyloid-beta levels and plaques in transgenic mice and humans. Proc Natl Acad Sci U S A 108(36):14968-14973, 2011 21873225

Cremers TI, Spoelstra EN, de Boer P, et al: Desensitisation of 5-HT autoreceptors upon pharmacokinetically monitored chronic treatment with citalopram. Eur J Pharmacol 397(2-3):351-357, 2000 10844134

Dalgaard L, Larsen C: Metabolism and excretion of citalopram in man: identification of O-acyl- and N-glucuronides. Xenobiotica 29(10):1033-1041, 1999 10574684

Davidson JR, Bose A, Korotzer A, et al: Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. Depress Anxiety 19(4):234-240, 2004 15274172

Davidson JR, Bose A, Wang Q: Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 66(11):1441-1446, 2005 16420082



- Dowlatshahi D, MacQueen GM, Wang JF, et al: Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. *Lancet* 352(9142):1754-1755, 1998 9848357
- Dwivedi Y, Rao JS, Rizavi HS, et al: Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 60(3):273-282, 2003a 12622660
- Dwivedi Y, Rizavi HS, Conley RR, et al: Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 60(8):804-815, 2003b 12912764
- Einarson TR: Evidence based review of escitalopram in treating major depressive disorder in primary care. *Int Clin Psychopharmacol* 19(5):305-310, 2004 15289704
- Emslie GJ, Ventura D, Korotzer A, et al: Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry* 48(7):721-729, 2009 19465881
- Etkin A, Patenaude B, Song YJ, et al: A cognitive-emotional biomarker for predicting remission with antidepressant medications: a report from the iSPOT-D trial. *Neuropsychopharmacology* 40(6):1332-1342, 2015 25547711
- Feighner JP, Overø K: Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. *J Clin Psychiatry* 60(12):824-830, 1999 10665628
- Findling RL, Robb A, Bose A: Escitalopram in the treatment of adolescent depression: a randomized, double-blind, placebo-controlled extension trial. *J Child Adolesc Psychopharmacol* 23(7):468-480, 2013 24041408
- Fineberg NA, Tonnoir B, Lemming O, et al: Escitalopram prevents relapse of obsessive-compulsive disorder. *Eur*

Neuropsychopharmacol 17(6-7):430-439, 2007  
17240120

Finkbeiner S: Calcium regulation of the brain-derived neurotrophic factor gene. Cell Mol Life Sci 57(3):394-401, 2000 10823240

Flandreau EI, Ressler KJ, Owens MJ, et al: Chronic overexpression of corticotropin-releasing factor from the central amygdala produces HPA axis hyperactivity and behavioral anxiety associated with gene-expression changes in the hippocampus and paraventricular nucleus of the hypothalamus. Psychoneuroendocrinology 37(1):27-38, 2012 21616602

Flandreau EI, Bourke CH, Ressler KJ, et al: Escitalopram alters gene expression and HPA axis reactivity in rats following chronic overexpression of corticotropin-releasing factor from the central amygdala. Psychoneuroendocrinology 38(8): 1349-1361, 2013 23267723

Flicker C, Hakkarainen H, Tanghoj P: Citalopram in anxious depression: anxiolytic effects and lack of activation. Biol Psychiatry 43 (8 suppl 1):106S, 1998 doi: [http://dx.doi.org/10.1016/S0006-3223\(98\)90799-5](http://dx.doi.org/10.1016/S0006-3223(98)90799-5)

Fredricson Overø K: Kinetics of citalopram in man; plasma levels in patients. Prog Neuropsychopharmacol Biol Psychiatry 6(3):311-318, 1982 6959195

Goodman WK, Bose A, Wang Q: Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord 87(2-3):161-167, 2005 15982747

Gyurak A, Patenaude B, Korgaonkar MS, et al: Frontoparietal activation during response inhibition predicts remission to antidepressants in patients with major depression. Biol Psychiatry 79(4):274-281, 2016 25891220

Hochstrasser B, Isaksen PM, Koponen H, et al: Prophylactic effect of citalopram in unipolar, recurrent depression:

- placebo-controlled study of maintenance therapy. *Br J Psychiatry* 178:304–310, 2001 11282808
- Holtzman DM, Morris JC, Goate AM: Alzheimer's disease: the challenge of the second century. *Sci Transl Med* 3(77):77sr1, 2011 21471435
- Hyttel J: Neurochemical characterization of a new potent and selective serotonin uptake inhibitor: Lu 10-171. *Psychopharmacology (Berl)* 51(3):225–233, 1977 403537
- Hyttel J: Effect of a specific 5-HT uptake inhibitor, citalopram (Lu 10-171), on 3H-5-HT uptake in rat brain synaptosomes in vitro. *Psychopharmacology (Berl)* 60(1):13–18, 1978 104340
- Hyttel J: Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). *Int Clin Psychopharmacol* 9 (suppl 1):19–26, 1994 8021435
- Hyttel J, Bøgesø KP, Perregaard J, et al: The pharmacological effect of citalopram residues in the (S)-(+)-enantiomer. *J Neural Transm* 88(2):157–160, 1992 1632943
- Hyttel J, Arnt J, Sanchez C: The pharmacology of citalopram. *Rev Contemp Pharmacother* 6:271–285, 1995
- Inoue T: [Effects of conditioned fear stress on monoaminergic systems in the rat brain]. *Hokkaido Igaku Zasshi* 68(3):377–390, 1993 7686527
- Invernizzi R, Bramante M, Samanin R: Chronic treatment with citalopram facilitates the effect of a challenge dose on cortical serotonin output: role of presynaptic 5-HT<sub>1A</sub> receptors. *Eur J Pharmacol* 260(2–3):243–246, 1994 7988650
- Jacob S, Spinler SA: Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother* 40(9):1618–1622, 2006 16896026
- Jiang W, Velazquez EJ, Kuchibhatla M, et al: Effect of escitalopram on mental stress-induced myocardial

- ischemia: results of the REMIT trial. JAMA 309(20):2139-2149, 2013 23695483
- Jick H, Kaye JA, Jick SS: Antidepressants and the risk of suicidal behaviors. JAMA 292(3):338-343, 2004 15265848
- Joffe P, Larsen FS, Pedersen V, et al: Single-dose pharmacokinetics of citalopram in patients with moderate renal insufficiency or hepatic cirrhosis compared with healthy subjects. Eur J Clin Pharmacol 54(3):237-242, 1998 9681666
- Karege F, Vaudan G, Schwald M, et al: Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. Brain Res Mol Brain Res 136(1-2):29-37, 2005 15893584
- Kasper S, Stein DJ, Loft H, et al: Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. Br J Psychiatry 186:222-226, 2005 15738503
- Keller MB: Citalopram therapy for depression: a review of 10 years of European experience and data from U.S. clinical trials. J Clin Psychiatry 61(12):896-908, 2000 11206593
- Kennedy SH, Andersen HF, Lam RW: Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. J Psychiatry Neurosci 31(2):122-131, 2006 16575428
- Khan A, Schwartz K: Suicide risk and symptom reduction in patients assigned to placebo in duloxetine and escitalopram clinical trials: analysis of the FDA summary basis of approval reports. Ann Clin Psychiatry 19(1):31-36, 2007 17453659
- Kim YK, Lee HP, Won SD, et al: Low plasma BDNF is associated with suicidal behavior in major depression. Prog Neuropsychopharmacol Biol Psychiatry 31(1):78-85, 2007 16904252

- Klysner R, Bent-Hansen J, Hansen HL, et al: Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. *Br J Psychiatry* 181:29-35, 2002 12091260
- Kobayashi K, Chiba K, Yagi T, et al: Identification of cytochrome P450 isoforms involved in citalopram N-demethylation by human liver microsomes. *J Pharmacol Exp Ther* 280(2):927-933, 1997 9023308
- Kornstein SG, Bose A, Li D, et al: Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial. *J Clin Psychiatry* 67(11):1767-1775, 2006 17196058
- Kragh-Sørensen P, Overø KF, Petersen OL, et al: The kinetics of citalopram: single and multiple dose studies in man. *Acta Pharmacol Toxicol (Copenh)* 48(1):53-60, 1981 6939299
- Lader M, Stender K, Bürger V, et al: Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 19(4):241-248, 2004 15274173
- Langenecker SA, Kennedy SE, Guidotti LM, et al: Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biol Psychiatry* 62(11):1272-1280, 2007 17585888
- Lepola U, Koponen H, Leinonen E: Citalopram in the treatment of social phobia: a report of three cases. *Pharmacopsychiatry* 27(5):186-188, 1994 7838888
- Lepola U, Leinonen E, Koponen H: Citalopram in the treatment of early onset panic disorder and school phobia. *Pharmacopsychiatry* 29(1):30-32, 1996 8852532
- Lepola UM, Wade AG, Leinonen EV, et al: A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. *J Clin Psychiatry* 59(10):528-534, 1998 9818634

- Lepola UM, Loft H, Reines EH: Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 18(4):211–217, 2003 12817155
- Llorca PM, Azorin JM, Despiegel N, et al: Efficacy of escitalopram in patients with severe depression: a pooled analysis. *Int J Clin Pract* 59(3):268–275, 2005 15857321
- Lomakin A, Teplov DB, Kirschner DA, et al: Kinetic theory of fibrillogenesis of amyloid beta-protein. *Proc Natl Acad Sci U S A* 94(15):7942–7947, 1997 9223292
- Markowitz JS, DeVane CL, Liston HL, et al: An assessment of selective serotonin reuptake inhibitor discontinuation symptoms with citalopram. *Int Clin Psychopharmacol* 15(6):329–333, 2000 11110008
- Martin P, Soubrié P, Puech AJ: Reversal of helpless behavior by serotonin uptake blockers in rats. *Psychopharmacology (Berl)* 101(3):403–407, 1990 2362957
- McMahon FJ, Buervenich S, Charney D, et al: Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet* 78(5):804–814, 2006 16642436
- McRae AL: Escitalopram. *Curr Opin Investig Drugs* 3(8):1225–1229, 2002 12211420
- The Medical Letter on Drugs and Therapeutics: Citalopram, Escitalopram, and the QT interval. *Med Lett Drugs Ther* 55(1421):59, 2013 23863918
- Mendels J, Kiev A, Fabre LF: Double-blind comparison of citalopram and placebo in depressed outpatients with melancholia. *Depress Anxiety* 9(2):54–60, 1999 10207659
- Montgomery SA, Rasmussen JG, Tanghøj P: A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. *Int Clin Psychopharmacol* 8(3):181–188, 1993 8263316

- Montgomery SA, Pedersen V, Tanghøj P, et al: The optimal dosing regimen for citalopram—a meta-analysis of nine placebo-controlled studies. *Int Clin Psychopharmacol* 9 (suppl 1):35–40, 1994 8021436
- Montgomery SA, Kasper S, Stein DJ, et al: Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 16(2):75–86, 2001a 11236072
- Montgomery SA, Loft H, Sánchez C, et al: Escitalopram (S-enantiomer of citalopram): clinical efficacy and onset of action predicted from a rat model. *Pharmacol Toxicol* 88(5):282–286, 2001b 11393591
- Montgomery SA, Nil R, Dürr-Pal N, et al: A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. *J Clin Psychiatry* 66(10): 1270–1278, 2005 16259540
- Muldoon C: The safety and tolerability of citalopram. *Int Clin Psychopharmacol* 11 (suppl 1):35–40, 1996 8732443
- Nemeroff CB: Overview of the safety of citalopram. *Psychopharmacol Bull* 37(1):96–121, 2003 14561952
- Nitsch RM, Deng M, Growdon JH, et al: Serotonin 5-HT<sub>2a</sub> and 5-HT<sub>2c</sub> receptors stimulate amyloid precursor protein ectodomain secretion. *J Biol Chem* 271(8):4188–4194, 1996 8626761
- Norton N, Owen MJ: HTR2A: association and expression studies in neuropsychiatric genetics. *Ann Med* 37(2):121–129, 2005 16026119
- Owens MJ, Morgan WN, Plott SJ, et al: Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Ther* 283(3):1305–1322, 1997 9400006
- Owens MJ, Knight DL, Nemeroff CB: Second-generation SSRIs: human monoamine transporter binding profile of

- escitalopram and R-fluoxetine. *Biol Psychiatry* 50(5):345-350, 2001 11543737
- Pariente CM, Alhaj HA, Arulnathan VE, et al: Central glucocorticoid receptor-mediated effects of the antidepressant, citalopram, in humans: a study using EEG and cognitive testing. *Psychoneuroendocrinology* 37(5):618-628, 2012 21958534
- Pedersen AG: Escitalopram and suicidality in adult depression and anxiety. *Int Clin Psychopharmacol* 20(3):139-143, 2005 15812263
- Peremans K, Audenaert K, Hoybergs Y, et al: The effect of citalopram hydrobromide on 5-HT<sub>2A</sub> receptors in the impulsive-aggressive dog, as measured with 123I-5-I-R91150 SPECT. *Eur J Nucl Med Mol Imaging* 32(6):708-716, 2005 15739093
- Perlis RH, Purcell S, Fava M, et al: Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR\*D study. *Arch Gen Psychiatry* 64(6):689-697, 2007 17548750
- Perroud N, Aitchison KJ, Uher R, et al: Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. *Neuropsychopharmacology* 34(12):2517-2528, 2009 19641488
- Perroud N, Uher R, Ng MY, et al: Genome-wide association study of increasing suicidal ideation during antidepressant treatment in the GENDEP project. *Pharmacogenomics J* 12(1):68-77, 2012 20877300
- Powell TR, Schalkwyk LC, Heffernan AL, et al: Tumor necrosis factor and its targets in the inflammatory cytokine pathway are identified as putative transcriptomic biomarkers for escitalopram response. *Eur Neuropsychopharmacol* 23(9):1105-1114, 2013a 23142150



- Powell TR, Smith RG, Hackinger S, et al: DNA methylation in interleukin-11 predicts clinical response to antidepressants in GENDEP. *Transl Psychiatry* 3:e300, 2013b 24002086
- Rantamäki T, Hendolin P, Kankaanpää A, et al: Pharmacologically diverse antidepressants rapidly activate brain-derived neurotrophic factor receptor TrkB and induce phospholipase-Cgamma signaling pathways in mouse brain. *Neuropsychopharmacology* 32(10):2152-2162, 2007 17314919
- Rantamäki T, Vesa L, Antila H, et al: Antidepressant drugs transactivate TrkB neurotrophin receptors in the adult rodent brain independently of BDNF and monoamine transporter blockade. *PLoS One* 6(6):e20567, 2011 21666748
- Rao N: The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet* 46(4):281-290, 2007 17375980
- Rapaport MH, Bose A, Zheng H: Escitalopram continuation treatment prevents relapse of depressive episodes. *J Clin Psychiatry* 65(1):44-49, 2004 14744167
- Richelson E, Nelson A: Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. *J Pharmacol Exp Ther* 230(1):94-102, 1984 6086881
- Robert P, Montgomery SA: Citalopram in doses of 20-60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. *Int Clin Psychopharmacol* 10 (suppl 1):29-35, 1995 7622809
- Rochat B, Amey M, Gillet M, et al: Identification of three cytochrome P450 isozymes involved in N-demethylation of citalopram enantiomers in human liver microsomes. *Pharmacogenetics* 7(1):1-10, 1997 9110356
- Rush AJ, Fava M, Wisniewski SR, et al; STAR\*D Investigators Group: Sequenced treatment alternatives to relieve depression (STAR\*D): rationale and design. *Control Clin Trials* 25(1):119-142, 2004 15061154

- Russo-Neustadt AA, Alexandre H, Garcia C, et al: Hippocampal brain-derived neurotrophic factor expression following treatment with reboxetine, citalopram, and physical exercise. *Neuropsychopharmacology* 29(12):2189-2199, 2004 15199375
- Sánchez C: Serotonergic mechanisms involved in the exploratory behaviour of mice in a fully automated two-compartment black and white text box. *Pharmacol Toxicol* 77(1):71-78, 1995 8532615
- Sánchez C: The pharmacology of citalopram enantiomers: the antagonism by R-citalopram on the effect of S-citalopram. *Basic Clin Pharmacol Toxicol* 99(2):91-95, 2006 16918708
- Sánchez C, Meier E: Behavioral profiles of SSRIs in animal models of depression, anxiety and aggression. Are they all alike? *Psychopharmacology (Berl)* 129(3):197-205, 1997 9084057
- Sánchez C, Bergqvist PB, Brennum LT, et al: Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. *Psychopharmacology (Berl)* 167(4):353-362, 2003 12719960
- Schneier FR, Blanco C, Campeas R, et al: Citalopram treatment of social anxiety disorder with comorbid major depression. *Depress Anxiety* 17(4):191-196, 2003 12820174
- Serra-Millàs M, López-Vílchez I, Navarro V, et al: Changes in plasma and platelet BDNF levels induced by S-citalopram in major depression. *Psychopharmacology (Berl)* 216(1):1-8, 2011 21308467
- Sheline YI, West T, Yarasheski K, et al: An antidepressant decreases CSF Abeta production in healthy individuals and in transgenic AD mice. *Sci Transl Med* 6:1-8, 2014 24828079

- Simon NM, Sharma SG, Worthington JJ, et al: Citalopram for social phobia: a clinical case series. *Prog Neuropsychopharmacol Biol Psychiatry* 25(7):1469-1474, 2001 11513360
- Sindrup SH, Brøsen K, Hansen MG, et al: Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. *Ther Drug Monit* 15(1):11-17, 1993 8451774
- Snyder HR: Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull* 139(1):81-132, 2013 22642228
- Stahl SM: Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry* 48(9):894-901, 2000 11074227
- Stahl SM, Gergel I, Li D: Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 64(11):1322-1327, 2003 14658946
- Stein DJ, Andersen HF, Goodman WK: Escitalopram for the treatment of GAD: efficacy across different subgroups and outcomes. *Ann Clin Psychiatry* 17(2):71-75, 2005 16075659
- Stein DJ, Andersen EW, Tonnoir B, et al: Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin* 23(4): 701-711, 2007 17407626
- Stein MB, Liebowitz MR, Lydiard RB, et al: Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. *JAMA* 280(8): 708-713, 1998 9728642
- Stórustovu SÍ, Sánchez C, Pörzgen P, et al: R-citalopram functionally antagonises escitalopram in vivo and in vitro: evidence for kinetic interaction at the serotonin

- transporter. *Br J Pharmacol* 142(1):172-180, 2004 15037515
- Strike PC, Steptoe A: Systematic review of mental stress-induced myocardial ischaemia. *Eur Heart J* 24(8):690-703, 2003 12713764
- Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR\*D Study Team: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psychiatry* 163(1):28-40, 2006 16390886
- Uher R, Perroud N, Ng MYM, et al: Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. *Am J Psychiatry* 167(5):555-564, 2010 20360315
- U.S. Food and Drug Administration: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. FDA Drug Safety Communication 2013. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm>. Accessed March 1, 2016.
- von Knorring AL, Olsson GI, Thomsen PH, et al: A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol* 26(3):311-315, 2006 16702897
- von Moltke LL, Greenblatt DJ, Grassi JM, et al: Citalopram and desmethylocitalopram in vitro: human cytochromes mediating transformation, and cytochrome inhibitory effects. *Biol Psychiatry* 46(6):839-849, 1999 10494454
- von Moltke LL, Greenblatt DJ, Giancarlo GM, et al: Escitalopram (S-citalopram) and its metabolites in vitro: cytochromes mediating biotransformation, inhibitory effects, and comparison to R-citalopram. *Drug Metab Dispos* 29(8):1102-1109, 2001 11454728

- Wade A, Michael Lemming O, Bang Hedegaard K:  
Escitalopram 10 mg/day is effective and well tolerated in  
a placebo-controlled study in depression in primary care.  
Int Clin Psychopharmacol 17(3):95-102, 2002 11981349
- Wagner KD, Robb AS, Findling RL, et al: A randomized,  
placebo-controlled trial of citalopram for the treatment  
of major depression in children and adolescents. Am J  
Psychiatry 161(6):1079-1083, 2004 15169696
- Wagner KD, Jonas J, Findling RL, et al: A double-blind,  
randomized, placebo-controlled trial of escitalopram in  
the treatment of pediatric depression. J Am Acad Child  
Adolesc Psychiatry 45(3):280-288, 2006 16540812
- Wiles NJ, Mulligan J, Peters TJ, et al: Severity of depression  
and response to antidepressants: GENPOD randomised  
controlled trial. Br J Psychiatry 200(2):130-136, 2012  
22194183
- Yu BN, Chen GL, He N, et al: Pharmacokinetics of  
citalopram in relation to genetic polymorphism of  
CYP2C19. Drug Metab Dispos 31(10):1255-1259, 2003  
12975335

## CHAPTER 15

# **Trazodone and Nefazodone**

Robert N. Golden, M.D.

Karon Dawkins, M.D.

Linda Nicholas, M.D.

**Trazodone** was among the earliest “second generation” antidepressants to become available for clinical use in the United States in the early 1980s. Its side-effect profile and potential toxicity were considerably different from—and in many instances preferable to—those of the original antidepressants (i.e., the monoamine oxidase inhibitors [MAOIs] and tricyclic antidepressants [TCAs]). Several years later, trazodone’s pharmacological “cousin,” nefazodone, also became available.

---

## **Trazodone**

---

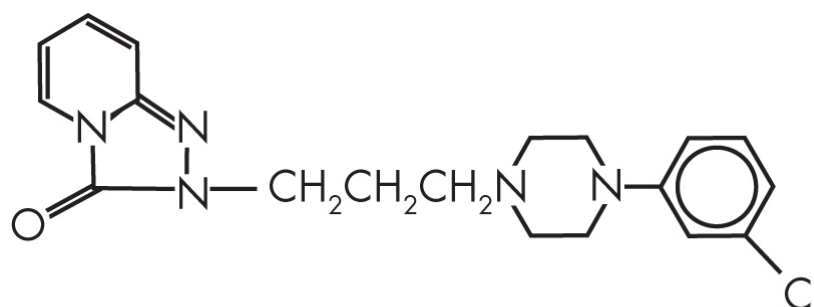
# History and Discovery

Trazodone was first synthesized in Italy about four decades ago, and clinical studies began in the United States in 1978. In sharp contrast to most other antidepressants available at the time, trazodone showed minimal effects on muscarinic cholinergic receptors.

In 1982, trazodone was introduced for clinical use in the United States under the brand name Desyrel. The medication is now available in generic formulation and also in an extended-release preparation (Oleptro).

## Pharmacological Profile

Trazodone is a relatively weak SSRI; however, it is relatively *specific* for serotonin (5-HT) uptake inhibition, with minimal effects on norepinephrine (NE) or dopamine reuptake (Hyttel 1982) (Figure 15-1). Trazodone appears to increase extracellular 5-HT concentrations through a combination of mechanisms involving the 5-HT transporter (5-HTT) and the serotonin<sub>2A/2C</sub> (5-HT<sub>2A/2C</sub>) receptors (Pazzagli et al. 1999). In addition, trazodone has some 5-HT receptor antagonist activity (Haria et al. 1994). Its active metabolite, *m*-chlorophenylpiperazine (mCPP), is a potent direct 5-HT receptor agonist. Thus, trazodone can be viewed as a mixed serotonergic agonist-antagonist, with the relative amount of mCPP accumulation affecting the relative degree of the predominant agonist activity. Sustained administration is associated with enhanced serotonergic neurotransmission in vivo in the rat brain (Ghanbari et al. 2010).



---

**FIGURE 15-1.** Chemical structure of trazodone.

In vivo, trazodone is virtually devoid of anticholinergic activity, and in clinical studies, the incidence of anticholinergic side effects is similar to that seen with placebo. Trazodone is a relatively potent antagonist of postsynaptic  $\alpha_1$ -adrenergic receptors, and it has a propensity to cause orthostatic hypotension. Trazodone has moderate antihistaminergic (histamine<sub>1</sub> [H<sub>1</sub>] receptor) activity.

## Pharmacokinetics and Disposition

Trazodone is well absorbed after oral administration, with peak blood levels occurring about 1-2 hours after dosing. Trazodone is 89%-95% bound to plasma protein. Elimination appears to be biphasic; the initial alpha and subsequent beta phases have half-lives of 3-6 and 5-9 hours, respectively. Bioavailability is not influenced by age or food intake.

Trazodone undergoes extensive hepatic metabolism. The active metabolite mCPP is cleared more slowly than the parent compound (4- to 14-hour half-life) and reaches higher concentrations in the brain than in plasma ([Caccia et](#)



[al. 1981](#)). The cytochrome P450 (CYP) 2D6 and 3A microsomal enzyme systems also appear to play a role in trazodone metabolism. The relation between steady-state blood levels and clinical response to trazodone is not well defined.

## Mechanism of Action

The ultimate mechanism of action of trazodone remains unclear. Although the drug is described as a 5-HT reuptake inhibitor, its effects on this neurotransmitter system are complex. Trazodone has relative selectivity for 5-HT reuptake sites ([Hyttel 1982](#)); however, in vivo, it blocks the head twitch response induced by classic 5-HT agonists in animals. The potent 5-HT receptor agonist properties of trazodone's major metabolite, mCPP, may play a role in the mechanism of action of the parent compound. Trazodone, unlike the vast majority of antidepressants, does not produce downregulation of  $\beta$ -adrenergic receptors in rat cortex ([Sulser 1983](#)).

## Indications and Efficacy

The primary indication for trazodone is treatment of major depressive disorder. Early reviews found that trazodone's antidepressive efficacy was similar to that of the TCAs and the tetracyclic mianserin ([Lader 1987](#); [Schatzberg \(1987\)](#)).

Questions have been raised about the effectiveness of trazodone in treating severely ill depressed patients, especially those with prominent psychomotor retardation. [Shopsin et al. \(1981\)](#) pointed out that in several

unpublished double-blind, controlled studies, the rates of clinical response to trazodone were low (i.e., 10%–20%).

The performance of trazodone, in direct comparisons with other second-generation antidepressants, has been mixed. In a double-blind, placebo-controlled comparison with venlafaxine, the final response rates were 55% for placebo, 60% for trazodone, and 72% for venlafaxine. Trazodone was more effective than venlafaxine in ameliorating sleep disturbances and was associated with the most dizziness and somnolence ([Cunningham et al. 1994](#)). In a double-blind comparison with bupropion, response rates were 46% for trazodone and 58% for bupropion ([Weisler et al. 1994](#)). In a double-blind study of 200 hospitalized patients experiencing a moderate to severe major depressive episode, mirtazapine yielded greater reductions in depression ratings than did trazodone ([van Moffaert et al. 1995](#)).

Three double-blind studies reported that trazodone had antidepressant efficacy similar to that of other antidepressants in geriatric patients ([Gerner 1987](#)). However, trazodone's association with orthostatic hypotension may increase the risk of falls, with devastating consequences in elderly patients. Still, trazodone is often helpful for geriatric patients with depression who have severe agitation and insomnia. A survey of British geropsychiatrists identified trazodone as one of their most popular adjuncts or alternatives to atypical antipsychotics in the management of behavioral symptoms in the elderly ([Condren and Cooney 2001](#)). A Cochrane Database review found insufficient evidence to support trazodone as a treatment for the behavioral and psychological symptoms of dementia, although the review could not conclude that trazodone was ineffective, given the limited number of

eligible studies ([Martinon-Torres et al. 2004](#)). A recent study of 30 patients with Alzheimer's disease found that trazodone produced a normalization of circadian rhythms, which are often disturbed in this patient population ([Grippe et al. 2015](#))

In a randomized, double-blind, placebo-controlled trial, the anxiolytic efficacy of trazodone was comparable to that of diazepam in weeks 3–8 of treatment for generalized anxiety disorder, although patients treated with diazepam had greater improvement during the first 2 weeks of treatment ([Rickels et al. 1993](#)).

Many clinicians use low-dose trazodone as an alternative to benzodiazepines for the treatment of insomnia. Trazodone is the second most prescribed agent for primary insomnia, even though there is minimal evidence to support its use for this indication ([Mendelson 2005](#); [Rosenberg 2006](#)). Controlled trials have confirmed trazodone's efficacy (at doses of 50–100 mg) in treating antidepressant-associated insomnia ([Nierenberg et al. 1994](#)). A retrospective analysis at a Department of Veterans Affairs (VA) medical center found that approximately 24% of patients receiving trazodone were taking other primary antidepressants ([Clark and Alexander 2000](#)). Another VA study of patients with posttraumatic stress disorder (PTSD) found that of those patients who were able to tolerate trazodone (60 of 72 patients), 92% reported that it improved sleep onset and 78% reported that it improved sleep maintenance ([Warner et al. 2001](#)). A recent study found that trazodone improved the Apnea-Hypopnea Index in patients with obstructive sleep apnea (OSA) without any deleterious effects on oxygen saturation or non-rapid eye movement (REM) arousal threshold, suggesting that the

drug might have potential as a treatment for OSA ([Smales et al. 2015](#)).

Trazodone is more effective than placebo when added to antipsychotic medication in the treatment of the negative symptoms of schizophrenia ([Singh et al. 2010](#); [Watanabe 2011](#)). A double-blind, placebo-controlled trial found trazodone to be effective in treating antipsychotic-induced akathisia ([Stryjer et al. 2010](#)).

A recent review highlighted the common off-label use of trazodone in a number of conditions, including bulimia, fibromyalgia, chronic pain, and diabetic neuropathy ([Bossini et al. 2015](#)). We agree with the authors' conclusion that large randomized controlled trials are needed to determine whether there is adequate scientific evidence to support trazodone's use for any of these indications.

Trazodone should be initiated at a low dose and increased gradually, based on clinical response and tolerance to side effects. For the treatment of a major depressive episode, the suggested initial dosage is 150 mg/day, with increases of 50-mg increments every 3–4 days. Doses may be divided, although many patients prefer bedtime dosing because of the sedating effects. The maximum dosage recommended for outpatients is 400 mg/day, although for inpatients with more severe depression, dosages up to 600 mg/day have been used. When trazodone is prescribed as a hypnotic agent, the usual dose is 50 mg at bedtime, although some patients may require as little as 25 mg or as much as 200–300 mg.

## Side Effects and Toxicology

Because of its lack of anticholinergic side effects, trazodone is especially useful for patients with prostatic hypertrophy, closed-angle glaucoma, or severe constipation. Trazodone's propensity to cause sedation is a dual-edged sword. For many patients, the relief from agitation, anxiety, and insomnia can be rapid; for others, including those with psychomotor retardation and low energy, trazodone may not be tolerable.

Trazodone was found to be among the top three medications associated with orthostatic hypotension in patients attending a VA geriatric clinic ([Poon and Braun 2005](#)). More than 200 cases of trazodone-associated priapism have been reported ([Thompson et al. 1990](#)), and the manufacturer estimates that the incidence of any abnormal erectile function is approximately 1 in 6,000 male patients. The risk appears to be greatest during the first month of treatment at low dosages (<150 mg/day). Early recognition of any abnormal erectile function is important and should prompt immediate discontinuation of trazodone treatment.

In overdose situations, trazodone appears to be *relatively* safer than TCAs, MAOIs, and a few of the other second-generation antidepressants, especially when it is the only agent taken. Fatalities are rare, and uneventful recoveries have been reported after ingestion of doses as high as 6,000–9,200 mg ([Ayd 1984](#)). When trazodone overdoses occur, clinicians should carefully monitor for hypotension.

In common with several other sedative-hypnotics, trazodone has the potential to impair driving skills, especially in new users, who have been shown to have an increased risk of motor vehicle crashes. The risk estimate for trazodone is roughly comparable to that of blood alcohol concentration levels of 0.09% ([Hansen et al. 2015](#)).

# Drug-Drug Interactions

Trazodone can potentiate the effects of other central nervous system (CNS) depressants. Patients should be warned about increased drowsiness and sedation when trazodone is combined with other CNS depressants, including alcohol.

The combination of trazodone with an MAOI, as with other antidepressants, should be handled with great caution, although there are case reports of the successful combination of trazodone with an MAOI. Development of the serotonin syndrome has been associated with the combination of trazodone with other proserotonergic agents. Trazodone inhibits the antihypertensive effects of clonidine. Trazodone can cause hypotension, especially orthostatic hypotension, and concomitant administration of trazodone with antihypertensive therapy may require a reduction in the dose of the antihypertensive agent.

Clinically significant cases of suspected trazodone-warfarin interactions have been described.

---

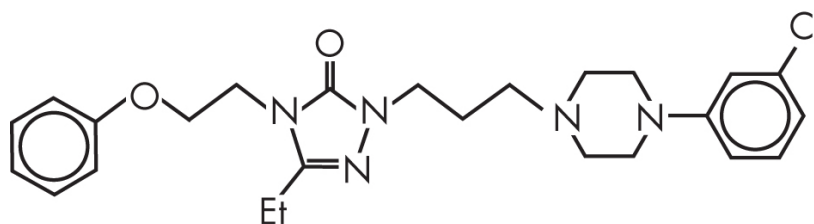
## Nefazodone

---

### History and Discovery

Trazodone's sedative properties and association with orthostatic hypotension inspired an effort to discover a modified molecule that would possess a more desirable pharmacological profile. This led to the development of nefazodone ([Figure 15-2](#)), which became available in the

United States in 1994. Nefazodone and trazodone share a common active metabolite.



**FIGURE 15-2.** Chemical structure of nefazodone.

In 2004, the manufacturer of Serzone (nefazodone) announced that it was discontinuing the drug's sale in the United States, citing declining sales. The drug had been banned in many countries because of its association with liver toxicity, and lawsuits against that manufacturer and the FDA had been initiated in this country. Nefazodone continues to be available in the United States as a generic medication.

## Pharmacological Profile

Nefazodone is a 5-HT<sub>2</sub> receptor antagonist and a weak inhibitor of 5-HT and NE reuptake ([Figure 15-2](#)). It has little affinity for  $\alpha_2$ -adrenergic,  $\beta$ -adrenergic, or serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) receptors, and its affinity for the  $\alpha_1$ -adrenergic receptor is less than that of trazodone. Nefazodone is inactive at most other receptor-binding sites ([Taylor et al. 1986](#)).

Nefazodone demonstrates several of the classic preclinical characteristics of antidepressants. In humans,

nefazodone does not suppress REM sleep, in contrast to most other antidepressants ([Sharpley et al. 1996](#)).

## Pharmacokinetics and Disposition

Nefazodone is rapidly and completely absorbed and is then extensively metabolized, resulting in a low (about 20%) and variable absolute bioavailability. The plasma half-life is only 2–4 hours. Nefazodone has three active metabolites: triazole dione, hydroxynefazodone, and mCPP. Triazole dione is a specific 5-HT<sub>2</sub> receptor antagonist with weaker affinity for that receptor than the parent compound and no appreciable effects on 5-HT reuptake. With a plasma half-life of 18 hours, triazole dione predominates in the plasma, occurring at concentrations approaching four times that of the parent compound. Hydroxynefazodone has affinities for the 5-HT<sub>2</sub> receptor and 5-HT reuptake site that are similar to those of the parent compound. Its plasma half-life is between 1.5 and 4 hours, and at steady state, plasma concentrations are approximately 40% of those of the parent compound. mCPP is a direct agonist at the 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, and serotonin<sub>3</sub> (5-HT<sub>3</sub>) receptors, with one order of magnitude higher affinity for 5-HT<sub>2C</sub> receptors. mCPP has a plasma half-life of 4–8 hours, and its plasma concentrations are only 7% of those seen with the parent compound ([DeVane et al. 2002](#)). However, the ratios of mCPP to nefazodone concentrations in the brain are 47:1 and 10:1 in the mouse and rat, respectively. Brain concentrations of hydroxynefazodone in the rat are less than 10% of those in plasma, suggesting very poor blood–brain barrier penetration. Thus, despite its relatively lower plasma concentrations, mCPP has substantial presence in the brain,



whereas the in vivo activity of hydroxynefazodone may be mostly the result of its biotransformation to mCPP ([Nacca et al. 1998](#)).

Nefazodone has nonlinear kinetics, which results in greater than proportional mean plasma concentrations with higher doses. Nefazodone is extensively (99%) but loosely protein bound ([Bristol-Myers Squibb 2003](#)). In patients with hepatic cirrhosis, single-dose nefazodone and hydroxynefazodone levels are about twice as high as in healthy volunteers, but the difference decreases to approximately 25% at steady state. Exposure to mCPP is about two- to threefold greater in patients with cirrhosis, and exposure to triazole dione is similar after a single dose and at steady state ([Barbhaiya et al. 1995](#)).

## Mechanism of Action

The mechanism of action of nefazodone is poorly understood. The manufacturer has indicated that nefazodone antagonizes 5-HT<sub>2</sub> receptors and also inhibits neuronal uptake of both 5-HT and NE ([Bristol-Myers Squibb 2003](#)). Several reviews refer to nefazodone as a “dual acting” antidepressant, suggesting that it enhances both serotonergic and noradrenergic neurotransmission via uptake blockade. Although nefazodone has similar effects on the 5-HT and NE transporters, this observation is potentially misleading. Nefazodone’s inhibition of NE reuptake is weaker than that of the SSRI fluoxetine and is approximately three orders of magnitude weaker than what is seen with conventional NE reuptake inhibitors. Furthermore, nefazodone’s inhibition of 5-HT reuptake is nearly identical to that of desipramine and more than 100-

fold less than that of fluoxetine ([Bolden-Watson and Richelson 1993](#)). Thus, the “dual action” of nefazodone refers to minimal, albeit equal, effects on 5-HT and NE reuptake inhibition.

In humans, therapeutic doses of nefazodone do not cause sustained 5-HT uptake inhibition at the platelet 5-HTT ([Narayan et al. 1998](#)). The active metabolite m-CCP, which appears to predominate in the brain because of greater penetration of the blood-brain barrier ([Nacca et al. 1998](#)), may play an important role in the mechanism of action.

## Indications and Efficacy

In three of four Phase III imipramine- and placebo-controlled studies, nefazodone was found to be an effective antidepressant with similar efficacy to imipramine; in one of these studies, neither active drug had significantly greater efficacy than did placebo. The incidence of premature treatment discontinuation and side effects was higher for the imipramine group than for the nefazodone treatment group ([Rickels et al. 1995](#)). In double-blind studies without placebo control groups, there were no significant differences in the clinical responses to nefazodone and sertraline or paroxetine in outpatients with depression ([Feiger et al. 1996](#)). Hospitalized patients with severe major depressive disorder had higher response rates to nefazodone compared with placebo ([Feighner et al. 1998](#)). In patients with moderate to severe major depression, the efficacy of amitriptyline was clearly superior to that of nefazodone ([Ansseau et al. 1994](#)). [Keller et al. \(2000\)](#) compared nefazodone, cognitive-behavioral therapy (CBT), and a combination of these two treatments in a double-blind

study of patients with chronic major depressive disorder. Each monotherapy yielded a response rate of 48%, whereas the combined treatment had a greater efficacy (73%). When patients who failed to respond to 12 weeks of treatment with either nefazodone or cognitive-behavioral analysis system psychotherapy are then switched to the other treatment, significant symptom improvement is achieved ([Schatzberg et al. 2005](#)). Nefazodone has also been shown to be effective in the continuation phase of treatment in double-blind studies ([Baldwin et al. 2001](#); [Feiger et al. 1999](#)).

In a double-blind, placebo-controlled study, nefazodone was found to be safe and effective in the treatment of depression in patients with alcohol dependence, although it did not add any advantage over psychoeducational group intervention in terms of drinking outcomes ([Roy-Byrne et al. 2000](#)). A double-blind, controlled study found that nefazodone was not efficacious for the treatment of alcohol dependence ([Kranzler et al. 2000](#)). A randomized, placebo-controlled, double-blind multicenter study compared nefazodone versus placebo and CBT versus nondirective group counseling (GC) for relapse prevention in alcohol dependence. Two hundred forty-two male patients received either nefazodone plus GC or CBT or placebo plus GC or CBT. There were no differences among the four groups in cumulative days of abstinence or amount of alcohol consumed during specified time periods during the initial 12-week study phase. After 1 year, the only significant difference among the groups was higher alcohol consumption in the nefazodone plus GC group, raising concerns that nefazodone may potentially increase the risk of relapse ([Wetzel et al. 2004](#)). Other potential clinical applications for nefazodone have been explored, including

treatment of PTSD (for which it is considered a second-line agent) ([Jeffreys et al. 2012](#)); however, nefazodone's current use is relatively limited.

The usual starting dosage of nefazodone is 200 mg/day in two divided doses. The suggested dosage range is 300–600 mg/day. Increases should be in increments of 100–200 mg/day at weekly intervals. The starting dosage in elderly or debilitated patients should be lowered to 100 mg/day, taken in two divided doses, and the rate of titration should be adjusted accordingly ([Bristol-Myers Squibb 2003](#)). [Zajack et al. \(2002\)](#) reported that in studies comparing low-dosage (50–250 mg/day) and high-dosage (100–500 mg/day) nefazodone, better clinical response was obtained in the latter group, and the mean effective dosage ranged from 375 mg/day to 460 mg/day. A lower starting dose should be considered when switching to nefazodone from an SSRI if a full washout has not been completed. Once-daily bedtime dosing appears to be well tolerated and effective.

## Side Effects and Toxicology

In initial clinical trials that included approximately 2,250 patients, side effects more frequently associated with nefazodone than with placebo included dizziness, asthenia, dry mouth, nausea, and constipation ([Fontaine 1993](#)).

[Preskorn \(1995\)](#) found that the total cumulative incidence of treatment-emergent adverse effects for nefazodone was lower than that of imipramine or fluoxetine. The most common placebo-adjusted adverse effects associated with nefazodone were dry mouth, somnolence, dizziness, nausea, constipation, blurred vision, and postural

hypotension. Nefazodone appears to have advantages over SSRIs in terms of treatment-associated sexual dysfunction ([Clayton et al. 2014](#); [Ferguson et al. 2001](#)).

There are now well-publicized concerns regarding the association of nefazodone with liver toxicity and liver failure, including fatalities ([Choi 2003](#); [Voican et al. 2014](#)). In 2001 the manufacturer added a black box warning to the package insert, describing a reported rate of life-threatening liver failure in the United States of 1 case per 250,000–300,000 patient-years of nefazodone treatment. In 2004 Serzone was withdrawn from the U.S. market, following its withdrawal from several international markets. The generic drug remains available in the United States. In a review of 1,338 humans with exposure to nefazodone overdoses, there were no reported deaths. The most common serious clinical effect was hypotension, reported in 1.6% of cases ([Benson et al. 2000](#)).

## Drug–Drug Interactions

The manufacturer of triazolam warns that its concurrent use with nefazodone is contraindicated. Increases in the plasma concentration of digoxin occur with concurrent nefazodone administration. Nefazodone increases the plasma concentrations of terfenadine and loratadine (with associated QTc prolongation), carbamazepine, and cyclosporine.

---

## Conclusion

---

Trazodone was one of the earliest second-generation antidepressants. Its lack of anticholinergic effects provided an advantage over the TCAs for many patients; its sedative properties are helpful for some patients but problematic for others; and orthostatic hypotension is a concern for elderly patients. Nefazodone is related to trazodone, and the two drugs share an active metabolite, mCPP, that may play an important role in their mechanism of action. The risk of serious liver damage led to Serzone's removal from the market in several countries, although generic nefazodone is currently available in the United States.

---

## References

---

- Ansseau M, Darimont P, Lecoq A, et al: Controlled comparison of nefazodone and amitriptyline in major depressive inpatients. *Psychopharmacology (Berl)* 115(1-2):254-260, 1994 7862904
- Ayd FJ Jr: Pharmacology update: which antidepressant to choose, II: the overdose factor. *Psychiatr Ann* 14(3):212-214, 1984
- Baldwin DS, Hawley CJ, Mellors K; CN104-070 Study Group: A randomized, double-blind controlled comparison of nefazodone and paroxetine in the treatment of depression: safety, tolerability and efficacy in continuation phase treatment. *J Psychopharmacol* 15(3):161-165, 2001 11565622
- Barbhaiya RH, Shukla UA, Natarajan CS, et al: Single- and multiple-dose pharmacokinetics of nefazodone in patients with hepatic cirrhosis. *Clin Pharmacol Ther* 58(4):390-398, 1995 7586930
- Benson BE, Mathiason M, Dahl B, et al: Toxicities and outcomes associated with nefazodone poisoning: an

- analysis of 1,338 exposures. *Am J Emerg Med* 18(5):587-592, 2000 10999575
- Bolden-Watson C, Richelson E: Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci* 52(12):1023-1029, 1993 8445992
- Bossini L, Coluccia A, Casolaro I, et al: Off-label trazodone prescription: evidence, benefits and risks. *Curr Pharm Des* 21(23): 3343-3351, 2015 26088119
- Bristol-Myers Squibb: Serzone (nefazodone hydrochloride) tablets [packet insert]. Revised September 2003. Available at: [http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1\\_11\\_Serzone-Label.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1_11_Serzone-Label.pdf). Accessed July 2012.
- Caccia S, Ballabio M, Fanelli R, et al: Determination of plasma and brain concentrations of trazodone and its metabolite, 1-m-chlorophenylpiperazine, by gas-liquid chromatography. *J Chromatogr A* 210(2): 311-318, 1981 7263792
- Choi S: Nefazodone (Serzone) withdrawn because of hepatotoxicity. *CMAJ* 169(11): 1187, 2003 14638657
- Clark NA, Alexander B: Increased rate of trazodone prescribing with bupropion and selective serotonin-reuptake inhibitors versus tricyclic antidepressants. *Ann Pharmacother* 34(9):1007-1012, 2000 10981245
- Clayton AH, Croft HA, Handiwala L: Antidepressants and sexual dysfunction: mechanisms and clinical implications. *Postgrad Med* 126(2):91-99, 2014 24685972
- Condren RM, Cooney C: Use of drugs by Old Age Psychiatrists in the treatment of psychotic and behavioural symptoms in patients with dementia. *Aging Ment Health* 5(3):235-241, 2001 11575062
- Cunningham LA, Borison RL, Carman JS, et al: A comparison of venlafaxine, trazodone, and placebo in major depression. *J Clin Psychopharmacol* 14(2):99-106, 1994 8195464

- DeVane CL, Grothe DR, Smith SL: Pharmacology of antidepressants: focus on nefazodone. *J Clin Psychiatry* 63 (suppl 1):10-17, 2002 11890560
- Feiger A, Kiev A, Shrivastava RK, et al: Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 57 (suppl 2):53-62, 1996 8626364
- Feiger AD, Bielski RJ, Bremner J, et al: Double-blind, placebo-substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. *Int Clin Psychopharmacol* 14(1):19-28, 1999 10221638
- Feighner J, Targum SD, Bennett ME, et al: A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression. *J Clin Psychiatry* 59(5):246-253, 1998 9632036
- Ferguson JM, Shrivastava RK, Stahl SM, et al: Reemergence of sexual dysfunction in patients with major depressive disorder: double-blind comparison of nefazodone and sertraline. *J Clin Psychiatry* 62(1):24-29, 2001 11235924
- Fontaine R: Novel serotonergic mechanisms and clinical experience with nefazodone. *Clin Neuropharmacol* 16 (suppl 3):S45-S50, 1993 8131154
- Gerner RH: Geriatric depression and treatment with trazodone. *Psychopathology* 20 (suppl 1):82-91, 1987 3321134
- Ghanbari R, El Mansari M, Blier P: Sustained administration of trazodone enhances serotonergic neurotransmission: in vivo electrophysiological study in the rat brain. *J Pharmacol Exp Ther* 335(1):197-206, 2010 20647493
- Grippe TC, Gonçalves BS, Louzada LL, et al: Circadian rhythm in Alzheimer disease after trazodone use. *Chronobiol Int* 32(9):1311-1314, 2015 26376345



- Hansen RN, Boudreau DM, Ebel BE, et al: Sedative hypnotic medication use and the risk of motor vehicle crash. *Am J Public Health* 105(8):e64-e69, 2015 26066943
- Haria M, Fitton A, McTavish D: Trazodone. A review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. *Drugs Aging* 4(4):331-355, 1994 8019056
- Hyttel J: Citalopram-pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity. *Prog Neuropsychopharmacol Biol Psychiatry* 6(3):277-295, 1982 6128769
- Jeffreys M, Capehart B, Friedman MJ: Pharmacotherapy for posttraumatic stress disorder: review with clinical applications. *J Rehabil Res Dev* 49(5):703-715, 2012 23015581
- Keller MB, McCullough JP, Klein DN, et al: A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 342(20):1462-1470, 2000 10816183
- Kranzler HR, Modesto-Lowe V, Van Kirk J: Naltrexone vs. nefazodone for treatment of alcohol dependence. A placebo-controlled trial. *Neuropsychopharmacology* 22(5):493-503, 2000 10731624
- Lader M: Recent experience with trazodone. *Psychopathology* 20 (suppl 1):39-47, 1987 3321129
- Martinon-Torres G, Fioravanti M, Grimley EJ: Trazodone for agitation in dementia. *Cochrane Database Syst Rev* (4):CD004990, 2004 15495135
- Mendelson WB: A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry* 66(4):469-476, 2005 15816789
- Nacca A, Guiso G, Fracasso C, et al: Brain-to-blood partition and in vivo inhibition of 5-hydroxytryptamine reuptake and quipazine-mediated behaviour of nefazodone and its

- main active metabolites in rodents. *Br J Pharmacol* 125(7):1617-1623, 1998 9884092
- Narayan M, Anderson G, Cellar J, et al: Serotonin transporter-blocking properties of nefazodone assessed by measurement of platelet serotonin. *J Clin Psychopharmacol* 18(1):67-71, 1998 9472845
- Nierenberg AA, Adler LA, Peselow E, et al: Trazodone for antidepressant-associated insomnia. *Am J Psychiatry* 151(7):1069-1072, 1994 8010365
- Pazzagli M, Giovannini MG, Pepeu G: Trazodone increases extracellular serotonin levels in the frontal cortex of rats. *Eur J Pharmacol* 383(3):249-257, 1999 10594316
- Poon IO, Braun U: High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. *J Clin Pharm Ther* 30(2):173-178, 2005 15811171
- Preskorn SH: Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry* 56 (suppl 6):12-21, 1995 7649968
- Rickels K, Downing R, Schweizer E, Hassman H: Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 50(11):884-895, 1993 8215814
- Rickels K, Robinson DS, Schweizer E, et al: Nefazodone: aspects of efficacy. *J Clin Psychiatry* 56 (suppl 6):43-46, 1995 7649973
- Rosenberg RP: Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. *Ann Clin Psychiatry* 18(1):49-56, 2006 16517453
- Roy-Byrne PP, Pages KP, Russo JE, et al: Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 20(2):129-136, 2000 10770449

- Schatzberg AF: Trazodone: a 5-year review of antidepressant efficacy. *Psychopathology* 20 (suppl 1):48-56, 1987 3321130
- Schatzberg AF, Rush AJ, Arnow BA, et al: Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Arch Gen Psychiatry* 62(5):513-520, 2005 15867104
- Sharpley AL, Williamson DJ, Attenburrow ME, et al: The effects of paroxetine and nefazodone on sleep: a placebo controlled trial. *Psychopharmacology (Berl)* 126(1):50-54, 1996 8853216
- Shopsin B, Cassano GB, Conti L: An overview of new "second generation" antidepressant compounds: research and treatment implications, in *Antidepressants: Neurochemical, Behavioral and Clinical Perspectives*. Edited by Enna SJ, Molick J, Richelson E. New York, Raven, 1981, pp 219-251
- Singh SP, Singh V, Kar N, Chan K: Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry* 197(3):174-179, 2010 20807960
- Smales ET, Edwards BA, Deyoung PN, et al: Trazodone effects on obstructive sleep apnea and non-REM arousal threshold. *Ann Am Thorac Soc* 12(5):758-764, 2015 25719754
- Stryjer R, Rosenczwaig S, Bar F, et al: Trazodone for the treatment of neuroleptic-induced acute akathisia: a placebo-controlled, double-blind, crossover study. *Clin Neuropharmacol* 33(5):219-222, 2010 20838215
- Sulser F: Mode of action of antidepressant drugs. *J Clin Psychiatry* 44(5 Pt 2):14-20, 1983 6406444
- Taylor DP, Smith DW, Hyslop DK, et al: Receptor binding and atypical antidepressant drug discovery, in *Receptor Binding in Drug Research*. Edited by O'Brien RA. New York, Marcel Dekker, 1986, pp 151-165

- Thompson JW Jr, Ware MR, Blashfield RK: Psychotropic medication and priapism: a comprehensive review. *J Clin Psychiatry* 51(10):430-433, 1990 2211542
- van Moffaert M, de Wilde J, Vereecken A, et al: Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. *Int Clin Psychopharmacol* 10(1):3-9, 1995 7622801
- Voican CS, Corruble E, Naveau S, Perlemuter G: Antidepressant-induced liver injury: a review for clinicians. *Am J Psychiatry* 171(4):404-415, 2014 24362450
- Warner MD, Dorn MR, Peabody CA: Survey on the usefulness of trazodone in patients with PTSD with insomnia or nightmares. *Pharmacopsychiatry* 34(4):128-131, 2001 11518472
- Watanabe N: Fluoxetine, trazodone and ritanserin are more effective than placebo when used as add-on therapies for negative symptoms of schizophrenia. *Evid Based Ment Health* 14(1):21, 2011 21266618
- Weisler RH, Johnston JA, Lineberry CG, et al: Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 14(3):170-179, 1994 8027413
- Wetzel H, Szegedi A, Scheurich A, et al; NeVeR Study Group: Combination treatment with nefazodone and cognitive-behavioral therapy for relapse prevention in alcohol-dependent men: a randomized controlled study. *J Clin Psychiatry* 65(10):1406-1413, 2004 15491246
- Zajacka J, McEnany GW, Lusk KM: Antidepressant dosing and switching guidelines: focus on nefazodone. *J Clin Psychiatry* 63 (suppl 1):42-47, 2002 11890564

## CHAPTER 16

### Vortioxetine

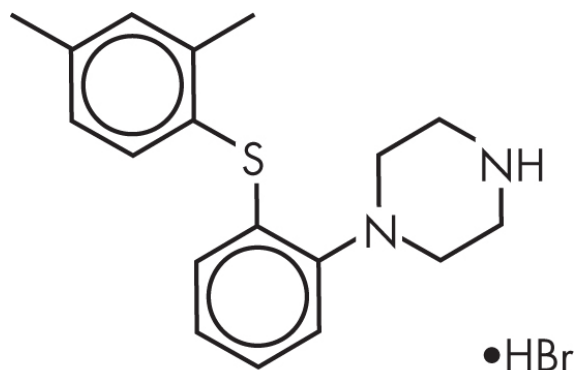
Pierre Blier, M.D., Ph.D.

#### History and Discovery

Vortioxetine, formerly designated Lu AA 21004, was developed by Lundbeck in an attempt to add to a selective serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitor (SSRI) additional properties, namely, 5-HT<sub>1A</sub> and 5-HT<sub>3</sub> receptor affinities ([Bang-Andersen et al. 2011](#)). These pharmacological targets were based on the premises that the antidepressant effect of SSRIs can be enhanced by combining them with a partial 5-HT<sub>1A</sub> agonist and that 5-HT<sub>3</sub> antagonists are antiemetic drugs, nausea being a common side effect of SSRIs ([Sanchez et al. 2015](#)). In 2013, vortioxetine, marketed under the brand name Brintellix, received approval from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of major depressive disorder ([Takeda Pharmaceuticals America 2016](#)). In the United States, at the behest of the FDA, the brand name was subsequently changed to Trintellix to avoid confusion with the anticoagulant drug Brilinta (ticagrelor).

#### Structure-Activity Relations

Vortioxetine is a piperazine derivative, and its chemical name is 1-[2-(2,4-dimethylphenyl)sulfanyl]-phenyl]-piperazine ([Figure 16-1](#)).



**FIGURE 16-1.** Chemical structure of vortioxetine.

The medication is produced in the form of a hydrobromide salt.

---

## Pharmacological Profile

---

Vortioxetine is described as a multimodal serotonin agent because it acts on two types of neuronal elements: the 5-HT transporter and several 5-HT receptor subtypes ([Zohar et al. 2015](#)). Among monoamine transporters, it binds selectively to the 5-HT transporter, but only to the same extent as other SSRIs at its maximum recommended dosage, as shown in positron emission tomography studies in humans ([Areberg et al. 2012](#); [Meyer et al. 2004](#); [Stenkrona et al. 2013](#)). Vortioxetine is a 5-HT<sub>3</sub> antagonist, a full 5-HT<sub>1A</sub> agonist, a 5-HT<sub>7</sub> antagonist, a partial 5-HT<sub>1B</sub> agonist, and a 5-HT<sub>1D</sub> antagonist ([Mørk et al. 2012](#)). On the basis of plasma levels and affinity values, all of these targets could be engaged by vortioxetine to physiologically relevant levels within its usual therapeutic dosage range. Although the clinical significance of these various activities at 5-HT receptors in the presence of lower occupancy of 5-HT transporters has not been determined, synergies between such neuronal elements on neurotransmitter levels have been documented in the brains of laboratory animals ([Sanchez et al. 2015](#)).

---

## Pharmacokinetics and Disposition

---

Vortioxetine is well absorbed from the gastrointestinal tract, and its bioavailability is similar under fasting and fed conditions. It reaches peak plasma concentrations in 7–11 hours and is 98% bound to plasma proteins. Vortioxetine is not a substrate for the permeability glycoproteins, indicating that brain levels will not be affected by possible polymorphisms of these efflux carriers. The terminal half-life of vortioxetine is about 66 hours, and steady-state concentrations are achieved after 2 weeks; consequently, complete elimination requires 2 weeks as well ([Areberg et al. 2014](#); [Bundgaard et al. 2016](#)).

Vortioxetine is extensively metabolized through oxidation and subsequently by glucuronic conjugation. The cytochrome P450 (CYP) 2D6 isoenzyme is the main enzyme catalyzing its catabolism to its major carboxylic acid metabolite, which is pharmacologically inactive. About two-thirds of the inactive metabolites are excreted in the urine, and the last third are excreted in the feces. A very small amount of unchanged vortioxetine is excreted in the urine. No dosage adjustment is necessary in patients with renal impairment or mild to moderate hepatic impairment; however, vortioxetine is not recommended in patients with severe hepatic insufficiency. The plasma levels of vortioxetine are about two times higher in poor metabolizers of CYP2D6 ([Chen et al. 2013](#)).

---

## Indications and Efficacy

---

At present, major depressive disorder is the only approved indication for vortioxetine worldwide. However, vortioxetine's efficacy has also been examined in generalized anxiety disorder. Of the five short-term placebo-controlled studies and one large relapse prevention trial conducted ([Fu et al. 2016](#)), one short-term trial ([Bidzan et al. 2012](#)) and the relapse prevention trial ([Baldwin et al. 2012b](#)) reported positive findings. Although

methodological issues may have been at play in the failed trials, there is not yet enough evidence to proceed with a vortioxetine indication for generalized anxiety disorder.

In contrast, the clinical development program for vortioxetine in major depressive disorder has been successful: thus far, 8 of the 12 placebo-controlled short-term studies, including one in elderly patients, have reported positive results, and a 24-week double-blind relapse prevention study also reported positive findings (Boulenger et al. 2012; Katona et al. 2012; Mahableshwarkar et al. 2015; McIntyre et al. 2014; Sanchez et al. 2015). Five of these studies included an active comparator—venlafaxine in one study, and duloxetine in the other four studies. Among patients participating in the acute studies, 2,080 received a placebo, 140 received 1 mg/day, 308 received 2.5 mg/day, 1,014 received 5 mg/day, 969 received 10 mg/day, 599 received 15 mg/day, and 615 received 20 mg/day (Table 16-1). On the basis of such results, the recommended effective dosage range is 5–20 mg/day. In adults ages 18–65 years, the usual recommended starting dosage is 10 mg/day, usually taken in the morning after a meal for convenience, but it can also be taken at night. In elderly patients, the starting dosage should be 5 mg/day. Although in the controlled studies the dosage was commonly increased after 1 week, in clinical practice a minimum of 2 weeks should elapse before an up-titration is implemented, mainly because this is the interval needed to achieve a steady-state concentration. One open-label study has assessed the safety, tolerability, and maintained effectiveness of vortioxetine in 535 patients with major depressive disorder over 52 weeks (Baldwin et al. 2016).

**TABLE 16-1. Vortioxetine versus placebo/active comparator in acute studies (≤ 8 depression**

Study	Duration (weeks)	Sample size (n)	Vortioxetine dosage (mg/day, n)	Comparator used (n)	Comparator dosage (mg/day)	Study results <sup>a</sup>
Alvarez et al. 2012	6	429	5 (108) 10 (100)	Venlafaxine (112)	225	Positive
Henigsberg et al. 2012	8	560	1 (140) 5 (140) 10 (140)	None	—	Positive
Katona et al. 2012	8	453	5 (157)	Duloxetine (151)	60	Positive
Jacobsen et al. 2015b	8	462	10 (155) 20 (150)	None	—	Positive
Boulenger et al. 2014	8	608	15 (149) 20 (151)	Duloxetine (146)	60	Positive
McIntyre et al. 2014	8	602	10 (195) 20 (207)	None	—	Positive

Note. “>” denotes significantly greater effect.

<sup>a</sup>A **Positive** study is one in which at least one vortioxetine arm statistically separated from placebo on the primary efficacy measure, a **Failed** study is a trial in which treatment group(s) did not separate from placebo and a **Negative** study is one in which the comparator separated from placebo but vortioxetine did not.

Study	Duration (weeks)	Sample size (n)	Vortioxetine dosage (mg/day, n)	Comparator used (n)	Comparator dosage (mg/day)	Study results <sup>a</sup>
Mahableshwarkar et al. 2015c	8	549	10-20 (175)	Duloxetine (187)	60	Positive
Mahableshwarkar et al. 2015a	8	614	15 (147) 20 (152)	Duloxetine (152)	60	Positive
Baldwin et al. 2012b	8	776	2.5 (155) 5 (157) 10 (151)	Duloxetine (155)	60	Failed
Jain et al. 2013	6	597	5 (299)	None	—	Failed
Mahableshwarkar et al. 2015b	8	469	10 (157) 15 (152)	None	—	Failed
Mahableshwarkar et al. 2013	8	611	2.5 (153) 5 (153)	Duloxetine (152)	60	Negative

*Note.* “>” denotes significantly greater effect.

<sup>a</sup>A **Positive** study is one in which at least one vortioxetine arm statistically separated from placebo on the primary efficacy measure, a **Failed** study is a trial in which treatment group(s) did not separate from placebo and a **Negative** study is one in which the comparator separated from placebo but vortioxetine did not.

One double-blind study examined the efficacy and tolerability of vortioxetine in 493 patients with major depressive disorder who had not responded adequately to an SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI) (Montgomery et al. 2014). In this study, patients were asked to decrease their current drug regimen to the minimum effective dosage in the week prior to being randomly assigned to either vortioxetine or the melatonin receptor agonist/5-HT<sub>2B/2C</sub> antagonist agomelatine. Both agents could be titrated to their maximum recommended dosages. The researchers found that vortioxetine was statistically superior to agomelatine.

It is important to mention that three short-term trials examined cognitive function with a battery of tests, one in elderly patients and two with a primary outcome measure being improvement in cognitive function. All three trials yielded positive antidepressant action above placebo (Katona et al. 2012; Mahableshwarkar et al. 2015; McIntyre et al. 2014). Vortioxetine demonstrated a significantly greater effect than placebo on the Digit Symbol Substitution Task (DSST; a pencil-and-paper task that assesses attention, speed of processing, and executive function) in all three studies. In contrast, duloxetine (60 mg/day) showed no significant effect on the DSST versus placebo in the two studies that used this medication as a comparator (Katona et al. 2012; Mahableshwarkar et al. 2015). Furthermore, vortioxetine’s beneficial effect on cognition was deemed through path



analysis to be mostly a direct effect that was independent of the drug's antidepressant effect. One study used more routine daily tasks (the University of California San Diego Performance-Based Skills Assessment), and vortioxetine but not duloxetine separated from placebo, with the difference being almost entirely attributable to a direct effect ([Mahableshwarkar et al. 2015](#)). Taken together, the results of these studies led the European Medicines Agency, but not the FDA, to label vortioxetine for the treatment of cognitive dysfunction associated with major depressive disorder ([McIntyre et al. 2016](#)). There are, however, no studies reporting this putative benefit in patients with other diagnoses.

---

## Side Effects and Toxicity

---

The main side effect of vortioxetine on treatment initiation is nausea, which occurs at about the same rate as with SSRIs and SNRIs, generally in about a quarter to a third of patients ([Citrome 2014](#)). This finding is somewhat surprising because vortioxetine is a potent 5-HT<sub>3</sub> receptor antagonist, which should prevent any nausea resulting from 5-HT reuptake inhibition. However, nausea can be produced by a variety of chemical actions, including opioid and dopamine receptor activation and, importantly, 5-HT<sub>1A</sub> receptor agonism (as is the case with the 5-HT<sub>1A</sub> receptor agonist buspirone). The latter effect is likely responsible for the transient nausea reported during the initial 2 weeks of vortioxetine administration, given the drug's potent 5-HT<sub>1A</sub> receptor agonism. This side effect led to treatment discontinuation in 1%–4% of subjects and appeared to be dose dependent ([Baldwin et al. 2016](#)).

Apart from gastrointestinal side effects, other side effects were generally not markedly different from those reported in the placebo group. Overall, discontinuation due to treatment-emergent adverse events was dose dependent and was between 4.5% and 8.5%, reaching the same level as with 60 mg/day of duloxetine, the placebo rate being 3.5% ([Baldwin et al. 2016](#)). When side effects are problematic, vortioxetine should be withheld for 3 days (given its long half-life) and restarted at half the previous daily dosage.

Vortioxetine has not been found to produce clinically meaningful effects on body weight in short-term and long-term clinical studies. It was not associated with an increased incidence of insomnia or daytime somnolence above the placebo level, in contrast to venlafaxine, which produced greater rates of insomnia, and duloxetine, which produced greater rates of somnolence. There are no significant discontinuation symptoms associated with abrupt cessation of vortioxetine, as expected from its long terminal half-life.

Sexual dysfunction is a classic side effect of drugs that potently inhibit the 5-HT transporter. For patients receiving vortioxetine 5 mg/day or 10 mg/day, rates of sexual dysfunction (as measured on the Arizona Sexual Experiences Scale) did not differ from rates for patients receiving placebo; however, for patients receiving vortioxetine 20 mg/day, rates of sexual dysfunction were equivalent to rates for patients receiving duloxetine 60 mg/day ([Baldwin et al. 2016](#)). These results are consistent with the lower occupancy of the 5-HT transporter with vortioxetine at dosages lower than 20 mg/day, which is about the same as with duloxetine 60 mg/day (i.e., 80%; [Takano et al. 2006](#)). In one study, 477 patients with major depressive disorder who were responding to paroxetine, sertraline, or citalopram but were experiencing treatment-emergent sexual dysfunction were switched to either vortioxetine or escitalopram (dosages for both drugs: 10 mg/day or 20 mg/day) ([Jacobsen et al. 2015a](#)). As measured by the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14), vortioxetine-treated patients showed

significant improvements in comparison with escitalopram-treated patients on four of five dimensions and all three phases of sexual functioning assessed by the CSFQ-14. Although the absolute difference between the two groups was significant, it is important to note that three-quarters of the patients receiving vortioxetine were taking the higher dosage (20 mg/day).

No cases of vortioxetine overdose have been reported in the literature. A supratherapeutic dosage of 40 mg/day for 14 days did not produce clinically relevant electrocardiography or hemodynamic changes (i.e., QTc prolongation of 5 milliseconds) (Wang et al. 2013).

---

## Drug-Drug Interactions

---

Vortioxetine must never be coadministered with a monoamine oxidase inhibitor (MAOI). Before a patient is started on vortioxetine, there must be an elimination period of 14 days for an irreversible MAOI or 2 days for the reversible MAOI moclobemide. Similarly, a 14-day elimination period for vortioxetine is necessary before initiating either an irreversible MAOI or moclobemide.

Vortioxetine is neither an inhibitor nor an inducer of any metabolic enzymes. Consequently, it will not alter the levels of other medications through metabolic interference. Complete inhibitors of CYP2D6, such as fluoxetine and paroxetine, as well as moderate inhibitors, such as bupropion and duloxetine, will approximately double the exposure (area under the curve) to vortioxetine. These interactions are expected to occur mainly in switch situations, which are discussed in the following section. In such concomitant regimens, the vortioxetine dosage should be reduced by half (D'Empaire et al. 2011; Hvenegaard et al. 2012).

Triptans used in the treatment of migraines may be less effective in the presence of vortioxetine. This class of agents acts mainly by activating 5-HT<sub>1D</sub> receptors, whereas vortioxetine is a 5-HT<sub>1D</sub> receptor antagonist. However, because vortioxetine's affinity for the 5-HT<sub>1D</sub> receptor is very low compared with its affinities for other 5-HT receptor subtypes (Mørk et al. 2012), the dampened activity of triptans may not occur with lower dosages of vortioxetine.

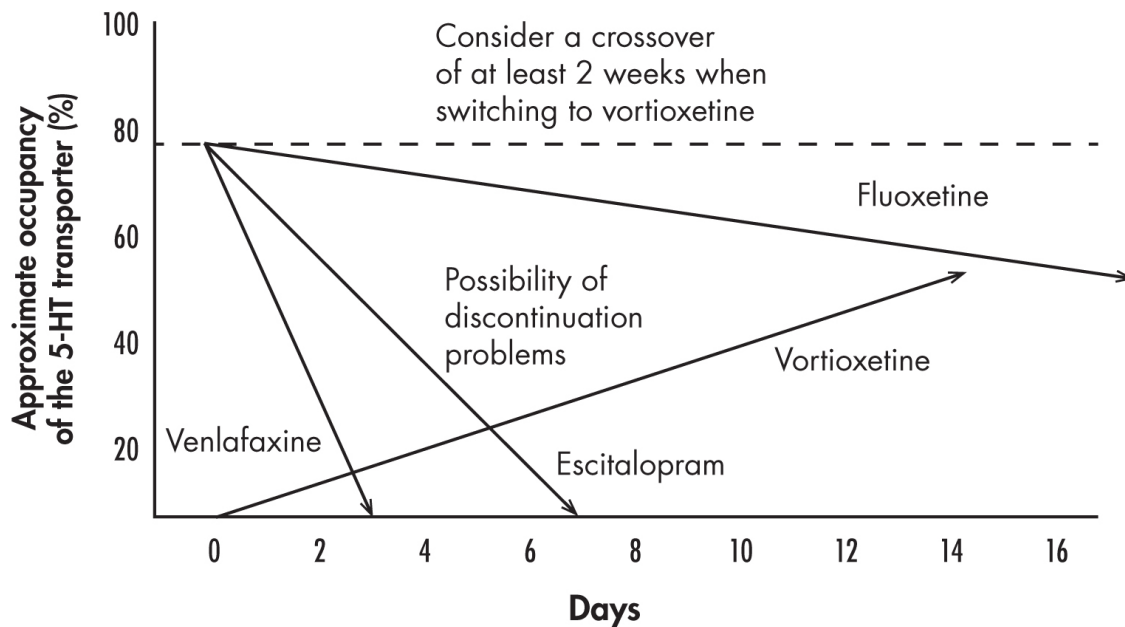
---

## Switching Strategies for Vortioxetine

---

Despite an extensive clinical program, there are only two studies reported on switching to vortioxetine from SSRIs and SNRIs (Jacobsen et al. 2015a; Montgomery et al. 2014). Although patients seemed to tolerate the transition to vortioxetine well, in clinical practice the switch process has been more problematic. It is likely that premature discontinuations of vortioxetine stem more from an abrupt, or a too-rapid, dosage decrease of the SSRI or SNRI than from the effects of vortioxetine itself (Rosenbaum and Zajecka 1997). As illustrated in Figure 16-2, SSRIs or SNRIs are eliminated within several days, thereby rapidly decreasing the occupancy of the 5-HT transporters, but vortioxetine steady-state plasma concentrations are achieved only after 2 weeks, producing a receptor occupancy of about 60% at 10 mg/day and 80% at 20 mg/day. Consequently, discontinuation symptoms could occur during a rapid switch that could be exacerbated by the potent 5-HT<sub>1A</sub> agonistic profile of vortioxetine. Therefore, implementation of a gradual crossover strategy

is recommended when switching a patient from SSRIs or SNRIs to vortioxetine. One exception would be a switch from fluoxetine, because of its long half-life. However, because fluoxetine is a CYP2D6 inhibitor, the initial dosage of vortioxetine should be 5 mg/day, and the dosage should be gradually increased as fluoxetine is slowly eliminated.



**FIGURE 16-2.** Relationship between occupancy of the serotonin transporter by various drugs used to treat depression and minimum time following their discontinuation and the introduction of vortioxetine.

The lines represent the decrease of serotonin (5-hydroxytryptamine [5-HT]) transporter occupancy following an abrupt cessation of the selective serotonin reuptake inhibitors escitalopram and fluoxetine and the serotonin-norepinephrine reuptake inhibitor venlafaxine in comparison with the rise of 5-HT transporter occupancy following the initiation of the multimodal agent vortioxetine at a dosage of 5–10 mg/day. When most 5-HT reuptake inhibitors (with the exception of fluoxetine) are discontinued abruptly before starting vortioxetine, discontinuation phenomena may be triggered, leading to an apparent intolerance of vortioxetine. Therefore, the previous medication should be gradually decreased while vortioxetine levels are building up.

## Conclusion

Vortioxetine is a multimodal serotonergic agent that inhibits the 5-HT transporter, albeit to a lesser extent than other SSRIs, and has a variety of actions at five 5-HT receptor subtypes. Its only approved indication is for the treatment of major depressive disorder. Although it may produce as much mild to moderate nausea as SSRIs on treatment initiation, this effect is generally transient and seldom leads to treatment discontinuation. At dosages of 10 mg/day or less, vortioxetine is expected to produce less sexual dysfunction than SSRIs and SNRIs. Vortioxetine does not impact the cardiovascular system, even at twice its maximum recommended dosage. Vortioxetine will not alter the levels of other medications because it is not a hepatic enzyme inducer or inhibitor. It is still too early to determine vortioxetine's role in treatment-resistant depression. However, in

some patients with major depressive disorder, vortioxetine may exert a beneficial action on cognitive functioning.

---

## References

---

- Alvarez E, Perez V, Dragheim M, et al: A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol* 15(5):589–600, 2012 21767441
- Areberg J, Luntang-Jensen M, Søgaaard B, et al: Occupancy of the serotonin transporter after administration of Lu AA21004 and its relation to plasma concentration in healthy subjects. *Basic Clin Pharmacol Toxicol* 110(4):401–404, 2012 21985522
- Areberg J, Petersen KB, Chen G, Naik H: Population pharmacokinetic meta-analysis of vortioxetine in healthy individuals. *Basic Clin Pharmacol Toxicol* 115(6):552–559, 2014 24766668
- Baldwin DS, Loft H, Dragheim M: A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *Eur Neuropsychopharmacol* 22(7):482–491, 2012a 22209361
- Baldwin DS, Loft H, Florea I: Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. *Int Clin Psychopharmacol* 27(4):197–207, 2012b 22475889
- Baldwin DS, Chrones L, Florea I, et al: The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. *J Psychopharmacol* 30(3):242–252, 2016 26864543
- Bang-Andersen B, Ruhland T, Jørgensen M, et al: Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J Med Chem* 54(9):3206–3221, 2011 21486038
- Bidzan L, Mahableshwarkar AR, Jacobsen P, et al: Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. *Eur Neuropsychopharmacol* 22(12):847–857, 2012 22898365
- Boulenger JP, Loft H, Florea I: A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. *J Psychopharmacol* 26(11):1408–1416, 2012 22495621
- Boulenger JP, Loft H, Olsen CK: Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol* 29(3):138–149, 2014 24257717
- Bundgaard C, Eneberg E, Sánchez C: P-glycoprotein differentially affects escitalopram, levomilnacipran, vilazodone and vortioxetine transport at the mouse blood-brain barrier in vivo. *Neuropharmacology* 103:104–111, 2016 26700248
- Chen G, Lee R, Højer AM, et al: Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clin Drug Investig* 33(10):727–736, 2013 23975654
- Citrome L: Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 68(1):60–82, 2014 24165478
- D'Empaire I, Guico-Pabia CJ, Preskorn SH: Antidepressant treatment and altered CYP2D6 activity: are pharmacokinetic variations clinically relevant? *J Psychiatr Pract* 17(5):330–339, 2011 21926528

- Fu J, Peng L, Li X: The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. *Neuropsychiatr Dis Treat* 12(12):951-959, 2016 27143896
- Henigsberg N, Mahableshwarkar AR, Jacobson P, Serenko M, et al: A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry* 73(7):953-959, 2012 22901346
- Hvenegaard MG, Bang-Andersen B, Pedersen H, et al: Identification of the cytochrome P450 and other enzymes involved in the in vitro oxidative metabolism of a novel antidepressant, Lu AA21004. *Drug Metab Dispos* 40(7):1357-1365, 2012 22496396
- Jacobsen PL, Mahableshwarkar AR, Chen Y, et al: Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *J Sex Med* 12(10):2036-2048, 2015a 26331383
- Jacobsen PL, Mahableshwarkar AR, Serenko M, et al: A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *J Clin Psychiatry* 76(5):575-582, 2015b 26035185
- Jain R, Mahableshwarkar AR, Jacobson PL, et al: A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol* 16(2):313-321, 2013 22963932
- Katona C, Hansen T, Olsen CK: A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol* 27(4):215-223, 2012 22572889
- Mahableshwarkar AR, Jacobson PL, Chen Y: A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin* 29(3):217-226, 2013 23252878
- Mahableshwarkar AR, Jacobson PL, Chen Y, et al: A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology (Berl)* 232(12):2061-2070, 2015a 25575488
- Mahableshwarkar AR, Jacobson PL, Serenko M, et al: A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. *J Clin Psychiatry* 76(5):583-591, 2015b 26035186
- Mahableshwarkar AR, Zajecka J, Jacobson W, et al: A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology* 40(8):2025-2037, 2015c 25687662
- McIntyre RS, Lophaven S, Olsen CK: A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol* 17(10):1557-1567, 2014 24787143
- McIntyre RS, Harrison J, Loft H, et al: The effects of vortioxetine on cognitive function in patients with major depressive disorder: a meta-analysis of three randomized controlled trials. *Int J Neuropsychopharmacol* Aug 24, 2016 [Epub ahead of print] 27312740
- Meyer JH, Wilson AA, Sagrati S, et al: Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [<sup>11</sup>C]DASB positron emission tomography study. *Am J Psychiatry* 161(5):826-835, 2004 15121647
- Montgomery SA, Nielsen RZ, Poulsen LH, et al: A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. *Hum Psychopharmacol* 29(5):470-482, 2014 25087600

- Mørk A, Pehrson A, Brennum LT, et al: Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp Ther* 340(3):666-675, 2012 22171087
- Rosenbaum JF, Zajecka J: Clinical management of antidepressant discontinuation. *J Clin Psychiatry* 58 (suppl 7):37-40, 1997 9219493
- Sanchez C, Asin KE, Artigas F: Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol Ther* 145:43-57, 2015 25016186
- Stenkrona P, Halldin C, Lundberg J: 5-HTT and 5-HT(1A) receptor occupancy of the novel substance vortioxetine (Lu AA21004). A PET study in control subjects. *Eur Neuropsychopharmacol* 23(10):1190-1198, 2013 23428337
- Takano A, Suzuki K, Kosaka J, et al: A dose-finding study of duloxetine based on serotonin transporter occupancy. *Psychopharmacology (Berl)* 185(3):395-399, 2006 16506079
- Takeda Pharmaceuticals America: TRINTELLIX (vortioxetine) tablets, full prescribing information. Deerfield, IL, Takeda Pharmaceuticals America, Inc., 2016. Available at: <http://general.takedapharm.com/content/file.aspx?filetypecode=BRINTELLIXPI&cacheRandomizer=59fe2b9b-08d3-44bb-a004-e6930f23abb3>. Accessed November 2016.
- Wang Y, Nomikos GG, Karim A, et al: Effect of vortioxetine on cardiac repolarization in healthy adult male subjects: results of a thorough QT/QTc study. *Clin Pharmacol Drug Dev* 2(4):298-309, 2013 27121934
- Zohar J, Stahl S, Moller HJ, et al: A review of the current nomenclature for psychotropic agents and an introduction to the neuroscience-based nomenclature. *Eur Neuropsychopharmacol* 25(12):2318-2325, 2015 26527055

# CHAPTER 17

## Mirtazapine

Alan F. Schatzberg, M.D.

---

### History and Discovery

---

Mirtazapine, originally known as ORG 3770, was first synthesized in the Netherlands by the Department of Medicinal Chemistry of NV Organon ([Kaspersen et al. 1989](#)). First approved for use in major depressive disorder in the Netherlands in 1994, mirtazapine was introduced in the United States in 1996.

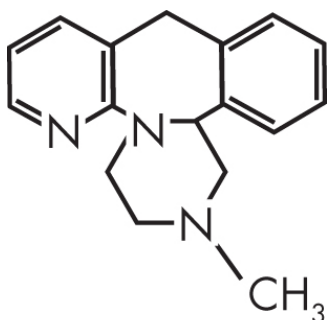
---

### Structure-Activity Relations

---

Mirtazapine ([Figure 17-1](#)) is a member of the piperazinoazepines, a class of chemical compounds that is unrelated to any other class used in the treatment of psychiatric conditions ([Maris et al. 1999](#)). Mirtazapine is also known by its chemical name, 1,2,3,4,10,14b-

hexahydro-2-methylpyrazino[2,1-a]pyridol[2,3-c]benzazepine ([Dahl et al. 1997](#); [Dodd et al. 2000](#)).



---

**FIGURE 17-1.** Chemical structure of mirtazapine.

---

## Pharmacological Profile

---

Mirtazapine is described as a noradrenergic and specific serotonergic antidepressant (NaSSA) ([Holm and Markham 1999](#); [Kent 2000](#); [Nutt 1998](#)). It is a potent serotonin<sub>2</sub> (5-HT<sub>2</sub>), serotonin<sub>3</sub> (5-HT<sub>3</sub>), and central  $\alpha_2$ -adrenergic receptor antagonist ([de Boer 1996](#); [De Boer et al. 1995](#); [Kooyman et al. 1994](#)). Antagonism of 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors results in an increase in serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) receptor-mediated transmission and, thus, a more specific effect on serotonergic transmission, relative to the selective serotonin reuptake inhibitor (SSRI) class of antidepressants ([Bengtsson et al. 2000](#); [Berendsen and Broekkamp 1997](#); [Kent 2000](#)). In addition, because  $\alpha_2$ -adrenergic receptors normally act to inhibit transmission at serotonergic and noradrenergic axon terminals, mirtazapine acts to increase the release of both serotonin (5-HT) and norepinephrine via blockade of central  $\alpha_2$  receptors ([Numazawa et al. 1995](#)).



Mirtazapine has no significant affinity for dopamine receptors, low affinity for muscarinic cholinergic receptors ([de Boer 1996](#)), and high affinity for histamine<sub>1</sub> (H<sub>1</sub>) receptors ([de Boer 1996](#)). Mirtazapine appears to have no effect on 5-HT and dopamine reuptake and only a minimal effect on norepinephrine reuptake ([de Boer 1996](#); [Kent 2000](#)). The drug appears to significantly reduce cortisol levels ([Laakmann et al. 2004](#); [Schmid et al. 2006](#)).

---

## Pharmacokinetics and Disposition

---

### Absorption

Mirtazapine is well absorbed from the gastrointestinal tract, and bioavailability does not appear to be affected by the presence of food in the stomach ([Fawcett and Barkin 1998b](#)). An oral rapidly disintegrating tablet has been available since 2001 ([Benkert et al. 2006](#)).

### Distribution

Mirtazapine appears to be 85% bound to plasma proteins ([Fawcett and Barkin 1998b](#)).

### Metabolism

Mirtazapine is primarily metabolized by the liver via demethylation and hydroxylation, followed by

glucuronidation ([Fawcett and Barkin 1998b](#); [Merck & Co., Inc. 2016](#)). Its major metabolite, desmethyilmirtazapine, is weakly active but is present in lower serum concentrations than the parent compound ([Fawcett and Barkin 1998b](#); [Kent 2000](#)). Mirtazapine lacks both autoinduction and autoinhibition of hepatic cytochrome P450 (CYP) enzymes ([Fawcett and Barkin 1998b](#)). Although in vitro studies do not demonstrate an inhibitory effect, mirtazapine is a substrate for CYP1A2, 2D6, and 3A4 ([Fawcett and Barkin 1998b](#); [Merck & Co., Inc. 2016](#)). Mirtazapine is a mild competitive inhibitor of CYP2D6 ([Barkin et al. 2000](#); [Fawcett and Barkin 1998b](#)). A pharmacogenetic study of CYP2D6 in geriatric depressed patients failed to reveal that slow and intermediate metabolizers demonstrate increased dropout rates due to side effects of the drug ([Murphy et al. 2003b](#)).

These findings suggest that mirtazapine is well tolerated in individuals who are slow metabolizers of CYP2D6.

## Elimination

Mirtazapine and its metabolites are eliminated primarily in the urine (up to 75%) and feces (up to 15%) ([Fawcett and Barkin 1998b](#)). The elimination half-life of mirtazapine is 20–40 hours ([Fawcett and Barkin 1998b](#); [Merck & Co., Inc. 2016](#); [Stimmel et al. 1997](#)). Of note, the clearance of mirtazapine may be affected by hepatic or renal impairment ([Fawcett and Barkin 1998b](#)). The elimination half-life may increase by 30%–40% in patients with hepatic impairment ([Fawcett and Barkin 1998b](#); [Kent 2000](#)). In patients with moderate to severe renal impairment, the clearance of mirtazapine may be decreased by 30%–50%

([Fawcett and Barkin 1998b](#); [Kent 2000](#); [Merck & Co., Inc. 2016](#)).

---

## Indications and Efficacy

---

### Major Depressive Disorder

Pooled data from the 6-week U.S. clinical trials that were part of the new drug application showed that approximately 50% of mirtazapine-treated patients and 20% of placebo-treated patients achieved at least a 50% improvement in scores on the Hamilton Rating Scale for Depression (Ham-D) ([Fawcett and Barkin 1998b](#)).

In a randomized, double-blind, placebo-controlled study of 90 outpatients with a major depressive episode, mirtazapine treatment resulted in clinically significant reductions in Ham-D scores by study endpoint at 6 weeks, although improvement was noted as early as the first week ([Claghorn and Lesem 1995](#)).

A meta-analysis of four randomized, double-blind 6-week studies demonstrated that mirtazapine was as effective as amitriptyline in the treatment of major depressive disorder but had significantly fewer anticholinergic, serotonergic, and cardiovascular adverse effects ([Stahl et al. 1997](#)).

In a randomized, double-blind multicenter study comparing mirtazapine and fluoxetine, both medications were found to be well tolerated in the treatment of major depressive disorder, although mirtazapine was noted to demonstrate a significantly greater improvement in Ham-D scores, beginning in the third week of treatment ([Wheatley et al. 1998](#)).

When mirtazapine was compared with paroxetine in a randomized, double-blind study of 275 patients with major depressive disorder, the two drugs were found to be equally well tolerated and efficacious overall, but mirtazapine-treated patients had significantly lower Ham-D and Hamilton Anxiety Scale (Ham-A) scores at week 1, possibly suggesting a faster onset of therapeutic benefit from mirtazapine ([Benkert et al. 2000](#)).

Similarly, when compared with citalopram in an 8-week randomized, double-blind multicenter study of 270 patients with major depressive disorder, mirtazapine was equally well tolerated and efficacious at study endpoint but was significantly more effective (as assessed by Ham-A, Montgomery-Åsberg Depression Rating Scale [MADRS], and Clinical Global Impression [CGI] Scale scores) at week 2 ([Leinonen et al. 1999](#)).

Of interest, in an 8-week randomized, double-blind multicenter study comparing two antidepressants with both serotonergic and noradrenergic activity, mirtazapine was found to be equal in efficacy to venlafaxine in the treatment of major depressive disorder with melancholic features, although it demonstrated a trend (not statistically significant) toward a higher percentage of responders and remitters ([Guelfi et al. 2001](#)).

In a meta-analysis of 15 studies comparing mirtazapine with an SSRI, [Thase et al. \(2010\)](#) concluded that mirtazapine was significantly more likely than the SSRI to induce remission at weeks 1, 2, 4, and 6. At week 2, the remission rates with mirtazapine were more than 70% higher than those with the SSRI, suggesting more rapid effects.

A study that investigated several antidepressant combinations versus monotherapy found that mirtazapine

coadministered with fluoxetine was significantly more effective than fluoxetine alone. Similarly high rates of remission were observed for mirtazapine coadministered with bupropion and mirtazapine coadministered with venlafaxine ([Blier et al. 2010](#)).

In contrast to the findings of the [Blier et al. \(2010\)](#) study, the National Institute of Mental Health (NIMH)-funded Combination Medication to Enhance Depression Outcomes (CO-MED) study—in which remission and response rates for two antidepressant combinations (escitalopram plus bupropion sustained release (SR) and venlafaxine plus mirtazapine) administered from treatment initiation were compared with those for antidepressant monotherapy (escitalopram plus placebo)—failed to detect differences between the groups ([Rush et al. 2011](#)). Baseline insomnia was not a predictor of response to single versus combination antidepressants ([Sung et al. 2015](#)).

The sleep effects of mirtazapine in major depressive disorder were reported by [Schmid et al. \(2006\)](#). Mirtazapine improved sleep continuity by day 2 of therapy, and the effect was sustained for at least 4 weeks. At day 28, significant increases in slow-wave and low-delta sleep were also observed.

An 8-week open-label trial of mirtazapine in 22 menopausal patients receiving estrogen replacement therapy who had major depressive disorder demonstrated an almost 90% remission rate among the study completers ([Joffe et al. 2001](#)).

## **Patients With Insufficient Response to Selective Serotonin Reuptake Inhibitor Treatment**

In an 8-week open-label study of 103 outpatients with DSM-IV ([American Psychiatric Association 1994](#)) major depressive disorder complicated by lack of response to (or intolerance of) treatment with fluoxetine, paroxetine, or sertraline, approximately one-half of the outpatients demonstrated a 50% reduction in the 17-item Ham-D (Ham-D-17) score when switched to treatment with mirtazapine ([Fava et al. 2001](#)).

In a 4-week study of patients with persistent major depressive disorder despite adequate antidepressant monotherapy, augmentation with mirtazapine resulted in a 45% remission rate, compared with a 13% remission rate among patients receiving placebo ([Carpenter et al. 2002](#)). Of note, in this study there were no significant differences in side effects between drug and placebo ([Carpenter et al. 2002](#)).

In level 3 of the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial, mirtazapine was compared with nortriptyline in patients whose symptoms had not responded to two previous consecutive antidepressant trials ([Fava et al. 2006](#)). Level 1 of STAR\*D employed citalopram; level 2 employed a switch to another drug or augmentation. Nortriptyline produced higher remission rates than did mirtazapine (19.8% vs. 12.3%); however, the difference was not statistically significant.

## **Patients With Depression and Sexual Dysfunction**

In an open-label study of 103 patients with depression treated with mirtazapine, 54% of patients who had reported poor or very poor sexual functioning during prior

treatment with an SSRI described an improvement in sexual functioning by study endpoint ([Fava et al. 2001](#)).

Similarly, [Gelenberg et al. \(2000\)](#) reported that 58% of patients with prior SSRI-induced sexual dysfunction had a return of normal sexual functioning when they switched to treatment with mirtazapine.

In contrast, augmentation with mirtazapine was no more effective than placebo augmentation in reversing SSRI-associated sexual side effects in patients with fluoxetine-associated sexual dysfunction ([Michelson et al. 2002](#)).

## **Depression in Elderly Patients**

In a 6-week study of 150 outpatients (ages 55–80 years) with moderate to severe depression, mirtazapine was found to be effective and well tolerated ([Halikas 1995](#)). Half of the mirtazapine-treated patients and 35% of the placebo-treated patients demonstrated at least a 50% reduction in Ham-D score ([Halikas 1995](#)). In another blinded study, mirtazapine was significantly more effective than paroxetine at weeks 1, 2, 3, and 6, but not at week 8, in subjects older than 65 years ([Schatzberg et al. 2002](#)). Differences were observed primarily on measures of anxiety and sleep. Apolipoprotein epsilon 4 (*ApoE-ε4*) carrier status predicted a positive response to mirtazapine ([Murphy et al. 2003a](#)).

The oral disintegrating tablet formulation of mirtazapine has been studied in elderly patients and appears to be well tolerated ([Nelson et al. 2007](#); [Varia et al. 2007](#)).

## **Patients With Comorbid or Primary Symptoms of Anxiety**

Meta-analyses of placebo-controlled studies of patients with depression and associated symptoms of anxiety have demonstrated that mirtazapine-treated patients exhibit significantly greater improvement in symptoms of anxiety compared with placebo-treated patients ([Fawcett and Barkin 1998a](#); [Nutt 1998](#)), beginning as early as the first week of treatment ([Fawcett and Barkin 1998a](#)).

In an 8-week open-label study of 10 patients with major depressive disorder and comorbid generalized anxiety disorder, mirtazapine treatment resulted in significant decreases in Ham-D and Ham-A scores, with improvement beginning as early as the first week of treatment ([Goodnick et al. 1999](#)).

## Dysthymia

In a 10-week open-label trial of the use of mirtazapine in 15 patients with DSM-IV dysthymic disorder, 8 patients demonstrated at least a 40% reduction in Ham-D scores, and 4 of these 8 patients showed symptom remission by study endpoint ([Dunner et al. 1999](#)).

## Social Anxiety Disorder (Social Phobia)

Mirtazapine was compared with placebo in a 10-week double-blind comparison study in 66 women with social phobia. Mirtazapine appeared to separate from placebo on several primary measures of social phobia symptoms ([Muehlbacher et al. 2005](#)).



# Generalized Anxiety Disorder

In an open-label trial of mirtazapine treatment in 44 adult patients with generalized anxiety disorder, response criteria were achieved in 80% of patients ([Gambi et al. 2005](#)). Controlled trial data are not available.

# Obsessive-Compulsive Disorder

[Koran et al. \(2005\)](#) reported on a two-phase study (a 12-week open-label phase followed by an 8-week double-blind discontinuation phase) of mirtazapine (maximum dosage of 60 mg/day) in 30 patients with obsessive-compulsive disorder (OCD). In the 8-week discontinuation phase, mirtazapine was significantly more effective than placebo in preventing symptom recurrence.

Mirtazapine augmentation of citalopram was assessed in 49 nondepressed OCD patients ([Pallanti et al. 2004](#)). Subjects were treated with citalopram plus placebo or citalopram plus mirtazapine under single-blind conditions. Mirtazapine appeared to speed the response to citalopram but not to improve overall response.

# Posttraumatic Stress Disorder

In an 8-week open-label study of 6 patients with severe chronic posttraumatic stress disorder (PTSD), mirtazapine treatment resulted in one-half of the patients demonstrating at least a 50% reduction on the CGI score and significant reductions on scales of PTSD severity ([Connor et al. 1999](#)).

In a 6-week double-blind comparison study, mirtazapine was compared with sertraline in Korean veterans with PTSD ([Chung et al. 2004](#)). At study endpoint, mirtazapine was statistically significantly superior to sertraline on several measures. Efficacy was apparently maintained to 24 weeks ([Kim et al. 2005](#)).

## Alcohol Use Disorder

Mirtazapine was not found to be significantly superior to placebo in reducing alcohol use in a study of men with high alcohol consumption ([de Bejczy and Söderpalm 2015](#)), although there was a suggestion that the drug might be helpful in subjects with a family history of alcohol use disorder.

## Sleep Disorders

Because of its sedating properties in depression, mirtazapine has been studied in patients with breathing-related sleep disorders. In a double-blind crossover study in 7 patients with obstructive sleep apnea, mirtazapine at dosages of 4.5 mg/day and 15 mg/day produced significantly greater reductions (on the order of 46%–52%) in apnea-hypopnea index (AHI) scores in comparison with placebo ([Carley et al. 2007](#)). However, because of concerns regarding weight gain and sedation, the authors concluded that mirtazapine could not at present be recommended as a primary therapy in this disorder.

## Chronic or Recurrent Pain

A number of case reports indicate that mirtazapine could be beneficial in chronic or recurrent pain ([Brannon and Stone 1999](#); [Brannon et al. 2000](#); [Kuiken et al. 2005](#); [Nutt and Law 1999](#)).

In a large observational study conducted in Germany ([Freynhagen et al. 2006](#)) and involving 600 patients with comorbid pain and depression treated with mirtazapine, the drug appeared to reduce pain effectively, with a relatively low-order risk of side effects (7%) at a mean dosage of 35 mg/day.

Mirtazapine at 15–30 mg/day was reported to be effective in a double-blind crossover study in 24 nondepressed patients with chronic tension headaches ([Bendtsen and Jensen 2004](#)). Area under the curve (intensity × duration) for headache was significantly lower for mirtazapine than for placebo.

## Nausea

A case series of 20 patients with breast or gynecological cancer who were treated with mirtazapine demonstrated a significant reduction in symptoms of depression, anxiety, nausea, anorexia, and insomnia in 19 of the patients, as well as a lack of adverse drug interactions with oncology treatment regimens, including chemotherapy ([Thompson 2000](#)).

A 7-week open-label crossover trial of mirtazapine in 20 patients with cancer found significant improvements in mood, anxiety, insomnia, appetite, weight, and pain symptoms by study endpoint ([Theobald et al. 2002](#)).

It has been suggested that mirtazapine could prove to be a safe and effective adjunct to cancer chemotherapy

because of its ability to treat nausea via a 5-HT<sub>3</sub> receptor antagonism effect; insomnia, anorexia, and weight loss via H<sub>1</sub> receptor antagonism; symptoms of depression via enhanced 5-HT and noradrenergic transmission by way of  $\alpha_2$ , 5-HT<sub>2</sub>, and 5-HT<sub>3</sub> receptor blockade; and symptoms of anxiety via 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor antagonism ([Kast 2001](#)). A randomized, double-blind trial reported that the incidence of nausea and vomiting after spinal anesthesia with intrathecal morphine was significantly lower in orthopedic surgery patients who received preoperative mirtazapine (30 mg) than in those who received placebo ([Chang et al. 2010](#)).

A review of seven cases of pregnant patients with treatment-refractory hyperemesis gravidarum and symptoms of depression and anxiety concluded that treatment with mirtazapine produced resolution of symptoms without adverse effects on the newborns ([Saks 2001](#)).

## Vasomotor Symptoms

[Waldinger et al. \(2000\)](#) described four cases in which women (ages between 39 and 60 years) experienced a near-complete resolution of symptoms of hot flushes and perspiration within the first week of treatment with mirtazapine.

## Pediatric Depression and Anxiety

Mirtazapine has been assessed in several trials involving children or adolescents with major depressive disorder or

anxiety disorders. In one trial in 24 adolescents with major depressive disorder, patients responded well to mirtazapine, with no dropouts due to side effects ([Haapasalo-Pesu et al. 2004](#)). In another small open-label trial in 18 patients with social phobia, mirtazapine also demonstrated efficacy ([Mrakotsky et al. 2008](#)). Although there was a very high dropout rate, most of the discontinuations were not due to side effects.

## Pervasive Developmental Disorders

In an open-label study on the use of mirtazapine in 26 patients with DSM-IV pervasive developmental disorders, 35% of subjects demonstrated significant improvement on CGI scores with respect to symptoms of aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia ([Posey et al. 2001](#)).

## Depression in Alzheimer's Disease

[Raji and Brady \(2001\)](#) described three cases of patients with comorbid Alzheimer's dementia (Mini-Mental State Exam [MMSE] scores of 21/30, 11/30, and 18/30) and depressive symptomatology (including weight loss, insomnia, and anxiety) who were treated safely with mirtazapine. The patients demonstrated significant improvements in appetite, weight, sleep, mood, and energy level.

However, in a large-scale trial comparing sertraline (up to 150 mg/day), mirtazapine (up to 45 mg/day), and placebo in Alzheimer's disease patients with depression, there were no differences among the three groups in reduction of

depressive symptoms ([Banerjee et al. 2011](#)). Given these negative findings regarding benefit and the heightened risk of side effects from these drugs, the authors recommended that the current practice of prescribing antidepressants in this patient population be reconsidered.

## Add-On Therapy in Schizophrenia

The utility of mirtazapine in the treatment of the negative symptoms of schizophrenia has been examined in several studies. In a 6-week double-blind, randomized, placebo-controlled trial, the addition of mirtazapine to haloperidol in the treatment of schizophrenia produced statistically significant reductions in Positive and Negative Syndrome Scale (PANSS) scores, as well as in CGI-Severity and CGI-Improvement scores ([Berk et al. 2001](#)). In addition, PANSS negative symptom scores in this study were found to be reduced by 42% in the group of patients who received adjunctive mirtazapine compared with the group who received placebo ([Berk et al. 2001](#)). Furthermore, the improvement in negative symptoms was not correlated with Ham-D scores at study endpoint, suggesting that the effect of mirtazapine on diminution of negative symptoms in schizophrenia was not a result of improvement in mood symptoms ([Berk et al. 2001](#)).

In a subsequent study, [Berk et al. \(2009\)](#) compared mirtazapine (30 mg/day) with placebo add-on in schizophrenia patients being treated with atypical antipsychotics. Mirtazapine's effects on negative symptoms or cognition failed to separate from those of placebo.

Several positive studies have followed the mixed findings of Berk and colleagues. [Abbasi et al. \(2010\)](#) reported that

mirtazapine add-on at 30 mg/day was significantly more effective than placebo in reducing negative symptoms and total PANSS scores in schizophrenia patients being treated with risperidone. Similarly, [Cho et al. \(2011\)](#) noted that mirtazapine augmentation separated from placebo in improving negative symptoms and cognition in patients undergoing treatment with risperidone. Neuropsychological testing results likewise showed significantly greater improvement with mirtazapine. [Stenberg et al. \(2010\)](#) reported that patients who were not sufficiently improved on first-generation antipsychotics showed significantly greater improvement in cognition with mirtazapine than with placebo.

A meta-analysis examining the safety and efficacy of adjunctive antidepressants for cognitive impairment in schizophrenia included four studies of mirtazapine. In this investigation, statistically significant but minimal clinical effects were noted for all drugs ([Vernon et al. 2014](#)).

## Akathisia

[Poyurovsky et al. \(2003, 2006\)](#) conducted two double-blind, placebo-controlled studies of mirtazapine treatment of antipsychotic-induced akathisia in patients with schizophrenia. In the first study ([Poyurovsky et al. 2003](#)), mirtazapine 15 mg/day was compared with placebo in 26 patients. The drug was significantly superior to placebo. In the second study ([Poyurovsky et al. 2006](#)), mirtazapine 15 mg/day was compared with propranolol 80 mg/day or placebo in 90 patients. Both drugs separated from placebo, but propranolol was associated with clinically significant bradycardia and hypotension.

---

## Side Effects and Toxicology

---

In a double-blind, placebo-controlled study of outpatients with depression, the most commonly reported side effects associated with mirtazapine treatment were somnolence, increased appetite, and weight gain ([Claghorn and Lesem 1995](#)).

In a review of data from the clinical development program for mirtazapine, the only adverse effects that occurred at a higher incidence with mirtazapine versus placebo were excessive sedation, increased appetite, weight gain, and dry mouth ([Montgomery 1995](#)). The authors noted that these side effects were typically mild and transient in nature and that they diminished over time even when dosages were increased ([Montgomery 1995](#)).

Side effects typical of SSRIs, such as nausea, diarrhea, and sexual dysfunction, appear to occur less frequently in patients treated with mirtazapine ([Boyarsky et al. 1999](#); [Farah 1998](#); [Montgomery 1995](#); [Stimmel et al. 1997](#)).

Mirtazapine appears to be well tolerated in elderly patients. The side effects most commonly reported—including somnolence, increased appetite, weight gain, and dry mouth—are of the same type as those reported in younger adults ([Fawcett and Barkin 1998b](#); [Halikas 1995](#)). In a large study of 170,000 psychiatric inpatients in German-speaking countries, mirtazapine was found to be associated with significantly fewer cardiovascular adverse events compared with all other antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and SSRIs) ([Spindelegger et al. 2014](#)).



Mirtazapine appears to have a very low propensity to cause clinically relevant laboratory abnormalities, such as transient elevations in liver enzymes (which occur in about 2% of patients) and severe neutropenia (in 0.1%) ([Claghorn and Lesem 1995](#); [Fawcett and Barkin 1998b](#); [Kent 2000](#); [Montgomery 1995](#)).

Mirtazapine appears to have no clinically significant effects on seizure threshold or on the cardiovascular system ([Claghorn and Lesem 1995](#); [Fawcett and Barkin 1998b](#); [Kent 2000](#); [Montgomery 1995](#)).

Of note, the noradrenergic effects of mirtazapine appear to be dose dependent and increase significantly at dosages >15 mg/day. Consistent with this pattern, the sedation associated with mirtazapine's affinity for H<sub>1</sub> receptors and typically experienced at dosages of ≤15 mg/day may be counteracted by enhancement of noradrenergic neurotransmission via increased dosages of ≥30 mg/day ([Claghorn and Lesem 1995](#); [Kent 2000](#)). It is likewise hypothesized that the risk of weight gain with mirtazapine is diminished at dosages ≥30 mg/day ([Barkin et al. 2000](#); [Fawcett and Barkin 1998b](#)). However, a recent meta-analysis indicated that mirtazapine was associated with considerable weight gain (average of 1.5 kg) in the randomized clinical trials ([Domecq et al. 2015](#)).

## Use During Pregnancy and Lactation

A study conducted across six countries ([Djulus et al. 2006](#)) assessed the risk associated with exposure to mirtazapine during pregnancy. Birth outcomes were examined for three groups: pregnant women taking mirtazapine, disease-matched pregnant women taking other antidepressants,

and pregnant women exposed to nonteratogens. There were approximately 100 patients per group. The rate of spontaneous abortions in the mirtazapine group (19%) was similar to that in the other antidepressant group (17%) and in the nonteratogen control group (11%). The rate of prematurity was significantly higher in the mirtazapine group (10%) versus the nonteratogen group (2%). The prematurity rate in the group taking other antidepressants was 7%. The rate of major malformations was not elevated in the mirtazapine group.

In a study of 8 women taking mirtazapine while breast feeding, concentrations of mirtazapine or desmethylmirtazapine were measured in milk and plasma ([Kristensen et al. 2007](#)). Low infant doses were observed, leading the authors to conclude that the drug is safe for lactating women who breast feed.

## Overdose

Mirtazapine appears to be safe in overdose. In one report ([Holzbach et al. 1998](#)), the cases of 2 patients who had overdosed with 30-50 times the average daily dose of mirtazapine were presented. In each case, the patient recovered fully and without any complications.

Symptoms reported in cases of mirtazapine overdose include disorientation, drowsiness, impaired memory, and tachycardia ([Fawcett and Barkin 1998b](#); [Kent 2000](#); [Montgomery 1995](#); [Stimmel et al. 1997](#)).

A review of 117 mirtazapine overdoses (average ingestion: 450 mg) in Scotland revealed the adverse consequences to be relatively mild ([Waring et al. 2007](#)).

Decreased consciousness was seen in 27% of subjects; 30% demonstrated tachycardia.

A more recent study of overdoses seen at six general hospitals in the United Kingdom between 2000 and 2006 indicated that mirtazapine was of intermediate toxicity between tricyclic antidepressants and venlafaxine, on the one hand, and SSRIs, on the other ([Hawton et al. 2010](#)). Another study of 239,000 patients in the United Kingdom reported that mirtazapine was significantly more likely than citalopram to be associated with suicide, attempted suicide, or self-harm; however, the number of events was low ([Coupland et al. 2015](#)). Trazodone and venlafaxine also were associated with more overdose events. That mirtazapine and trazodone—two sedating antidepressants often prescribed for depressed patients with comorbid sleep problems—were both noted to be associated with suicidal behavior raises the possibility that baseline insomnia, rather than specific drug effects, might explain at least some of the increased risk of suicide attempts.

---

## Drug-Drug Interactions

---

In vitro data suggest that mirtazapine is unlikely to have clinically significant effects on the metabolism of drugs by CYP enzymes ([Barkin et al. 2000](#); [Fawcett and Barkin 1998b](#); [Kent 2000](#)). Analyses of data from the clinical development program for mirtazapine and postmarketing surveillance reveal no clinically relevant drug-drug interactions from the concomitant use of medications such as opiates, anticonvulsants, analgesics, antihypertensives, diuretics, or nonsteroidal anti-inflammatory drugs (NSAIDs)

(Barkin et al. 2000; Fawcett and Barkin 1998b). However, few formal drug interaction studies involving mirtazapine have been conducted (Barkin et al. 2000; Fawcett and Barkin 1998b; Holm and Markham 1999). Of note, a study of elderly patients with depression allowed for patients to be on drugs that are CYP2D6 substrates (Schatzberg et al. 2002). In this study, no increase in side effects was observed in these patients compared with patients who were not taking CYP2D6 substrate agents (Schatzberg et al. 2002).

---

## Conclusion

---

Mirtazapine is derived from the piperazinoazepine class of compounds and, as such, is structurally unrelated to any other psychotropic medications. Mirtazapine also is unique as an antidepressant because of its 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, and  $\alpha_2$  receptor antagonist pharmacodynamic profile, which results in enhancement of noradrenergic and serotonergic transmission. It is an antidepressant that has been shown to be efficacious and well tolerated in the treatment of depression, and there are indications that it may be effective in a number of other medical and psychiatric conditions. Moreover, mirtazapine may offer a more rapid amelioration of symptoms of depression and anxiety compared with other antidepressants. The most common side effects reported with mirtazapine are somnolence, increased appetite, weight gain, and dry mouth. It otherwise appears to be free of many of the adverse effects typical of the SSRIs, especially sexual dysfunction.

Furthermore, mirtazapine appears to be well tolerated and effective in the treatment of geriatric depression and to have benefit as an add-on agent in schizophrenia. In addition, mirtazapine is considered to be relatively safe in overdose, with case reports documenting complete and uncomplicated recovery following ingestion of up to 50 times the average daily dosage. Finally, mirtazapine appears to be devoid of clinically significant drug-drug interactions, although larger formal clinical trials are still needed to verify this.

---

## References

---

- Abbasi SH, Behpournia H, Ghoreschi A, et al: The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. *Schizophr Res* 116(2-3):101-106, 2010 19959338
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Banerjee S, Hellier J, Dewey M, et al: Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 378(9789):403-411, 2011 21764118
- Barkin RL, Schwer WA, Barkin SJ: Recognition and management of depression in primary care: a focus on the elderly. A pharmacotherapeutic overview of the selection process among the traditional and new antidepressants. *Am J Ther* 7(3):205-226, 2000 11317169

- Bendtsen L, Jensen R: Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. *Neurology* 62(10):1706-1711, 2004 15159466
- Bengtsson HJ, Kele J, Johansson J, Hjorth S: Interaction of the antidepressant mirtazapine with  $\alpha_2$ -adrenoceptors modulating the release of 5-HT in different rat brain regions in vivo. *Naunyn Schmiedeberg's Arch Pharmacol* 362(4-5):406-412, 2000 11111835
- Benkert O, Szegedi A, Kohnen R: Mirtazapine compared with paroxetine in major depression. *J Clin Psychiatry* 61(9):656-663, 2000 11030486
- Benkert O, Szegedi A, Philipp M, et al: Mirtazapine orally disintegrating tablets versus venlafaxine extended release: a double-blind, randomized multicenter trial comparing the onset of antidepressant response in patients with major depressive disorder. *J Clin Psychopharmacol* 26(1):75-78, 2006 16415711
- Berendsen HH, Broekkamp CL: Indirect in vivo 5-HT<sub>1A</sub>-agonistic effects of the new antidepressant mirtazapine. *Psychopharmacology (Berl)* 133(3):275-282, 1997 9361334
- Berk M, Ichim C, Brook S: Efficacy of mirtazapine add on therapy to haloperidol in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Int Clin Psychopharmacol* 16(2):87-92, 2001 11236073
- Berk M, Gama CS, Sundram S, et al: Mirtazapine add-on therapy in the treatment of schizophrenia with atypical antipsychotics: a double-blind, randomised, placebo-controlled clinical trial. *Hum Psychopharmacol* 24(3):233-238, 2009 19330802
- Blier P, Ward HE, Tremblay P, et al: Combination of antidepressant medications from treatment initiation for

- major depressive disorder: a double-blind randomized study. *Am J Psychiatry* 167(3):281-288, 2010 20008946
- Boyarsky BK, Haque W, Rouleau MR, Hirschfeld RM: Sexual functioning in depressed outpatients taking mirtazapine. *Depress Anxiety* 9(4):175-179, 1999 10431683
- Brannon GE, Stone KD: The use of mirtazapine in a patient with chronic pain. *J Pain Symptom Manage* 18(5):382-385, 1999 10584463
- Brannon GE, Rolland PD, Gary JM: Use of mirtazapine as prophylactic treatment for migraine headache. *Psychosomatics* 41(2):153-154, 2000 10749956
- Carley DW, Olopade C, Ruigt GS, Radulovacki M: Efficacy of mirtazapine in obstructive sleep apnea syndrome. *Sleep* 30(1):35-41, 2007 17310863
- Carpenter LL, Yasmin S, Price LH: A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry* 51(2):183-188, 2002 11822997
- Chang FL, Ho ST, Sheen MJ: Efficacy of mirtazapine in preventing intrathecal morphine-induced nausea and vomiting after orthopaedic surgery. *Anaesthesia* 65(12):1206-1211, 2010 21182602
- Cho SJ, Yook K, Kim B, et al: Mirtazapine augmentation enhances cognitive and reduces negative symptoms in schizophrenia patients treated with risperidone: a randomized controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* 35(1):208-211, 2011 21095214
- Chung MY, Min KH, Jun YJ, et al: Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. *Hum Psychopharmacol* 19(7):489-494, 2004 15378676
- Claghorn JL, Lesem MD: A double-blind placebo-controlled study of Org 3770 in depressed outpatients. *J Affect Disord* 34(3):165-171, 1995 7560544

- Connor KM, Davidson JRT, Weisler RH, Ahearn E: A pilot study of mirtazapine in post-traumatic stress disorder. *Int Clin Psychopharmacol* 14(1):29–31, 1999 10221639
- Coupland C, Hill T, Morriss R, et al: Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ* 350:h517, 2015 25693810
- Dahl ML, Voortman G, Alm C, et al: In vitro and in vivo studies on the disposition of mirtazapine in humans. *Clinical Drug Investigation* 13(1):37–46, 1997
- de Bejczy A, Söderpalm B: The effects of mirtazapine versus placebo on alcohol consumption in male high consumers of alcohol: a randomized, controlled trial. *J Clin Psychopharmacol* 35(1):43–50, 2015 25517204
- de Boer T: The pharmacologic profile of mirtazapine. *J Clin Psychiatry* 57 (suppl 4): 19–25, 1996 8636062
- De Boer T, Ruigt GS, Berendsen HH: The alpha 2-selective adrenoceptor antagonist org 3770 (mirtazapine, Remeron) enhances noradrenergic and serotonergic transmission. *Human Psychopharmacology: Clinical and Experimental* 10 (suppl 2):S107–S118, 1995
- Djulus J, Koren G, Einarson TR, et al: Exposure to mirtazapine during pregnancy: a prospective, comparative study of birth outcomes. *J Clin Psychiatry* 67(8):1280–1284, 2006 16965209
- Dodd S, Burrows GD, Norman TR: Chiral determination of mirtazapine in human blood plasma by high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl* 748(2):439–443, 2000 11087086
- Domecq JP, Prutsky G, Leppin A, et al: Clinical review: Drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 100(2):363–370, 2015 25590213
- Dunner DL, Hendrickson HE, Bea C, et al: Dysthymic disorder: treatment with mirtazapine. *Depress Anxiety* 10(2):68–72, 1999 10569129



- Farah A: Lack of sexual adverse effects with mirtazapine. Am J Health Syst Pharm 55(20):2195-2196, 1998 9812164
- Fava M, Dunner DL, Greist JH, et al: Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. J Clin Psychiatry 62(6):413-420, 2001 11465517
- Fava M, Rush AJ, Wisniewski SR, et al: A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR\*D report. Am J Psychiatry 163(7):1161-1172, 2006 16816220
- Fawcett J, Barkin RL: A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. J Clin Psychiatry 59(3):123-127, 1998a 9541155
- Fawcett J, Barkin RL: Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. J Affect Disord 51(3):267-285, 1998b 10333982
- Freyenhagen R, Muth-Selbach U, Lipfert P, et al: The effect of mirtazapine in patients with chronic pain and concomitant depression. Curr Med Res Opin 22(2):257-264, 2006 16466597
- Gambi F, De Berardis D, Campanella D, et al: Mirtazapine treatment of generalized anxiety disorder: a fixed dose, open label study. J Psychopharmacol 19(5):483-487, 2005 16166185
- Gelenberg AJ, McGahuey C, Laukes C, et al: Mirtazapine substitution in SSRI-induced sexual dysfunction. J Clin Psychiatry 61(5):356-360, 2000 10847310
- Goodnick PJ, Puig A, DeVane CL, Freund BV: Mirtazapine in major depression with comorbid generalized anxiety

- disorder. J Clin Psychiatry 60(7):446-448, 1999 10453798
- Guelfi JD, Ansseau M, Timmerman L, Kørsgaard S; Mirtazapine-Venlafaxine Study Group: Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol 21(4):425-431, 2001 11476127
- Haapasalo-Pesu KM, Vuola T, Lahelma L, Marttunen M: Mirtazapine in the treatment of adolescents with major depression: an open-label, multicenter pilot study. J Child Adolesc Psychopharmacol 14(2):175-184, 2004 15319015
- Halikas JA: Org 3770 (mirtazapine) versus trazodone: a placebo controlled trial in depressed elderly patients. Human Psychopharmacology: Clinical and Experimental 10 (suppl 2):S125-S133, 1995
- Hawton K, Bergen H, Simkin S, et al: Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry 196(5):354-358, 2010 20435959
- Holm KJ, Markham A: Mirtazapine: a review of its use in major depression. Drugs 57(4):607-631, 1999 10235695
- Holzbach R, Jahn H, Pajonk FG, Mähne C: Suicide attempts with mirtazapine overdose without complications. Biol Psychiatry 44(9):925-926, 1998 9807651
- Joffe H, Groninger H, Soares CN, et al: An open trial of mirtazapine in menopausal women with depression unresponsive to estrogen replacement therapy. J Womens Health Gend Based Med 10(10):999-1004, 2001 11788110
- Kaspersen FM, Van Rooij FA, Sperling EG, Wieringa JH: The synthesis of org 3770 labelled with 3H, 13C and 14C. Journal of Labelled Compounds and Radiopharmaceuticals 27(9):1055-1068, 1989
- Kast RE: Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy. Support Care Cancer

9(6):469-470, 2001 11585276

Kent JM: SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet* 355(9207):911-918, 2000 10752718

Kim W, Pae CU, Chae JH, et al: The effectiveness of mirtazapine in the treatment of post-traumatic stress disorder: a 24-week continuation therapy. *Psychiatry Clin Neurosci* 59(6):743-747, 2005 16401254

Kooyman AR, Zwart R, Vanderheijden PM, et al: Interaction between enantiomers of mianserin and ORG3770 at 5-HT<sub>3</sub> receptors in cultured mouse neuroblastoma cells. *Neuropharmacology* 33(3-4):501-507, 1994 7984289

Koran LM, Gamel NN, Choung HW, et al: Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *J Clin Psychiatry* 66(4):515-520, 2005 15816795

Kristensen JH, Ilett KF, Rampono J, et al: Transfer of the antidepressant mirtazapine into breast milk. *Br J Clin Pharmacol* 63(3):322-327, 2007 16970569

Kuiken TA, Schechtman L, Harden RN: Phantom limb pain treatment with mirtazapine: a case series. *Pain Pract* 5(4):356-360, 2005 17177770

Laakmann G, Hennig J, Baghai T, Schüle C: Mirtazapine acutely inhibits salivary cortisol concentrations in depressed patients. *Ann N Y Acad Sci* 1032:279-282, 2004 15677428

Leinonen E, Skarstein J, Behnke K, et al; Nordic Antidepressant Study Group: Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. *Int Clin Psychopharmacol* 14(6):329-337, 1999 10565799

Maris FA, Dingler E, Niehues S: High-performance liquid chromatographic assay with fluorescence detection for the routine monitoring of the antidepressant mirtazapine and its demethyl metabolite in human

- plasma. J Chromatogr B Biomed Sci Appl 721(2):309-316, 1999 10052704
- Merck & Co., Inc.: REMERON (mirtazapine) tablets, full prescribing information. Whitehouse Station, NJ, Merck & Co., Inc., 2016. Available at: [http://www.merck.com/product/usa/pi\\_circulars/r/remeron/remeron\\_tablets\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/r/remeron/remeron_tablets_pi.pdf). Accessed November 2016.
- Michelson D, Kociban K, Tamura R, Morrison MF: Mirtazapine, yohimbine or olanzapine augmentation therapy for serotonin reuptake-associated female sexual dysfunction: a randomized, placebo controlled trial. J Psychiatr Res 36(3):147-152, 2002 11886692
- Montgomery SA: Safety of mirtazapine: a review. Int Clin Psychopharmacol 10 (suppl 4):37-45, 1995 8930008
- Mrakotsky C, Masek B, Biederman J, et al: Prospective open-label pilot trial of mirtazapine in children and adolescents with social phobia. J Anxiety Disord 22(1):88-97, 2008 17419001
- Muehlbacher M, Nickel MK, Nickel C, et al: Mirtazapine treatment of social phobia in women: a randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 25(6):580-583, 2005 16282842
- Murphy GM, Kremer C, Rodrigues H, Schatzberg AF; Mirtazapine Versus Paroxetine Study Group: The apolipoprotein E epsilon4 allele and antidepressant efficacy in cognitively intact elderly depressed patients. Biol Psychiatry 54(7): 665-673, 2003a 14512205
- Murphy GM Jr, Kremer C, Rodrigues HE, Schatzberg AF: Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 160(10):1830-1835, 2003b 14514498
- Nelson JC, Holden K, Roose S, et al: Are there predictors of outcome in depressed elderly nursing home residents during treatment with mirtazapine orally disintegrating tablets? Int J Geriatr Psychiatry 22(10):999-1003, 2007 17447229

- Numazawa R, Yoshioka M, Matsumoto M, et al: Pharmacological characterization of alpha 2-adrenoceptor regulated serotonin release in the rat hippocampus. *Neurosci Lett* 192(3):161-164, 1995 7566640
- Nutt DJ: Efficacy of mirtazapine in clinically relevant subgroups of depressed patients. *Depress Anxiety* 7 (suppl 1):7-10, 1998 9597345
- Nutt D, Law J: Treatment of cluster headache with mirtazapine. *Headache* 39(8):586-587, 1999 11279976
- Pallanti S, Quercioli L, Bruscoli M: Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: a pilot study. *J Clin Psychiatry* 65(10):1394-1399, 2004 15491244
- Posey DJ, Guenin KD, Kohn AE, et al: A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 11(3):267-277, 2001 11642476
- Poyurovsky M, Epshtein S, Fuchs C, et al: Efficacy of low-dose mirtazapine in neuroleptic-induced akathisia: a double-blind randomized placebo-controlled pilot study. *J Clin Psychopharmacol* 23(3):305-308, 2003 12826992
- Poyurovsky M, Pashinian A, Weizman R, et al: Low-dose mirtazapine: a new option in the treatment of antipsychotic-induced akathisia. A randomized, double-blind, placebo- and propranolol-controlled trial. *Biol Psychiatry* 59(11):1071-1077, 2006 16497273
- Raji MA, Brady SR: Mirtazapine for treatment of depression and comorbidities in Alzheimer disease. *Ann Pharmacother* 35(9):1024-1027, 2001 11573849
- Rush AJ, Trivedi MH, Stewart JW, et al: Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry* 168(7):689-701, 2011 21536692

- Saks BR: Mirtazapine: treatment of depression, anxiety, and hyperemesis gravidarum in the pregnant patient: a report of 7 cases. *Archives of Women's Mental Health* 3(4):165-170, 2001
- Schatzberg AF, Kremer C, Rodrigues HE, Murphy GM Jr; Mirtazapine vs. Paroxetine Study Group: Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 10(5):541-550, 2002 12213688
- Schmid DA, Wichniak A, Uhr M, et al: Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. *Neuropsychopharmacology* 31(4):832-844, 2006 16237393
- Spindelegger CJ, Papageorgiou K, Grohmann R, et al: Cardiovascular adverse reactions during antidepressant treatment: a drug surveillance report of German-speaking countries between 1993 and 2010. *Int J Neuropsychopharmacol* 18(4):pyu080, 2014 25522416
- Stahl S, Zivkov M, Reimitz PE, et al: Meta-analysis of randomized, double-blind, placebo-controlled, efficacy and safety studies of mirtazapine versus amitriptyline in major depression. *Acta Psychiatr Scand Suppl* 391:22-30, 1997 9265948
- Stenberg JH, Terevnikov V, Joffe M, et al: Effects of add-on mirtazapine on neurocognition in schizophrenia: a double-blind, randomized, placebo-controlled study. *Int J Neuropsychopharmacol* 13(4):433-441, 2010 19941694
- Stimmel GL, Dopheide JA, Stahl SM: Mirtazapine: an antidepressant with noradrenergic and specific serotonergic effects. *Pharmacotherapy* 17(1):10-21, 1997 9017762
- Sung SC, Wisniewski SR, Luther JF, et al; COMED Study Team: Pre-treatment insomnia as a predictor of single

- and combination antidepressant outcomes: a CO-MED report. *J Affect Disord* 174:157–164, 2015 25497473
- Thase ME, Nierenberg AA, Vrijland P, et al: Remission with mirtazapine and selective serotonin reuptake inhibitors: a meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression. *Int Clin Psychopharmacol* 25(4):189–198, 2010 20531012
- Theobald DE, Kirsh KL, Holtsclaw E, et al: An open-label, crossover trial of mirtazapine (15 and 30 mg) in cancer patients with pain and other distressing symptoms. *J Pain Symptom Manage* 23(5):442–447, 2002 12007762
- Thompson DS: Mirtazapine for the treatment of depression and nausea in breast and gynecological oncology. *Psychosomatics* 41(4):356–359, 2000 10906359
- Varia I, Venkataraman S, Hellegers C, et al: Effect of mirtazapine orally disintegrating tablets on health-related quality of life in elderly depressed patients with comorbid medical disorders: a pilot study. *Psychopharmacol Bull* 40(1):47–56, 2007 17285095
- Vernon JA, Grudnikoff E, Seidman AJ, et al: Antidepressants for cognitive impairment in schizophrenia—a systematic review and meta-analysis. *Schizophr Res* 159(2–3):385–394, 2014 25240772
- Waldinger MD, Berendsen HH, Schweitzer DH: Treatment of hot flushes with mirtazapine: four case reports. *Maturitas* 36(3):165–168, 2000 11063897
- Waring WS, Good AM, Bateman DN: Lack of significant toxicity after mirtazapine overdose: a five-year review of cases admitted to a regional toxicology unit. *Clin Toxicol (Phila)* 45(1):45–50, 2007 17357381
- Wheatley DP, van Moffaert M, Timmerman L, Kremer CM; Mirtazapine-Fluoxetine Study Group: Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. *J Clin Psychiatry* 59(6):306–312, 1998 9671343

# CHAPTER 18

## Bupropion

David V. Hamilton, M.D., M.A.

Anita H. Clayton, M.D.

---

### History and Discovery

---

Bupropion was discovered 50 years ago when investigators were searching for an antidepressant with a novel mechanism of action and safer side-effect profile compared with the antidepressants available at that time. Synthesized in 1966, this unique compound, different from the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs), was found to have antidepressant activity in animal models that are predictive of antidepressant activity in humans ([Soroko and Maxwell 1983](#)).

Bupropion's mechanism of action is thought to be related to its dual inhibition of norepinephrine and dopamine reuptake and its lack of clinically significant serotonin reuptake inhibition ([Horst and Preskorn 1998](#); [Stahl et al.](#)



2004). Bupropion and selective serotonin reuptake inhibitors (SSRIs) appear to be equally efficacious in the treatment of major depressive disorder (Feighner et al. 1991). The sustained-release formulation of bupropion, approved in 1996, was also shown to be significantly better than placebo in preventing depression relapse (Weihs et al. 2002). Bupropion's tolerability is superior to that of the SSRIs, with less weight gain, less sedation, no withdrawal symptoms upon discontinuation, and minimal sexual side effects (Thase et al. 2005).

In addition to its demonstrated benefit in the treatment of major depressive disorder, bupropion has been found to be effective across a wide range of depressive conditions, subtypes, and comorbidities (Clayton 2007), including depression with concomitant anxiety, depression in the elderly, seasonal depression, and bipolar depression, and also as an augmentation agent in patients with insufficient response to SSRIs. Bupropion's efficacy in other conditions has also been shown in studies of smoking cessation, obesity, attention-deficit/hyperactivity disorder (ADHD), and DSM-IV (American Psychiatric Association 1994) hypoactive sexual desire disorder (HSDD). Overall, bupropion is a unique antidepressant with a broad therapeutic spectrum and a superior tolerability profile.

Bupropion first received U.S. Food and Drug Administration (FDA) approval in 1985 and was on the brink of release when a study by Horne et al. (1988) reported that 4 of 55 subjects with bulimia experienced seizures during treatment with the medication. Further research revealed that the risk of seizures increased with dosage, from a risk of 0.3%–0.4% at a dosage of 450 mg/day to a risk of almost 2% at a dosage of 600 mg/day. Bupropion was reintroduced in 1989 with a maximum recommended

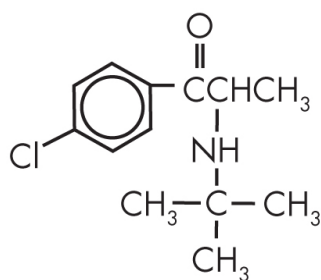
dosage of 450 mg/day ([Davidson 1989](#)). The original immediate-release (IR) formulation of bupropion was dosed three times daily ([GlaxoSmithKline 2016a](#)). In an effort to improve tolerability and safety, a sustained-release (SR) formulation of bupropion, dosed twice daily, was subsequently introduced ([GlaxoSmithKline 2016b](#)), and a once-daily extended-release (XL) formulation became available in 2003 ([Valeant Pharmaceuticals North America 2014](#)).

---

## Structure-Activity Relations

---

Bupropion, 2-(tert-butylamino)-1-(3'-chlorophenyl)propan-1-one, is a monocyclic antidepressant and a member of the aminoketone group ([Figure 18-1](#)). It was designed as a simple chemical structure that in vivo would result in relatively innocuous metabolites ([Mehta 1983](#)). Chemically, bupropion is an organic base with a high degree of both water and lipid solubility, resulting in good systemic absorption. Its relatively benign side-effect profile in comparison with that of tricyclic and tetracyclic antidepressants is due to the absence of heterocyclic rings as well as other common functional groups ([Mehta 1983](#)).



Bupropion

---

**FIGURE 18-1.** Chemical structure of bupropion.

---

## Pharmacological Profile

---

Bupropion inhibits the reuptake of dopamine and norepinephrine by acting as a nonselective inhibitor of the dopamine transporter (DAT) and the norepinephrine transporter (NET). Studies show that bupropion also acts as an antagonist to nicotinic acetylcholine (nACh) receptors. Bupropion does not inhibit monoamine oxidase A or B, nor are its effects mediated by serotonin ([Ascher et al. 1995](#)).

Studies have demonstrated that bupropion raises dopamine concentrations by causing a rapid and reversible increase in vesicular dopamine reuptake via cellular redistribution of the vesicular monoamine transporter 2 (VMAT2) protein. By increasing the presynaptic pool of dopamine available for release, the concentration of dopamine in the extracellular space is further augmented, adding to the therapeutic efficacy of this compound ([Dwoskin et al. 2006](#); [Rau et al. 2005](#)).

Although more is known about the dopaminergic effects of bupropion, interaction with the noradrenergic system also plays an important role in the drug's antidepressant activity. Bupropion is a weak competitive inhibitor of norepinephrine; in comparison with imipramine, it is 65 times less potent ([Ferris and Beaman 1983](#)). Research using various cellular expression systems has elucidated the ability of bupropion to interact with specific nACh receptors. Bupropion has been shown to work by noncompetitive inhibition of nACh receptors ([Dwoskin et al. 2006](#)). This action may partially contribute to bupropion's

efficacy not only as an antidepressant but also as an agent to facilitate tobacco cessation.

It has been noted that bupropion shares some structural and neurochemical properties with sympathomimetics and has a phenylethylamine skeleton similar to that of amphetamine. An early study by [Griffith et al. \(1983\)](#) comparing the effects of bupropion and amphetamine in individuals with a history of amphetamine abuse concluded that bupropion had little abuse potential in humans. However, recent reports have described cases in which bupropion was perceived as a psychostimulant by patients with a previous history of cocaine abuse ([Vento et al. 2013](#)). An 11-year review by [Lewis et al. \(2014\)](#) of data from the California Poison Control Center found that 3.6% of all calls to the center regarding bupropion were due to intentional insufflation in order to achieve a psychostimulant effect, with an average dose of 1,500 mg. [Hilliard et al. \(2013\)](#) reported that bupropion is especially valued as a stimulant of abuse in the incarcerated population. These preliminary data point to the need to continue to monitor bupropion users for potential abuse, especially in patient populations that are at increased risk of developing substance use disorders and in those patients with a history of stimulant use disorders.

---

## Pharmacokinetics and Disposition

---

Bupropion is rapidly absorbed in the gastrointestinal tract after oral administration ([Findlay et al. 1981](#); [Jefferson et al. 2005](#)). Absorption has been found to be close to 100%

([Schroeder 1983](#)). After first-pass metabolism, systemic bioavailability of the drug is decreased. Peak plasma levels occur within 2 hours for the IR preparation. As expected, absorption is prolonged for the SR and XL formulations, for which peak plasma concentrations occur at 3 and 5 hours, respectively ([Jefferson et al. 2005](#); [Schroeder 1983](#)). Food does not impair absorption, and protein binding ranges from 82% to 88%, which is not high enough to be of clinical importance ([Jefferson et al. 2005](#)). The elimination half-life for bupropion is 21 ( $\pm 9$ ) hours, and the half-life for hydroxybupropion, the major metabolite of bupropion, is close to 20 ( $\pm 5$ ) hours ([Clayton 2007](#); [Jefferson et al. 2005](#)). Steady state occurs in 7–10 days. Finally, excretion in the urine occurs with 0.5% of the drug unchanged ([Findlay et al. 1981](#); [Jefferson et al. 2005](#)).

Bupropion is extensively metabolized by the liver. The major metabolite, hydroxybupropion, is hydrolyzed by cytochrome P450 (CYP) 2B6 ([Hesse et al. 2000](#); [Kirchheiner et al. 2003](#)). The peak plasma concentration of hydroxybupropion at steady state is four- to sevenfold higher than that of bupropion. Although CYP2B6 is the primary isoenzyme involved in bupropion's metabolism, other isoforms, including 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4, play a small role ([Hesse et al. 2000](#); [Kirchheiner et al. 2003](#)). Bupropion inhibits CYP2D6 and therefore may interfere with drugs that are metabolized by this enzyme, such as desipramine and nortriptyline ([Hesse et al. 2000](#); [Jefferson et al. 2005](#)). A recent study showed that increased levels of estradiol produce a 1.5- to 3-fold increase in CYP2B6 activity, making estradiol as strong an inducer as rifampin ([Dickmann and Isoherranen 2013](#)). Theoretically, this interaction could lead to decreased levels of bupropion and its active metabolite, with worsening therapeutic

outcomes in pregnancy (although such outcomes have not yet been demonstrated).

In examining the pharmacokinetics of bupropion in regard to gender, age, and smoking status, no significant effect has been found, and definitive results have been inconclusive ([Daviss et al. 2006](#); [Hsyu et al. 1997](#); [Jefferson et al. 2005](#)). One study in elderly patients found evidence for an extended half-life of bupropion and for accumulation of metabolites ([Sweet et al. 1995](#)). Because levels of bupropion and its metabolites have been found to be increased in populations with impaired renal and/or hepatic function relative to healthy control subjects ([DeVane et al. 1990](#); [Jefferson et al. 2005](#); [Worrall et al. 2004](#)), dosing should be initiated at lower levels in these patients. [Worrall et al. \(2004\)](#) showed that accumulation of two of the metabolites of bupropion—hydroxybupropion and threohydrobupropion—was significantly elevated in patients with end-stage renal disease compared with matched controls. Other studies found increased levels of both bupropion and hydroxybupropion in patients with hepatic dysfunction ([DeVane et al. 1990](#); [GlaxoSmithKline 2016a, 2016b](#); [Jefferson et al. 2005](#)). These results prompted the manufacturer to recommend that bupropion be used with caution in patients with mild to moderate liver disease and with extreme caution in patients with severe liver disease ([GlaxoSmithKline 2016a, 2016b](#)).

---

## Mechanism of Action

---

Despite considerable effort spent in elucidating bupropion's mechanism of action, what we know is limited. Preclinical

data indicate that bupropion does not bind to postsynaptic histamine,  $\alpha$ - or  $\beta$ -adrenergic, or serotonin receptors, nor does it inhibit monoamine oxidase ([Ascher et al. 1995](#); [Baldessarini 2001](#); [Fava et al. 2005](#); [Stahl et al. 2004](#)). Thus, among the myriad of antidepressants now available, bupropion is the only agent without substantial serotonergic activity ([Ascher et al. 1995](#); [Richelson 1996](#); [Stahl et al. 2004](#)).

Bupropion's three major metabolites—hydroxybupropion, threohydrobupropion, and erythrohydrobupropion—play a crucial role in its antidepressant activity (GlaxoSmithKline [2016a](#), [2016b](#)). In vitro studies have demonstrated that bupropion and its active metabolites inhibit both the NET and the DAT (described in [Fava et al. 2005](#)).

Although other antidepressants that affect NET receptors are thought to produce their effects by downregulation of postsynaptic noradrenergic receptors, bupropion differs in that it decreases the firing rate of neurons in the locus coeruleus in a dose-dependent manner (B.R. [Cooper et al. 1994](#); T.B. [Cooper et al. 1984](#)). Acute administration of bupropion not only decreases firing of brain-stem norepinephrine and dopamine neurons but also increases extracellular norepinephrine and dopamine concentrations in the nucleus accumbens ([Fava et al. 2005](#)). Furthermore, the efficacy of bupropion and hydroxybupropion has been shown to diminish in animal models when norepinephrine- or dopamine-blocking drugs are administered (B.R. [Cooper et al. 1980](#); [Dwoskin et al. 2006](#)).

---

## Indications and Efficacy

---

# Primary Indications

## Major Depressive Disorder

Bupropion's efficacy in the treatment of major depressive disorder (MDD) is supported by many clinical trials. The drug's three formulations are equally useful for this therapeutic indication ([Fabre et al. 1983](#); [Lineberry et al. 1999](#)). Comparison trials have demonstrated that bupropion is as effective as other classes of antidepressants, including TCAs and SSRIs ([Branconnier et al. 1983](#); [Clayton et al. 2006](#); [Coleman et al. 1999, 2001](#); [Croft et al. 1999](#); [Feighner et al. 1986](#); [Kavoussi et al. 1997](#); [Mendels et al. 1983](#); [Thase et al. 2005](#); [Weihs et al. 2000](#)). In comparisons with specific drugs, bupropion's efficacy in depression was found to be equal to that of fluoxetine ([Feighner et al. 1991](#)) and of trazodone ([Weisler et al. 1994](#)).

The development of bupropion SR launched several comparison studies with SSRIs, including fluoxetine, sertraline, and paroxetine. In most studies, the effective daily dosage of bupropion SR was between 300 mg and 400 mg. All studies demonstrated that bupropion's effectiveness in treating symptoms of depression was equal to that of SSRIs ([Coleman et al. 1999, 2001](#); [Croft et al. 1999](#); [Kavoussi et al. 1997](#); [Weihs et al. 2000](#)). In a meta-analysis of remission data from all existing bupropion SR versus SSRI comparative trials, [Thase et al. \(2005\)](#) found that remission rates were essentially the same for the two types of antidepressants. Although both bupropion SR and SSRIs were generally well tolerated, bupropion SR treatment was associated with lower rates of sexual dysfunction ([Thase et al. 2005](#)). Bupropion SR has also been shown to prevent



relapse of depressive symptoms in continuation treatment extending up to 1 year ([Weihs et al. 2002](#)).

The release of bupropion XL in 2003 also generated several comparison studies. In two 8-week placebo-controlled comparative trials with bupropion XL and escitalopram, pooled analysis confirmed equivalent efficacy of the two agents based on mean change in Hamilton Rating Scale for Depression (Ham-D; [Hamilton 1960](#)) score. Both antidepressants produced remission rates greater than the rate with placebo alone ([Clayton et al. 2006](#)). Other studies comparing bupropion XL with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR demonstrated clinical equivalence for the two drugs in the treatment of depression. Notably, a study that used higher dosages of bupropion XL (300–450 mg/day) found statistically significantly higher remission rates for bupropion XL relative to venlafaxine XR ([Thase et al. 2006](#)). By contrast, two studies by Hewitt and colleagues found low dosages of venlafaxine XR (75–150 mg/day) to be superior to low dosages of bupropion XL (150–300 mg/day). In both studies, a flexible dosing schedule was employed; that is, patients were given the option of doubling the dosage at week 5 if their response was inadequate. Of note, in these studies bupropion XL was not superior to placebo ([Hewitt et al. 2009, 2010](#)).

Although bupropion has not been shown in a naturalistic setting to have better effectiveness than other antidepressant agents, specific neurocognitive markers may help steer the clinician toward the choice of bupropion for a specific patient. In a small-sample study, [Bruder et al. \(2014\)](#) found that performance on brief tests of word fluency and psychomotor speed predicted which patients would preferentially respond to bupropion monotherapy

relative to either SSRI monotherapy or SSRI + bupropion combination therapy. However, other small (but statistically significant) studies have suggested that SSRIs may be more effective than bupropion in decreasing suicidal thoughts during the initial weeks of pharmacotherapy in high-risk patients ([Grunebaum et al. 2013](#)).

Studies have shown bupropion to be efficacious in the treatment of MDD not only as monotherapy but also as an augmenting agent with SSRIs or SNRIs ([Bodkin et al. 1997](#); [DeBattista et al. 2003](#); [Fava et al. 2003](#); [Ferguson et al. 1994](#); [Lam et al. 2004](#); [Rush et al. 2006](#); [Spier 1998](#); [Stern et al. 1983](#); [Trivedi et al. 2006](#)). Whereas the “triple monoamine approach” (i.e., using an SSRI with bupropion in order to block reuptake of serotonin, dopamine, and norepinephrine) is often a useful strategy, [Stewart et al. \(2014\)](#) demonstrated that the addition of bupropion XL at a relatively high dosage (i.e., 450 mg/day) to a similarly high dosage of escitalopram (i.e., 40 mg/day) increased neither the speed of recovery nor the likelihood of recovery from a major depressive episode. [Nasr et al. \(2014\)](#) compared the outcomes of patients who received either aripiprazole or bupropion as an adjunct to SSRI treatment. Although no overall differences were found between the two augmenting agents, bupropion was significantly more helpful in treating poor energy and motivation, whereas aripiprazole proved superior in reducing suicidal ideation. This finding suggests that a careful symptom inventory is the best guide in selecting an augmenting agent.

The Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study was the largest protocol-driven study of MDD ever undertaken, with an initial study population of 4,041. A retrospective analysis of this study directly addressed the question of which next-step strategy

—medication augmentation or medication switching—yields the best outcome for patients whose symptoms have not improved after an adequate trial of antidepressant monotherapy ([Gaynes et al. 2012](#)). Findings specific to bupropion suggested that patients who completed an initial 12-week period of citalopram treatment without experiencing complete symptom remission received more benefit from augmenting citalopram with bupropion than from discontinuing citalopram and switching to bupropion.

**Depression in the elderly.** Depression in the elderly is often underdiagnosed and may go untreated. Older individuals tend to describe nonspecific somatic symptoms, such as insomnia, anorexia, and low energy, instead of reporting depressed mood ([Birrer and Vemuri 2004](#)). Bupropion has been found to be an effective antidepressant in elderly patients ([Birrer and Vemuri 2004](#); [Branconnier et al. 1983](#); [Weihs et al. 2000](#)). A study comparing bupropion SR and the SSRI paroxetine noted that although both agents were effective in treating depression, bupropion SR had a more favorable side-effect profile ([Weihs et al. 2000](#)). Like bupropion SR, bupropion XL has shown efficacy in the treatment of depression in elderly individuals ([Clayton 2007](#)). However, a study examining whether gender- or age-related differences in efficacy exist between SSRIs and bupropion for treatment of depressive symptoms, anxious/somatic symptoms, and insomnia found SSRIs and bupropion to be equally effective in treating these symptoms across all age and gender groups ([Papakostas et al. 2007](#)).

**Depression with decreased energy, interest, and pleasure.** Bupropion XL has been studied

specifically in depressed patients with a retarded/anergic symptom profile. [Jefferson et al. \(2006\)](#) showed that bupropion XL was more effective than placebo in depressed patients with decreased energy, pleasure, and interest. Bupropion's unique norepinephrine-dopamine reuptake inhibitor (NDRI) mechanism of action may play a role in its effectiveness in treating these symptoms ([Jefferson et al. 2006](#)).

**Anxiety symptoms in depression.** Studies have demonstrated the effectiveness of bupropion dosages of 300–400 mg/day in reducing symptoms of anxiety ([Fabre et al. 1983](#)). Moreover, bupropion and SSRIs appear to be equally effective in reducing symptoms of anxiety associated with MDD in both the general population and the elderly ([Feighner et al. 1991](#); [Weihs et al. 2000](#)). In 2001, Trivedi et al. published results of a study examining the effects of bupropion SR versus sertraline on anxiety in depressed patients, reporting that both bupropion SR and sertraline were superior to placebo in allaying depressive symptoms; however, treatment of anxious symptoms did not significantly differ from placebo for either active medication. The study concluded that bupropion and SSRIs were comparable in their antidepressant and anxiolytic effects in patients with MDD. Neither was favored for more specific management of anxiety ([Trivedi et al. 2001](#)). A meta-analysis comparing the efficacy of bupropion and SSRIs for treatment of anxious symptoms in MDD concluded that both classes of medication led to a similar degree of improvement in anxiety symptoms, with no significant difference in the severity of residual anxiety symptoms ([Papakostas et al. 2008](#)).

**Bipolar depression.** A small number of early studies demonstrated the advantages of bupropion in the treatment of depression in bipolar disorder ([Haykal and Akiskal 1990](#); [Shopsin 1983](#); [Wright et al. 1985](#)). Although these investigations yielded positive results, they were limited by small numbers of subjects and lack of placebo control. Several trials have examined the risk of treatment-emergent mania with adjunctive use of bupropion in bipolar disorder. Although there appeared to be a lower risk of mania with bupropion and SSRIs than with the SNRI venlafaxine, findings regarding bupropion's efficacy in treating depressive symptoms in bipolar disorder were mixed ([Leverich et al. 2006](#); [Post et al. 2006](#); [Sachs et al. 2007](#)).

## **Prevention of Seasonal Major Depressive Episodes**

In 2006, bupropion XL ([Valeant Pharmaceuticals North America 2014](#)) became the first medication—and is still the only medication—to receive a labeled indication for the preventive treatment of seasonal depressive symptoms. A study published in 1992 initially suggested bupropion's efficacy as treatment for winter depression ([Dilsaver et al. 1992](#)). In 2005, Modell et al. published results of three prospective randomized, placebo-controlled prevention trials involving 1,042 outpatients with a diagnosis of seasonal major depressive episodes. Patients received 150–300 mg/day of bupropion XL or placebo in autumn while they were still well. Bupropion XL reduced the frequency of emergence of winter depression by 44% and protected against the recurrence of seasonal major depressive episodes. Furthermore, there was no noticeable increase in

major depressive episodes following discontinuation of bupropion in the springtime ([Modell et al. 2005](#)).

## Smoking Cessation

In 1997, bupropion SR received FDA approval for use as a smoking-cessation aid under the trade name Zyban (GlaxoSmithKline [2015](#)). The beneficial effect of bupropion on smoking cessation was first noted when researchers observed unplanned suspension of smoking in depressed subjects who were being treated with bupropion (reviewed in [Hudziak and Rettew 2004](#)). In a double-blind, placebo-controlled trial of bupropion SR therapy for smoking cessation ([Hurt et al. 1997](#)), 615 subjects received bupropion SR at dosages of 100, 150, or 300 mg/day for 7 weeks, with a target quit date of 1 week after beginning treatment. Brief counseling was also provided. Rates of smoking cessation at the end of 7 weeks were 29% for the 100-mg/day group, 39% for the 150-mg/day group, and 44% for the 300-mg/day group, versus 10% for placebo. At 1 year, rates for the three bupropion dosage groups were 20%, 23%, and 23%, respectively, compared with 12% for the placebo group.

Studies examining the long-term efficacy of bupropion SR for smoking relapse prevention have reported mixed findings. [Hays et al. \(2001\)](#) showed that subjects who had successfully stopped smoking for 7 weeks with bupropion treatment had a significant delay in smoking relapse with continued bupropion SR therapy compared with placebo. By contrast, a trial looking specifically at extended treatment with bupropion SR for smoking cessation reported that bupropion SR did not surpass placebo in efficacy ([Killen et al. 2006](#)). However, a meta-analysis of randomized controlled trials of pharmacotherapies for

smoking cessation subsequently confirmed the efficacy of bupropion in promoting smoking abstinence ([Eisenberg et al. 2008](#)).

Although more work needs to be done in the areas of relapse prevention and long-term abstinence, it appears evident that bupropion SR is helpful in smoking cessation. Recommended dosing is 150 mg/day for 3 days, increasing to 150 mg two times a day for 7–12 weeks, with patients setting a quit date of 1–2 weeks after treatment has been initiated. In 2003, Ferry and Johnston published a 5-year review of the accumulated efficacy and safety data for bupropion SR since its 1997 approval for smoking cessation. A benefit-risk analysis assuming a 30% 1-year quit rate concluded that for every 10,000 smokers treated with bupropion SR, 19 lives are saved and 86 cases of smoking-attributed morbidity are avoided, whereas the risk of a serious adverse effect from treatment is 0.22% ([Ferry and Johnston 2003](#)). Recent data have confirmed that bupropion evidences no increased risk of self-harm, suicide, or depression compared with either varenicline or nicotine replacement therapy ([Thomas et al. 2013](#)).

## **Obesity**

Unlike other classes of antidepressants, bupropion is well known for its lack of association with weight gain. Alternatively, mild, acute weight loss has been noted in many clinical trials. To further investigate this observation, [Gadde et al. \(2001\)](#) conducted a randomized, placebo-controlled trial investigating the tolerability and efficacy of bupropion (100–400 mg/day) for weight loss in 50 obese women. All subjects kept a food journal and were placed on a 1,600 kcal/day diet. At 8 weeks, subjects receiving bupropion had achieved greater weight loss compared with



those on placebo. At 24 weeks, responders to bupropion had lost an average of 13% of their baseline body weight ([Gadde et al. 2001](#)). Following this initial study of bupropion for weight loss, two larger studies confirmed these results ([Anderson et al. 2002](#); [Jain et al. 2002](#)).

In 2013, the FDA approved Contrave ([Orexigen Therapeutics 2014](#)), a bupropion/naltrexone combination, for the treatment of patients who are obese (defined as body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) or overweight (defined as BMI  $\geq 27$  kg/m<sup>2</sup>) and have at least one cardiovascular risk factor ([Apovian et al. 2013](#)). FDA approval followed studies showing that bupropion/naltrexone combination therapy led to reductions in total and visceral adiposity ([Smith et al. 2013](#)). A drug safety evaluation of bupropion/naltrexone concluded that it led to greater weight loss compared with two other medications FDA approved for the treatment of obesity, orlistat and lorcaserin, but less weight loss compared with topiramate/phentermine combination therapy ([Verpeut and Bello 2014](#)). Furthermore, a study using functional magnetic resonance imaging demonstrated decreased reactivity to food cues following a course of bupropion/naltrexone therapy ([Wang et al. 2014](#)).

## Other Uses

### **Attention-Deficit/Hyperactivity Disorder**

Currently there is no FDA indication for bupropion's use in ADHD, although studies have demonstrated that it may be helpful in treating symptoms of ADHD in both children and adults ([Conners et al. 1996](#); [Simeon et al. 1986](#)). Clinical trials in children with ADHD have shown bupropion to be a



safe and effective alternative for treatment of this disorder (Conners et al. 1996). A comparison trial of bupropion and methylphenidate found that both drugs were effective in the treatment of ADHD and had similar efficacy (Barrickman et al. 1995). Bupropion has also been studied in adults with ADHD and has demonstrated statistically significant symptom improvement in this population (Wilens et al. 2001). In a meta-analysis by Peterson et al. (2008), long-acting forms of bupropion appeared to exhibit similar clinical effectiveness compared with long-acting stimulants in adults. An open trial by Riggs et al. (1998) suggested that bupropion may also be useful for the treatment of ADHD in adolescents with comorbid conduct disorder and substance use disorders. A recent large review of meta-analyses to date (Moriyama et al. 2013) concluded that bupropion therapy is more effective than placebo but less effective than stimulant therapy in the treatment of ADHD.

## **Sexual Dysfunction**

Bupropion has been studied as an antidote to SSRI-induced sexual dysfunction. A placebo-controlled comparative trial of bupropion SR treatment in 42 patients with SSRI-induced sexual dysfunction concluded that bupropion SR improved both the desire to engage in sexual activity and the frequency of engaging in sexual activity relative to placebo (Clayton et al. 2004). Safarinejad et al. (2010) demonstrated bupropion's efficacy in reversing SSRI-induced sexual dysfunction in men.

Segraves et al. (2001) found that bupropion may be helpful in the treatment of DSM-IV-TR HSDD. Subsequently, a double-blind, placebo-controlled trial supported this finding and also revealed increases in sexual arousal, orgasm completion, and sexual satisfaction in women with

DSM-IV-TR HSDD who received bupropion ([Segraves et al. 2004](#)). Another study of bupropion SR treatment of patients with SSRI-induced sexual dysfunction found that bupropion improved the desire to engage in sexual activity and increased the frequency of engaging in sexual activity ([Clayton et al. 2004](#)). Additional studies have also demonstrated that bupropion may be helpful for treating sexual disorders in both men and women ([Modell et al. 2000](#)). In a review of nontestosterone treatment options available for HSDD, [Lodise \(2013, p. 411\)](#) concluded that “bupropion is the primary pharmacologic agent that has shown positive results.”

## **Amphetamine Use Disorder**

Earlier in this chapter we discussed a burgeoning set of data pointing to the possibility that bupropion may be an emerging drug of abuse. Bupropion has been shown in vitro to increase dopamine uptake in the reward pathways in the brain, the very pathways whose function is deregulated or destroyed by chronic amphetamine abuse ([Simmler et al. 2013](#)). On the basis of its unique pharmacodynamics, bupropion is now being investigated as a possible treatment for stimulant use disorders, although results thus far have been mixed. In a review of randomized controlled trials, [Brensilver et al. \(2013\)](#) concluded that bupropion had not “produced an unambiguous, replicable signal of efficacy” in reducing stimulant use.

---

## **Side Effects and Toxicology**

---

Evidence from thousands of clinical trials and millions of patient exposures confirms that bupropion is a safe and generally well-tolerated medication across populations. Because of bupropion's unique mechanism of action and structure, its reported side effects are somewhat different from those of other antidepressants.

In a series of large randomized, placebo-controlled multicenter trials evaluating the safety of bupropion SR in the treatment of depressed outpatients, [Settle et al. \(1999\)](#) found that the most commonly reported adverse effects (occurring in >5% of subjects) were headache, dry mouth, nausea, insomnia, constipation, and dizziness. Only three of these—dry mouth, nausea, and insomnia—occurred at higher rates in patients taking bupropion SR than in those receiving placebo. The rate of discontinuation due to adverse effects was low: 7% for bupropion SR, compared with 4% for placebo. Rash, nausea, agitation, and migraine were the most common adverse effects leading to discontinuation ([Settle et al. 1999](#)). Similarly favorable safety and tolerability findings were reported for continuation-phase bupropion SR treatment in a longer-term (up to 44 weeks) relapse prevention trial ([Weihs et al. 2002](#)).

The side-effect profile of bupropion XL is similar to that of the other bupropion formulations and compares favorably with that of other controlled-release antidepressants. Compared with venlafaxine XR, bupropion XL was found to be associated with lower rates of dry mouth, nausea, diarrhea, somnolence, sedation, and yawning. These data indicate that bupropion XL does not appear to cause somnolence ([Clayton et al. 2006](#)). A review by [Fava et al. \(2005\)](#) also concluded that bupropion produces much less somnolence compared with SSRIs. Moreover, insomnia,

thought to be a particular side effect of bupropion, in fact occurs at rates similar to those seen with SSRIs ([Fava et al. 2005](#)).

Less common but potentially harmful adverse effects associated with bupropion include allergic reactions, seizures, and vital-sign changes. Allergic reactions, including rash, arthralgias, fever, and serum sickness-like reactions, have all been reported ([McCollom et al. 2000](#); [Tripathi and Greenberger 1999](#)). In light of these data, it is important to fully evaluate any reports of previous hypersensitivity before prescribing bupropion.

Screening for a history of seizure disorder or other organic brain disease should be performed before commencing a trial of bupropion. Seizure has been reported at a rate of 0.1% at dosages up to 300 mg/day with bupropion SR, with a dose-related effect ([Dunner et al. 1998](#)). This rate is similar to rates observed with other newer antidepressants, such as SSRIs and mirtazapine, but is lower than rates associated with therapeutic dosages of TCAs ([Montgomery 2005](#)).

Although cases of spontaneous hypertension with bupropion therapy have been reported, clinical trials across the approved dosage range have shown minimal changes in heart rate and blood pressure, even among patients with hypertension ([Jorenby et al. 1999](#); [Settle et al. 1999](#); [Thase et al. 2008](#)). In a smoking cessation study, patients receiving combination treatment with bupropion SR and a nicotine patch had a higher incidence of new or worsening hypertension compared with patients receiving either treatment alone or placebo ([Jorenby et al. 1999](#)). [Thase et al. \(2008\)](#) conducted a dose-response study to evaluate the potential of bupropion to elevate blood pressure. Bupropion SR dosages of 150–400 mg/day were administered to 296

nondepressed volunteers with mild hypertension. Findings indicated that bupropion SR did not separate from placebo on blood pressure changes. However, clinicians should be aware that elevated blood pressure is a possibility with bupropion therapy and should monitor patients accordingly.

Many agents used to treat depression have been associated with weight gain. This effect is thought to be associated with affinity for the H<sub>1</sub> histamine receptor, which is not a factor with bupropion. In fact, mild weight loss over time, rather than weight gain, has been reported with bupropion treatment ([Harto-Truax et al. 1983](#)). Studies have shown bupropion XL to be associated with weight loss of 0.1–1.1 kg in the short term, compared with placebo, which was associated with a small gain of 0.1–0.8 kg ([Jefferson et al. 2006](#); [Modell et al. 2005](#); [Thase et al. 2006](#)). In a longer-term depression relapse prevention study, [Croft et al. \(2002\)](#) observed that patients with higher BMIs at baseline experienced greater weight loss with bupropion XL than did patients with lower baseline BMIs.

Overall, at approved dosages, bupropion is a safe medication for depression in most populations and has an excellent tolerability profile. However, high blood levels of bupropion can be fatal. Serious medical consequences, such as hypertension, acidosis, sinus tachycardia, seizures, cardiotoxicity with QRS widening, and even death, have been reported with overdoses of bupropion ([Bhattacharjee et al. 2001](#); [Curry et al. 2005](#); [Shrier et al. 2000](#)).

On initiation of bupropion therapy, it is usually not necessary to obtain routine laboratory evaluations, although cases of elevated serum transaminase ([Oslin and Duffy 1993](#)) and rare cases of hepatitis ([Hu et al. 2000](#)) have been reported. Other unexpected changes in laboratory values have also occurred with bupropion

therapy and include false-positive results for urine amphetamine screening ([Weintraub and Linder 2000](#)).

Unfortunately, few data are available on the safety of bupropion in pregnancy. In a study by [Cole et al. \(2007\)](#), bupropion exposure in the first trimester was not associated with teratogenic effects. However, as previously described (see “Pharmacokinetics and Disposition” earlier in this chapter), the rapid increase in estradiol levels that occurs during pregnancy leads to strong induction of the CYP2B6 isoenzyme, the substrate primarily responsible for metabolizing bupropion ([Dickmann and Isoherranen 2013](#)). Further studies, with collection of hydroxybupropion levels, are needed to establish bupropion’s therapeutic effectiveness and safety in pregnant women.

---

## Drug-Drug Interactions

---

As discussed earlier, the main enzyme responsible for the metabolism of bupropion is CYP2B6. Competitive inhibition of metabolism can occur with other drugs processed by this enzyme, such as paroxetine, sertraline, diazepam, clonazepam, clopidogrel, ritonavir, and efavirenz ([Hesse et al. 2000](#); [Jefferson et al. 2005](#)). A study examining the effects of concurrent use of lopinavir/ritonavir on bupropion pharmacokinetics in 12 healthy subjects found that maximum plasma concentrations of bupropion and hydroxybupropion decreased by 57% and 31%, respectively ([Hogeland et al. 2007](#)).

Bupropion and its major metabolite hydroxybupropion are also inhibitors of CYP2D6, an enzyme that plays a role in the metabolism of several classes of medications,

including antidepressants, antipsychotics,  $\beta$ -blockers, and antiarrhythmic agents (Wilkinson 2005). Studies of the effects of bupropion on CYP2D6 activity are limited, but results of those conducted suggest that bupropion may increase blood levels of drugs metabolized by CYP2D6, such as desipramine and venlafaxine ([Jefferson et al. 2005](#); [Kennedy et al. 2002](#)). An 8-week open-label study of bupropion SR coadministered with venlafaxine, paroxetine, or fluoxetine found inhibition of venlafaxine metabolism and higher concentrations of venlafaxine. No significant interaction effects from bupropion were found for paroxetine or fluoxetine ([Kennedy et al. 2002](#)). Other agents known to induce various metabolic pathways have also been shown to affect the metabolism of bupropion. Carbamazepine, which induces CYP2B6, 3A4, and 1A2 activity, has been shown to decrease bupropion concentrations but increase hydroxybupropion concentrations ([Ketter et al. 1995](#)).

Bupropion should be used with caution in combination with other psychotropic agents that can lower the seizure threshold, such as tramadol, certain antidepressants, and antipsychotics ([Delanty et al. 1998](#); [Gardner et al. 2000](#)). It should also be used with caution in patients who abuse alcohol, because this population may have a higher risk of seizures ([Dunner et al. 1998](#)). In addition, because bupropion increases dopamine reuptake, additive effects with other dopaminergic agents (e.g., levodopa) are a possibility ([Goetz et al. 1984](#)).

---

## Conclusion

---

Bupropion is unique among the newer antidepressants in that it functions as a dopamine and norepinephrine reuptake inhibitor and as an antagonist of nACh receptors. Because bupropion has very little serotonergic activity, its side-effect profile differs markedly from that of other first-line agents, providing a treatment alternative for patients who cannot tolerate or who do not respond to SSRIs. Although its current FDA-approved indications are limited to the treatment of MDD, tobacco use disorder, and obesity and the prevention of seasonal major depressive episodes, bupropion has also demonstrated utility in child and adult ADHD and in sexual disorders. For targeted treatment of depression characterized by decreased energy and interest, depression with concomitant anxiety, and bipolar depression, bupropion may be particularly beneficial. Bupropion may also be used to augment other antidepressants in the treatment of MDD and to reverse SSRI-induced side effects. Greater tolerability, including low risk of weight gain, minimal sedation, and few sexual side effects, adds to bupropion's value as an effective antidepressant.

---

## References

---

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Anderson JW, Greenway FL, Fujioka K, et al: Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. *Obes Res* 10(7):633-641, 2002 12105285



- Apovian CM, Aronne L, Rubino D, et al; COR-II Study Group: A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)* 21(5):935-943, 2013 23408728
- Ascher JA, Cole JO, Colin JN, et al: Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry* 56(9):395-401, 1995 7665537
- Baldessarini RJ: Drugs and the treatment of psychiatric disorders: depression and anxiety disorders, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. New York, McGraw-Hill, 2001, pp 447-483
- Barrickman LL, Perry PJ, Allen AJ, et al: Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 34(5):649-657, 1995 7775360
- Bhattacharjee C, Smith M, Todd F, et al: Bupropion overdose: a potential problem with the new 'miracle' anti-smoking drug. *Int J Clin Pract* 55(3):221-222, 2001 11351778
- Birrer RB, Vemuri SP: Depression in later life: a diagnostic and therapeutic challenge. *Am Fam Physician* 69(10):2375-2382, 2004 15168957
- Bodkin JA, Lasser RA, Wines JD Jr, et al: Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. *J Clin Psychiatry* 58(4):137-145, 1997 9164423
- Branconnier RJ, Cole JO, Ghazvinian S, et al: Clinical pharmacology of bupropion and imipramine in elderly depressives. *J Clin Psychiatry* 44(5 Pt 2):130-133, 1983 6406441
- Brensilver M, Heinzerling KG, Shoptaw S: Pharmacotherapy of amphetamine-type stimulant dependence: an update. *Drug Alcohol Rev* 32(5):449-460, 2013 23617468

- Bruder GE, Alvarenga JE, Alschuler D, et al: Neurocognitive predictors of antidepressant clinical response. *J Affect Disord* 166:108-114, 2014 25012418
- Clayton AH: Extended-release bupropion: an antidepressant with a broad spectrum of therapeutic activity? *Expert Opin Pharmacother* 8(4):457-466, 2007 17309340
- Clayton AH, Warnock JK, Kornstein SG, et al: A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry* 65(1):62-67, 2004 14744170
- Clayton AH, Croft HA, Horrigan JP, et al: Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. *J Clin Psychiatry* 67(5):736-746, 2006 16841623
- Cole JA, Modell JG, Haight BR, et al: Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 16(5):474-484, 2007 16897811
- Coleman CC, Cunningham LA, Foster VJ, et al: Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann Clin Psychiatry* 11(4):205-215, 1999 10596735
- Coleman CC, King BR, Bolden-Watson C, et al: A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. *Clin Ther* 23(7):1040-1058, 2001 11519769
- Conners CK, Casat CD, Gualtieri CT, et al: Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 35(10):1314-1321, 1996 8885585
- Cooper BR, Hester TJ, Maxwell RA: Behavioral and biochemical effects of the antidepressant bupropion

- (Wellbutrin): evidence for selective blockade of dopamine uptake in vivo. *J Pharmacol Exp Ther* 215(1):127-134, 1980 6778989
- Cooper BR, Wang CM, Cox RF, et al: Evidence that the acute behavioral and electrophysiological effects of bupropion (Wellbutrin) are mediated by a noradrenergic mechanism. *Neuropsychopharmacology* 11(2):133-141, 1994 7840865
- Cooper TB, Suckow RF, Glassman A: Determination of bupropion and its major basic metabolites in plasma by liquid chromatography with dual-wavelength ultraviolet detection. *J Pharm Sci* 73(8):1104-1107, 1984 6436464
- Croft H, Settle E Jr, Houser T, et al: A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther* 21(4):643-658, 1999 10363731
- Croft H, Houser TL, Jamerson BD, et al: Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. *Clin Ther* 24(4):662-672, 2002 12017410
- Curry SC, Kashani JS, LoVecchio F, Holubek W: Intraventricular conduction delay after bupropion overdose. *J Emerg Med* 29(3):299-305, 2005 16183450
- Davidson J: Seizures and bupropion: a review. *J Clin Psychiatry* 50(7):256-261, 1989 2500425
- Daviss WB, Perel JM, Birmaher B, et al: Steady-state clinical pharmacokinetics of bupropion extended-release in youths. *J Am Acad Child Adolesc Psychiatry* 45(12):1503-1509, 2006 17135996
- DeBattista C, Solvason HB, Poirier J, et al: A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. *J Clin Psychopharmacol* 23(1):27-30, 2003 12544372
- Delanty N, Vaughan CJ, French JA: Medical causes of seizures. *Lancet* 352(9125):383-390, 1998 9717943

- DeVane CL, Laizure SC, Stewart JT, et al: Disposition of bupropion in healthy volunteers and subjects with alcoholic liver disease. *J Clin Psychopharmacol* 10(5):328-332, 1990 2124217
- Dickmann LJ, Isoherranen N: Quantitative prediction of CYP2B6 induction by estradiol during pregnancy: potential explanation for increased methadone clearance during pregnancy. *Drug Metab Dispos* 41(2):270-274, 2013 22815312
- Dilsaver SC, Qamar AB, Del Medico VJ: The efficacy of bupropion in winter depression: results of an open trial. *J Clin Psychiatry* 53(7):252-255, 1992 1639745
- Dunner DL, Zisook S, Billow AA, et al: A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry* 59(7):366-373, 1998 9714265
- Dwoskin LP, Rauhut AS, King-Pospisil KA, et al: Review of the pharmacology and clinical profile of bupropion, an antidepressant and tobacco use cessation agent. *CNS Drug Rev* 12(3-4):178-207, 2006 17227286
- Eisenberg MJ, Filion KB, Yavin D, et al: Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. *CMAJ* 179(2):135-144, 2008 18625984
- Fabre LF, Brodie HK, Garver D, et al: A multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. *J Clin Psychiatry* 44(5 Pt 2):88-94, 1983 6406472
- Fava M, Papakostas GI, Petersen T, et al: Switching to bupropion in fluoxetine-resistant major depressive disorder. *Ann Clin Psychiatry* 15(1):17-22, 2003 12839429
- Fava M, Rush AJ, Thase ME, et al: 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry* 7(3):106-113, 2005 16027765

- Feighner J, Hendrickson G, Miller L, et al: Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharmacol* 6(1):27-32, 1986 3081600
- Feighner JP, Gardner EA, Johnston JA, et al: Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J Clin Psychiatry* 52(8):329-335, 1991 1907963
- Ferguson J, Cunningham L, Merideth C, et al: Bupropion in tricyclic antidepressant nonresponders with unipolar major depressive disorder. *Ann Clin Psychiatry* 6(3):153-160, 1994 7881495
- Ferris RM, Beaman OJ: Bupropion: a new antidepressant drug, the mechanism of action of which is not associated with down-regulation of postsynaptic beta-adrenergic, serotonergic (5-HT<sub>2</sub>), alpha 2-adrenergic, imipramine and dopaminergic receptors in brain. *Neuropharmacology* 22(11):1257-1267, 1983 6320035
- Ferry L, Johnston JA: Efficacy and safety of bupropion SR for smoking cessation: data from clinical trials and five years of postmarketing experience. *Int J Clin Pract* 57(3):224-230, 2003 12723728
- Findlay JW, Van Wyck Fleet J, Smith PG, et al: Pharmacokinetics of bupropion, a novel antidepressant agent, following oral administration to healthy subjects. *Eur J Clin Pharmacol* 21(2):127-135, 1981 6804243
- Gadde KM, Parker CB, Maner LG, et al: Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. *Obes Res* 9(9):544-551, 2001 11557835
- Gardner JS, Blough D, Drinkard CR, et al: Tramadol and seizures: a surveillance study in a managed care population. *Pharmacotherapy* 20(12):1423-1431, 2000 11130214
- Gaynes BN, Dusetzina SB, Ellis AR, et al: Treating depression after initial treatment failure: directly

- comparing switch and augmenting strategies in STAR\*D. J Clin Psychopharmacol 32(1):114-119, 2012 22198447
- GlaxoSmithKline: ZYBAN (bupropion hydrochloride) sustained-release tablets, for oral use; full prescribing information. Research Triangle Park, NC, GlaxoSmithKline, revised January 2015. Available at: [https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing\\_Information/Zyban/pdf/ZYBAN-PI-MG.PDF](https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Zyban/pdf/ZYBAN-PI-MG.PDF). Accessed May 5, 2016.
- GlaxoSmithKline: WELLBUTRIN (bupropion hydrochloride) tablets, for oral use; full prescribing information. Research Triangle Park, NC, GlaxoSmithKline, revised April 2016a. Available at: [https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing\\_Information/Wellbutrin\\_Tablets/pdf/WELLBUTRIN-TABLETS-PI-MG.PDF](https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Wellbutrin_Tablets/pdf/WELLBUTRIN-TABLETS-PI-MG.PDF). Accessed May 5, 2016.
- GlaxoSmithKline: WELLBUTRIN SR (bupropion hydrochloride) sustained-release tablets, for oral use; full prescribing information. Research Triangle Park, NC, GlaxoSmithKline, revised April 2016b. Available at: [https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing\\_Information/Wellbutrin\\_SR/pdf/WELLBUTRIN-SR-PI-MG.PDF](https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Wellbutrin_SR/pdf/WELLBUTRIN-SR-PI-MG.PDF). Accessed May 5, 2016.
- Goetz CG, Tanner CM, Klawans HL: Bupropion in Parkinson's disease. Neurology 34(8):1092-1094, 1984 6431314
- Griffith JD, Carranza J, Griffith C, et al: Bupropion: clinical assay for amphetamine-like abuse potential. J Clin Psychiatry 44(5 Pt 2):206-208, 1983 6406459
- Grunebaum MF, Keilp JG, Ellis SP, et al: SSRI versus bupropion effects on symptom clusters in suicidal depression: post hoc analysis of a randomized clinical trial. J Clin Psychiatry 74(9):872-879, 2013 24107760

- Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56-62, 1960 14399272
- Harto-Truax N, Stern WC, Miller LL, et al: Effects of bupropion on body weight. *J Clin Psychiatry* 44(5 Pt 2):183-186, 1983 6406454
- Haykal RF, Akiskal HS: Bupropion as a promising approach to rapid cycling bipolar II patients. *J Clin Psychiatry* 51(11):450-455, 1990 2121720
- Hays JT, Hurt RD, Rigotti NA, et al: Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. A randomized, controlled trial. *Ann Intern Med* 135(6):423-433, 2001 11560455
- Hesse LM, Venkatakrishnan K, Court MH, et al: CYP2B6 mediates the in vitro hydroxylation of bupropion: potential drug interactions with other antidepressants. *Drug Metab Dispos* 28(10):1176-1183, 2000 10997936
- Hewett K, Chrzanowski W, Schmitz M, et al: Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J Psychopharmacol* 23(5):531-538, 2009 18635695
- Hewett K, Gee MD, Krishen A, et al: Double-blind, placebo-controlled comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J Psychopharmacol* 24(8):1209-1216, 2010 19939870
- Hilliard WT, Barloon L, Farley P, et al: Bupropion diversion and misuse in the correctional facility. *J Correct Health Care* 19(3):211-217, 2013 23788587
- Hogeland GW, Swindells S, McNabb JC, et al: Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 81(1):69-75, 2007 17186001
- Horne RL, Ferguson JM, Pope HG Jr, et al: Treatment of bulimia with bupropion: a multicenter controlled trial. *J Clin Psychiatry* 49(7):262-266, 1988 3134343

- Horst WD, Preskorn SH: Mechanisms of action and clinical characteristics of three atypical antidepressants: venlafaxine, nefazodone, bupropion. *J Affect Disord* 51(3):237-254, 1998 10333980
- Hsyu PH, Singh A, Giargiari TD, et al: Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. *J Clin Pharmacol* 37(8):737-743, 1997 9378846
- Hu KQ, Tiyyagura L, Kanel G, Redeker AG: Acute hepatitis induced by bupropion. *Dig Dis Sci* 45(9):1872-1873, 2000 11052334
- Hudziak JJ, Rettew DC: Bupropion, in *The American Psychiatric Publishing Textbook of Psychopharmacology*, 3rd Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, American Psychiatric Publishing, 2004, pp 327-339
- Hurt RD, Sachs DP, Glover ED, et al: A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 337(17):1195-1202, 1997 9337378
- Jain AK, Kaplan RA, Gadde KM, et al: Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obes Res* 10(10):1049-1056, 2002 12376586
- Jefferson JW, Pradko JF, Muir KT: Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. *Clin Ther* 27(11):1685-1695, 2005 16368442
- Jefferson JW, Rush AJ, Nelson JC, et al: Extended-release bupropion for patients with major depressive disorder presenting with symptoms of reduced energy, pleasure, and interest: findings from a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 67(6):865-873, 2006 16848645
- Jorenby DE, Leischow SJ, Nides MA, et al: A controlled trial of sustained-release bupropion, a nicotine patch, or both



for smoking cessation. *N Engl J Med* 340(9): 685–691, 1999 10053177

Kavoussi RJ, Segraves RT, Hughes AR, et al: Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 58(12):532–537, 1997 9448656

Kennedy SH, McCann SM, Masellis M, et al: Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry* 63(3):181–186, 2002 11926715

Ketter TA, Jenkins JB, Schroeder DH, et al: Carbamazepine but not valproate induces bupropion metabolism. *J Clin Psychopharmacol* 15(5):327–333, 1995 8830063

Killen JD, Fortmann SP, Murphy GM Jr, et al: Extended treatment with bupropion SR for cigarette smoking cessation. *J Consult Clin Psychol* 74(2):286–294, 2006 16649873

Kirchheiner J, Klein C, Meineke I, et al: Bupropion and 4-OH-bupropion pharmacokinetics in relation to genetic polymorphisms in CYP2B6. *Pharmacogenetics* 13(10):619–626, 2003 14515060

Lam RW, Hossie H, Solomons K, et al: Citalopram and bupropion-SR: combining versus switching in patients with treatment-resistant depression. *J Clin Psychiatry* 65(3):337–340, 2004 15096072

Leverich GS, Altshuler LL, Frye MA, et al: Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* 163(2):232–239, 2006 16449476

Lewis JC, Sutter ME, Albertson TE, et al: An 11-year review of bupropion insufflation exposures in adults reported to the California Poison Control System. *Clin Toxicol (Phila)* 52(9):969–972, 2014 25308323

- Lineberry CG, Johnston JA, Raymond RN, et al: A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry* 51(5):194-199, 1999 2110559
- Lodise NM: Hypoactive sexual desire disorder in women: treatment options beyond testosterone and approaches to communicating with patients on sexual health. *Pharmacotherapy* 33(4):411-421, 2013 23553810
- McCollom RA, Elbe DH, Ritchie AH: Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 34(4):471-473, 2000 10772432
- Mehta NB: The chemistry of bupropion. *J Clin Psychiatry* 44(5 Pt 2):56-59, 1983 6406464
- Mendels J, Amin MM, Chouinard G, et al: A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry* 44(5 Pt 2):118-120, 1983 6406439
- Modell JG, May RS, Katholi CR: Effect of bupropion-SR on orgasmic dysfunction in nondepressed subjects: a pilot study. *J Sex Marital Ther* 26(3):231-240, 2000 10929571
- Modell JG, Rosenthal NE, Harriett AE, et al: Seasonal affective disorder and its prevention by anticipatory treatment with bupropion XL. *Biol Psychiatry* 58(8):658-667, 2005 16271314
- Montgomery SA: Antidepressants and seizures: emphasis on newer agents and clinical implications. *Int J Clin Pract* 59(12):1435-1440, 2005 16351676
- Moriyama TS, Polanczyk GV, Terzi FS, et al: Psychopharmacology and psychotherapy for the treatment of adults with ADHD-a systematic review of available meta-analyses. *CNS Spectr* 18(6):296-306, 2013 23739183
- Nasr S, Wendt B, Popli A, Crayton J: Comparing outcomes of adjunctive treatment in depression: aripiprazole versus bupropion. *J Affect Disord* 162:50-54, 2014 24767005

- Orexigen Therapeutics: CONTRAVE (naltrexone HCl and bupropion HCl) extended-release tablets; full prescribing information. La Jolla, CA, Orexigen Therapeutics, Inc., revised September 2014. Available at: <http://general.takedapharm.com/content/file.aspx?filetypecode=CONTRAVEPI&cacheRandomizer=aa4a415c-7cee-4ed3-9127-a3ad944e9bd2>. Accessed May 5, 2016.
- Oslin DW, Duffy K: The rise of serum aminotransferases in a patient treated with bupropion. *J Clin Psychopharmacol* 13(5): 364-365, 1993 8227497
- Papakostas GI, Kornstein SG, Clayton AH, et al: Relative antidepressant efficacy of bupropion and the selective serotonin reuptake inhibitors in major depressive disorder: gender-age interactions. *Int Clin Psychopharmacol* 22(4):226-229, 2007 17519646
- Papakostas GI, Trivedi MH, Alpert JE, et al: Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of anxiety symptoms in major depressive disorder: a meta-analysis of individual patient data from 10 double-blind, randomized clinical trials. *J Psychiatr Res* 42(2):134-140, 2008 17631898
- Peterson K, McDonagh MS, Fu R: Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. *Psychopharmacology (Berl)* 197(1):1-11, 2008 18026719
- Post RM, Altshuler LL, Leverich GS, et al: Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 189:124-131, 2006 16880481
- Rau KS, Birdsall E, Hanson JE, et al: Bupropion increases striatal vesicular monoamine transport. *Neuropharmacology* 49(6):820-830, 2005 16005476

- Richelson E: Synaptic effects of antidepressants. J Clin Psychopharmacol 16 (3 suppl 2):1S-7S; discussion 7S-9S, 1996 8784643
- Riggs PD, Leon SL, Mikulich SK, et al: An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry 37(12):1271-1278, 1998 9847499
- Rush AJ, Trivedi MH, Wisniewski SR, et al; STAR\*D Study Team: Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 354(12):1231-1242, 2006 16554525
- Sachs GS, Nierenberg AA, Calabrese JR, et al: Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 356(17):1711-1722, 2007 17392295
- Safarinejad MR, Hosseini SY, Asgari MA, et al: A randomized, double-blind, placebo-controlled study of the efficacy and safety of bupropion for treating hypoactive sexual desire disorder in ovulating women. BJU Int 106(6):832-839, 2010 20151970
- Schroeder DH: Metabolism and kinetics of bupropion. J Clin Psychiatry 44(5 Pt 2): 79-81, 1983 6406469
- Segraves RT, Croft H, Kavoussi R, et al: Bupropion sustained release (SR) for the treatment of hypoactive sexual desire disorder (HSDD) in nondepressed women. J Sex Marital Ther 27(3):303-316, 2001 11354935
- Segraves RT, Clayton A, Croft H, et al: Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. J Clin Psychopharmacol 24(3):339-342, 2004 15118489
- Settle EC, Stahl SM, Batey SR, et al: Safety profile of sustained-release bupropion in depression: results of three clinical trials. Clin Ther 21(3):454-463, 1999 10321415
- Shopsin B: Bupropion's prophylactic efficacy in bipolar affective illness. J Clin Psychiatry 44(5 Pt 2):163-169,

1983 6406450

Shrier M, Díaz JE, Tsarouhas N: Cardiotoxicity associated with bupropion overdose. *Ann Emerg Med* 35(1):100, 2000 10613954

Simeon JG, Ferguson HB, Van Wyck Fleet J: Bupropion effects in attention deficit and conduct disorders. *Can J Psychiatry* 31(6):581–585, 1986 3093046

Simmler LD, Wandeler R, Liechti ME: Bupropion, methylphenidate, and 3,4-methylenedioxypyrovalerone antagonize methamphetamine-induced efflux of dopamine according to their potencies as dopamine uptake inhibitors: implications for the treatment of methamphetamine dependence. *BMC Res Notes* 6:220, 2013 23734766

Smith SR, Fujioka K, Gupta AK, et al: Combination therapy with naltrexone and bupropion for obesity reduces total and visceral adiposity. *Diabetes Obes Metab* 15(9):863–866, 2013 23489381

Soroko FE, Maxwell RA: The pharmacologic basis for therapeutic interest in bupropion. *J Clin Psychiatry* 44(5 Pt 2):67–73, 1983 6406467

Spier SA: Use of bupropion with SRIs and venlafaxine. *Depress Anxiety* 7(2):73–75, 1998 9614595

Stahl SM, Pradko JF, Haight BR, et al: A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry* 6(4):159–166, 2004 15361919

Stern WC, Harto-Truax N, Bauer N: Efficacy of bupropion in tricyclic-resistant or intolerant patients. *J Clin Psychiatry* 44(5 Pt 2):148–152, 1983 6406447

Stewart JW, McGrath PJ, Blouin C, et al: Combination antidepressant therapy for major depressive disorder: speed and probability of remission. *J Psychiatr Res* 52:7–14, 2014 24485847

Sweet RA, Pollock BG, Kirshner M, et al: Pharmacokinetics of single- and multiple-dose bupropion in elderly patients

with depression. *J Clin Pharmacol* 35(9):876–884, 1995 8786247

Thase ME, Haight BR, Richard N, et al: Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiatry* 66(8):974–981, 2005 16086611

Thase ME, Clayton AH, Haight BR, et al: A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. *J Clin Psychopharmacol* 26(5):482–488, 2006 16974189

Thase ME, Haight BR, Johnson MC, et al: A randomized, double-blind, placebo-controlled study of the effect of sustained-release bupropion on blood pressure in individuals with mild untreated hypertension. *J Clin Psychopharmacol* 28(3): 302–307, 2008 18480687

Thomas KH, Martin RM, Davies NM, et al: Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ* 347:f5704, 2013 24124105

Tripathi A, Greenberger PA: Bupropion hydrochloride induced serum sickness-like reaction. *Ann Allergy Asthma Immunol* 83(2):165–166, 1999 10480592

Trivedi MH, Rush AJ, Carmody TJ, et al: Do bupropion SR and sertraline differ in their effects on anxiety in depressed patients? *J Clin Psychiatry* 62(10):776–781, 2001 11816866

Trivedi MH, Fava M, Wisniewski SR, et al; STAR\*D Study Team: Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 354(12):1243–1252, 2006 16554526

Valeant Pharmaceuticals North America: WELLBUTRIN XL (bupropion hydrochloride extended-release) tablets, for oral use; full prescribing information. Bridgewater, NJ,

Valeant Pharmaceuticals North America LLC, revised December 2014. Available at: <http://www.valeant.com/Portals/25/Pdf/PI/Wellbutrin-XL-PI.pdf>. Accessed May 5, 2016.

Vento AE, Schifano F, Gentili F, et al: Bupropion perceived as a stimulant by two patients with a previous history of cocaine misuse. *Ann Ist Super Sanita* 49(4):402-405, 2013 24334787

Verpeut JL, Bello NT: Drug safety evaluation of naltrexone/bupropion for the treatment of obesity. *Expert Opin Drug Saf* 13(6):831-841, 2014 24766397

Wang GJ, Tomasi D, Volkow ND, et al: Effect of combined naltrexone and bupropion therapy on the brain's reactivity to food cues. *Int J Obes* 38(5):682-688, 2014 23924756

Weihs KL, Settle EC Jr, Batey SR, et al: Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psychiatry* 61(3):196-202, 2000 10817105

Weihs KL, Houser TL, Batey SR, et al: Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. *Biol Psychiatry* 51(9):753-761, 2002 11983189

Weintraub D, Linder MW: Amphetamine positive toxicology screen secondary to bupropion. *Depress Anxiety* 12(1):53-54, 2000 10999247

Weisler RH, Johnston JA, Lineberry CG, et al: Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 14(3):170-179, 1994 8027413

Wilens TE, Spencer TJ, Biederman J, et al: A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry* 158(2):282-288, 2001 11156812

Wilkinson GR: Drug metabolism and variability among patients in drug response. *N Engl J Med* 352(21):2211-

2221, 2005 15917386

Worrall SP, Almond MK, Dhillon S: Pharmacokinetics of bupropion and its metabolites in haemodialysis patients who smoke. A single dose study. Nephron Clin Pract 97(3):c83-c89, 2004 15292684

Wright G, Galloway L, Kim J, et al: Bupropion in the long-term treatment of cyclic mood disorders: mood stabilizing effects. J Clin Psychiatry 46(1):22-25, 1985 2856918



# CHAPTER 19

## Venlafaxine and Desvenlafaxine

Michael E. Thase, M.D.

---

### History and Discovery

---

Venlafaxine was developed as the first selective serotonin-norepinephrine reuptake inhibitor (SNRI) in the late 1980s and early 1990s ([Bolden-Watson and Richelson 1993](#); [Muth et al. 1986](#)). Several early randomized controlled trials (RCTs) confirmed that venlafaxine had antidepressant effects comparable to those of tricyclic antidepressants (TCAs), with fewer side effects attributable to anticholinergic and antihistaminergic activity (see, e.g., [Einarson et al. 1999](#)). An immediate-release (IR) form of venlafaxine was approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD) in 1994, and the extended-release (XR) formulation was introduced in 1997. Made available after several widely prescribed newer-generation

antidepressants (e.g., fluoxetine, sertraline, paroxetine), venlafaxine became one of the leading alternatives for patients who do not respond to selective serotonin reuptake inhibitors (SSRIs).

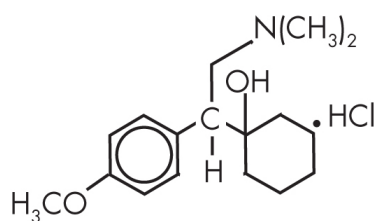
*O*-Desmethylvenlafaxine (ODV), the primary active metabolite of venlafaxine, is also classified as an SNRI. An extended-release formulation of ODV was developed and tested, and in 2008 desvenlafaxine succinate (DVS) received FDA approval for the treatment of MDD. Compared with venlafaxine, desvenlafaxine has somewhat greater potency for blockade of the norepinephrine transporter, and the succinate formulation has substantially greater bioavailability ([Deecher et al. 2006](#)).

---

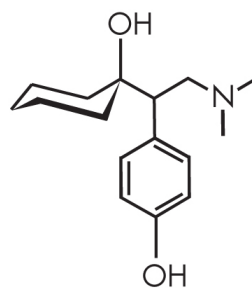
## Structure-Activity Relations and Pharmacological Profile

---

Venlafaxine and desvenlafaxine are bicyclic phenylethylamine compounds and are structurally and chemically unrelated to all other available antidepressants and anxiolytics ([Figure 19-1](#)). Venlafaxine and desvenlafaxine inhibit the neuronal reuptake of serotonin (5-HT) and norepinephrine in both in vitro and ex vivo experimental paradigms ([Bolden-Watson and Richelson 1993](#); [Muth et al. 1986](#); [Owens et al. 1997, 2008](#)). Neither drug inhibits monoamine oxidase or has meaningful affinity for muscarinic, cholinergic, histaminergic H<sub>1</sub>, or  $\alpha$ -adrenergic receptors ([Bolden-Watson and Richelson 1993](#); [Muth et al. 1986](#)).



Venlafaxine



Desvenlafaxine

---

**FIGURE 19-1.** Chemical structures of venlafaxine and desvenlafaxine.

---

---

## Pharmacokinetics and Disposition

---

Venlafaxine and desvenlafaxine are well absorbed after oral ingestion and undergo extensive first-pass hepatic metabolism. ODV is the only active metabolite of venlafaxine, and ODV (desvenlafaxine) itself has no active metabolites. Following ingestion of venlafaxine IR, peak plasma concentrations are achieved within 2 hours for venlafaxine and within 3 hours for ODV ([Troy et al. 1995](#)). Venlafaxine XR is absorbed more slowly than the IR formulation (peak plasma concentrations are achieved within 5.5 hours for venlafaxine and within 9 hours for ODV), resulting in lower peak and higher trough plasma concentrations. Steady-state plasma concentrations of both venlafaxine and ODV are reached within 3–4 days of therapy. For extensive (i.e., normal) metabolizers, ODV accounts for at least 70% of the total drug concentration at steady state ([Klamerus et al. 1992](#)). Venlafaxine and

desvenlafaxine exhibit linear kinetics across clinically relevant dosages (i.e., 50–450 mg/day) ([Klamerus et al. 1992](#)). Both drugs are minimally bound to plasma albumin, and both are primarily eliminated by the kidneys ([Howell et al. 1993](#)). Clearance of ODV (half-life=10 hours) is slower than that of venlafaxine (half-life=4 hours).

The recommended starting dosage of venlafaxine is 75 mg/day (taken either in divided doses [IR] or once daily [XR]), which is the minimum effective dosage. A lower starting dosage (37.5 mg/day) is often used in older patients or those who have a history of tolerability problems. The maximum approved dosages for the IR and XR formulations are 375 mg/day and 225 mg/day, respectively. The recommended starting dosage of desvenlafaxine is 50 mg/day, which is also the minimum effective dosage; 100 mg/day is the maximum approved dosage. Lower dosages of both drugs are recommended for patients with renal insufficiency; lower dosages of venlafaxine are also recommended for patients with liver disease.

Venlafaxine shows a dose-response relationship for efficacy in MDD ([Kelsey 1996](#); [Khan et al. 1998](#); [Rudolph et al. 1998](#); [Thase et al. 2006](#)). Whereas the original form of venlafaxine was approved for treatment at dosages of up to 375 mg/day given in divided doses, the recommended maximum daily dosage of the once-daily XR formulation was “capped” at 225 mg.

Desvenlafaxine (administered as DVS) does not exhibit a positive dose-response curve for efficacy in MDD: drug-versus-placebo differences for 50 mg/day are as large as those observed for higher dosages ([Thase et al. 2009](#)). It has not been determined whether patients who do not respond to 50 mg/day might benefit from upward titration.

As we discuss later (see “Side Effects and Toxicology” section), there is a negative dose-response curve for tolerability, with any potential for added benefit at dosages above 100 mg/day offset by increased attrition due to intolerable side effects.

---

## Mechanism of Action

---

Venlafaxine and desvenlafaxine are potent inhibitors of 5-HT reuptake at minimum therapeutic dosages; inhibition of norepinephrine reuptake is lower at these dosages ([Bolden-Watson and Richelson 1993](#); [Deecher et al. 2006](#); [Owens et al. 2008](#); [Vaishnavi et al. 2004](#)). Studies using positron emission tomography (PET) to estimate receptor occupancy demonstrate that the minimum effective total daily dosage of venlafaxine (75 mg) yields about 80% occupancy of the 5-HT transporter ([Voineskos et al. 2007](#)). It has long been thought that the ascending dose-response relationship of venlafaxine is linked to a dose-dependent increase in norepinephrine transporter (NET) occupancy ([Kelsey 1996](#); [Thase and Sloan 2006](#)). Although some experimental ([Harvey et al. 2000](#)) and clinical ([Davidson et al. 2005](#); [Entsuah and Gao 2002](#); [Rudolph et al. 1998](#); [Thase 1998](#); [Thase et al. 2006](#)) data support this hypothesis, significant effects on autonomic measures of noradrenergic function are evident in healthy volunteers at “5-HT selective” dosages (i.e., 37.5 and 75 mg/day) of venlafaxine ([Bitsios et al. 1999](#); [Siepmann et al. 2007](#)). To date, PET studies of NET occupancy in depressed patients receiving venlafaxine have not been conducted. Results of one small PET study in primates suggested that in vivo NET occupancy of SNRIs is

greater than would be predicted from in vitro studies ([Takano et al. 2013](#)). There is no consensus about the optimal degree of NET inhibition during SNRI therapy.

---

## Indications and Efficacy

---

Venlafaxine is approved by the FDA for the treatment of MDD, generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder. Desvenlafaxine is approved only for the treatment of MDD.

### Major Depressive Disorder

Venlafaxine's antidepressant efficacy at dosages ranging from 75 mg/day to 375 mg/day was established in a large number of RCTs (see [Thase and Sloan 2006](#) for a review). Meta-analyses of studies using active comparators concluded that venlafaxine is, at the least, one of the more effective newer-generation antidepressants ([Cipriani et al. 2009](#); [Nemeroff et al. 2008](#); [Schueler et al. 2011](#); [Smith et al. 2002](#); [Thase et al. 2001](#)). Evidence of venlafaxine's superiority over the SSRIs as a class is largely dependent on the high proportion of early studies using fluoxetine ([Cipriani et al. 2009](#); [Nemeroff et al. 2008](#)), and there is no evidence that venlafaxine is more effective than certain other members of the SSRI class, such as sertraline ([Cipriani et al. 2009](#)) and escitalopram ([Kennedy et al. 2009](#)).

The antidepressant efficacy of desvenlafaxine versus placebo was established at dosages ranging from 50 mg/day to 400 mg/day ([Kornstein et al. 2014](#); [Thase et al.](#)

2009). Only a handful of studies have compared desvenlafaxine with other active antidepressants, and there was no evidence for its greater efficacy. A meta-analysis of studies of desvenlafaxine at approved dosages (50–100 mg/day) concluded that its efficacy was similar to that of venlafaxine XR at comparable dosages (i.e., 75–225 mg/day) (Coleman et al. 2012).

With respect to other newer antidepressants, venlafaxine has been compared with mirtazapine (Benkert et al. 2006; Guelfi et al. 2001), bupropion (Hewett et al. 2010; Thase et al. 2006), duloxetine (Perahia et al. 2008), agomelatine (Kennedy et al. 2008), and vortioxetine (Alvarez et al. 2012; Wang et al. 2015). Overall, the results of these studies do not support the hypothesis that venlafaxine routinely conveys an efficacy advantage over other non-SSRI options. Furthermore, the results of these studies suggest that the various non-SSRI antidepressants may offer certain tolerability advantages over venlafaxine. For example, in comparison with venlafaxine, mirtazapine and agomelatine were more effective in insomnia, agomelatine and bupropion caused less treatment-emergent sexual dysfunction, and vortioxetine produced fewer noradrenergically mediated side effects (e.g., light-headedness) (Wang et al. 2015).

Neither venlafaxine nor desvenlafaxine has established efficacy in the adjunctive treatment of bipolar depression. In two comparison studies that enrolled patients with bipolar I depression who were being treated with mood stabilizers, adjunctive therapy with venlafaxine was associated with somewhat higher rates of treatment-emergent affective switches in comparison with adjunctive paroxetine (Vieta et al. 2002) and in comparison with adjunctive sertraline or bupropion (Post et al. 2006).

Interestingly, several studies comparing venlafaxine and lithium as monotherapy in outpatients with bipolar II depression ([Amsterdam and Shults 2008](#); [Amsterdam et al. 2016](#)) found significant advantages for the SNRI, with no increased risk of treatment-emergent affective shifts. Although it is difficult to reconcile these discrepancies, these results do suggest that a subset of patients within the broader bipolar spectrum can be treated safely and effectively with venlafaxine.

In an era in which most depressed patients are first treated with an SSRI, venlafaxine has for more than two decades been one of the preferred second-line choices for patients who do not respond to SSRI treatment ([Thase et al. 2000](#)). A meta-analysis of randomized trials of patients with SSRI-resistant depression comparing venlafaxine with other second-line antidepressants confirmed a modest advantage for switching outside the SSRI class ([Papakostas et al. 2008](#)).

Both venlafaxine and desvenlafaxine have demonstrated preventive efficacy in studies of longer-term therapy of MDD ([Boyer et al. 2015](#); [Rickels et al. 2010a](#); [Simon et al. 2004](#)). A large long-term study of patients with recurrent depression similarly demonstrated significant prophylactic effects for venlafaxine (versus placebo) after 12 months ([Kocsis et al. 2007](#)) and 24 months ([Keller et al. 2007](#)) of maintenance therapy. This study also included an active comparison group treated with fluoxetine. Although results were generally comparable across the acute and continuation phases and during the first year of maintenance treatment, a strong trend emerged during the second year of maintenance phase therapy suggesting greater efficacy for venlafaxine ([Thase et al. 2011](#)).



# Generalized Anxiety Disorder

Venlafaxine XR was approved by the FDA for the treatment of GAD on the basis of a series of placebo-controlled RCTs (see [Thase and Sloan 2006](#)). Across studies, efficacy was established for dosages ranging from 75 mg/day to 225 mg/day, with little evidence of a dose-response relationship. Sustained efficacy across 12 months was subsequently demonstrated in a study using a classic placebo-controlled discontinuation design ([Rickels et al. 2010b](#)).

With respect to comparative efficacy, the superiority of venlafaxine XR to buspirone was found on some—although not all—measures in one study ([Davidson et al. 1999](#)), and neither venlafaxine nor diazepam was found to be effective in the only study to use a benzodiazepine comparison group ([Hackett et al. 2003](#)). Venlafaxine XR, when compared with duloxetine and escitalopram, was found to be comparably effective in the only studies of GAD to use antidepressant comparators ([Allgulander et al. 2008](#); [Bose et al. 2008](#)).

## Social Anxiety Disorder (Social Phobia)

Venlafaxine XR was approved for the treatment of social anxiety disorder on the basis of a series of RCTs that confirmed its efficacy and safety relative to placebo across up to 6 months of double-blind therapy (see [Thase and Sloan 2006](#)). As was the case in GAD, effective dosages ranged from 75 mg/day to 225 mg/day, with little evidence of an ascending dose-response relationship. In the two studies that included paroxetine as an active comparator,

the SSRI and the SNRI were comparably effective and similarly well tolerated ([Allgulander et al. 2004](#); [Liebowitz et al. 2005](#)).

## Panic Disorder

The efficacy of venlafaxine XR in panic disorder was demonstrated in three placebo-controlled studies of acute-phase therapy ([Bradwejn et al. 2005](#); [Pollack et al. 2007a, 2007b](#)). These studies, which used a 37.5-mg/day starting dosage to minimize side effects, established an effective dosage range for venlafaxine of 75–225 mg/day. Two of the studies included paroxetine (40 mg/day) as an active comparator ([Pollack et al. 2007a, 2007b](#)). In the first comparison study, two fixed dosages of venlafaxine XR (75 mg/day or 150 mg/day) were comparable to paroxetine in both efficacy and tolerability ([Pollack et al. 2007a](#)). In the second comparison study, an RCT in which two fixed dosages (75 mg/day or 225 mg/day) were also used, the higher dosage of venlafaxine was significantly more effective than paroxetine on several secondary outcome measures, including proportion of patients experiencing complete relief from full-symptom panic attacks (70% vs. 58%) ([Pollack et al. 2007b](#)). Finally, a fourth study using a relapse prevention design demonstrated sustained efficacy for venlafaxine XR across 6 months of therapy ([Ferguson et al. 2007](#)).

## Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder

The efficacy of venlafaxine therapy in posttraumatic stress disorder was established in two large placebo-controlled studies ([Davidson et al. 2006a, 2006b](#)). Although no pivotal studies of venlafaxine therapy were conducted in obsessive-compulsive disorder, the results of a 12-week single-blind study indicated that venlafaxine might be at least as effective as clomipramine and significantly better tolerated ([Albert et al. 2002](#)).

## Premenstrual Dysphoric Disorder

A double-blind RCT evaluated the efficacy of venlafaxine IR in the treatment of premenstrual dysphoric disorder in 157 women across four menstrual cycles ([Freeman et al. 2001](#)). Dosages ranged from 50 mg/day to 200 mg/day, with adjustments for adverse events or lack of efficacy early in each cycle. Analyses of daily symptom rating scores revealed significantly greater improvement in the venlafaxine group compared with the placebo group at endpoint on the primary factors of emotion, function, physical symptoms, and pain.

## Vasomotor Symptoms Associated With Menopause

An extensive research program evaluated the efficacy, tolerability, and safety of desvenlafaxine for the treatment of vasomotor symptoms associated with menopause (see [Sun et al. 2013](#) and [Tella and Gallagher 2014](#) for a meta-analysis and a review, respectively). Evidence confirmed the efficacy of desvenlafaxine at dosages of at least 100 mg/day

and showed safety and tolerability profiles comparable to those seen in studies of MDD. Despite such findings, the FDA did not approve desvenlafaxine for this indication. Although less extensively studied than desvenlafaxine, venlafaxine also is widely used for the treatment of vasomotor symptoms associated with menopause, with an efficacy profile comparable to that of SSRIs ([Davari-Tanha et al. 2016](#); [Ensrud et al. 2015](#)). Likewise, venlafaxine has been shown to be an effective treatment for hot flashes and related symptoms following total hysterectomy in cancer patients ([Ramaswami et al. 2015](#)).

## Treatment of Children and Adolescents

Neither venlafaxine XR nor desvenlafaxine is approved for the treatment of individuals younger than 18 years. Six studies of venlafaxine XR and one study of desvenlafaxine have been completed in pediatric populations. With respect to venlafaxine, there were a pair of studies in MDD ([Emslie et al. 2007](#)), two RCTs in GAD ([Rynn et al. 2007](#)), one study in social anxiety disorder ([March et al. 2007](#)), and a large RCT in SSRI-resistant depression ([Brent et al. 2008](#)). For desvenlafaxine, there was one small study in MDD ([Findling et al. 2014](#)).

Results in the depression studies of venlafaxine XR (pooled  $N=334$ ) indicated that drug was significantly more effective than placebo among participants ages 12–17 years, but not among those ages 7–11 years ([Emslie et al. 2007](#)). Overall, venlafaxine XR therapy was associated with an increased risk of treatment-emergent suicidal and aggressive behaviors compared with placebo. In the pair of

GAD studies (pooled  $N=330$ ), venlafaxine XR was significantly more effective than placebo in the pooled data set; one study was unequivocally positive, but the second study failed to find a separation between drug and placebo on the primary outcome measure ([Rynn et al. 2007](#)). In the social anxiety disorder study ( $N=293$ ), venlafaxine XR was significantly more effective than placebo on both primary and secondary outcome measures ([March et al. 2007](#)). Finally, in a large National Institute of Mental Health-funded study of adolescents with a history of nonresponse to antidepressant medication, switching to venlafaxine XR therapy was no more effective—and was somewhat less well tolerated—than switching to a second SSRI. Both venlafaxine XR and SSRIs were more effective when used in combination with cognitive-behavioral therapy than when used as monotherapy ([Brent et al. 2008](#)).

[Findling et al. \(2014\)](#) conducted an 8-week open-label, fixed-dose multicenter study of desvenlafaxine in children ( $n=20$ ; ages 7–11 years) and adolescents ( $n=20$ ; ages 12–17 years) with MDD. Children received dosages of 10–100 mg/day, and adolescents received 25–200 mg/day. Desvenlafaxine was generally tolerable, with only 4 children (20%) and 3 adolescents (15%) withdrawing from treatment because of side effects. Both pulse rates and blood pressures increased significantly during treatment; however, there were no cases in which these values were judged to be of clinical concern. Although the absence of a placebo control group precluded an assessment of efficacy, mean Hamilton Rating Scale for Depression (Ham-D; [Hamilton 1960](#)) total scores decreased by more than 50% during the 8-week fixed-dose study, and these improvements were sustained across 6 months of flexible-

dose extension therapy. Two adolescents reported suicidal ideation before and during desvenlafaxine treatment.

---

## Side Effects and Toxicology

---

The tolerability profiles of venlafaxine and desvenlafaxine include all of the characteristic side effects associated with 5-HT uptake inhibition (i.e., nausea, insomnia, tremor, and sexual dysfunction) as well as side effects attributable to norepinephrine reuptake inhibition (i.e., sweating, light-headedness, and dry mouth); therefore, therapy with these SNRIs is associated with a somewhat higher side-effect burden than is usual with the SSRIs ([Schueler et al. 2011](#); [Thase and Sloan 2006](#)). In the meta-analysis of patient-level data conducted by [Nemeroff et al. \(2008\)](#), for example, 11% of the patients treated with venlafaxine withdrew from therapy because of adverse events, compared with 9% of the patients treated with SSRIs. Because relatively low dosages of desvenlafaxine are now recommended, its side-effect profile in controlled studies tends to be more favorable than that of venlafaxine ([Coleman et al. 2012](#)). Available evidence suggests that rates of sexual side effects with venlafaxine or desvenlafaxine are comparable to those with SSRIs ([Clayton et al. 2002](#); [Kennedy et al. 2000](#); [Montejo et al. 2001](#); [Serretti and Chiesa 2009](#)).

Venlafaxine and desvenlafaxine do not adversely affect cardiac conduction or lower the seizure threshold at therapeutic dosages. Both drugs are associated with small average increases in pulse rate and dose-dependent increases in the risk of elevated blood pressure ([Clayton et al. 2009](#); [Thase 1998](#); [Thase et al. 2015](#)). It is recommended

that blood pressure be documented before initiating therapy with these medications and that blood pressure be periodically checked during ongoing therapy. At higher therapeutic dosages, venlafaxine is associated with a reduction in heart rate variability ([Davidson et al. 2005](#)); this effect may be exaggerated when venlafaxine is prescribed in combination with certain other medications, including mirtazapine or quetiapine ([Huang et al. 2016](#)).

Like the SSRIs, venlafaxine is associated with a small but significant increase in bleeding disorders. For example, in studies of the risk of bleeding following childbirth, venlafaxine was associated with an excess risk of postpartum hemorrhage (ranging from 1% to 4%) ([Gahr et al. 2015](#); [Hanley et al. 2016](#); [Palmsten et al. 2013](#)). In one study, the risk of bleeding during the final month of pregnancy was greater for SNRIs than for SSRIs ([Hanley et al. 2016](#)). Such risks have not yet been shown with desvenlafaxine, but given its substantial similarity to venlafaxine, comparable risks are likely to be demonstrated.

Venlafaxine and desvenlafaxine are classified by the FDA as pregnancy Category C drugs, indicating that there are no adequate and well-controlled studies in pregnant women and that the drugs should be used during pregnancy only if they are clearly clinically indicated. As noted above, venlafaxine has been associated with an increased risk of hemorrhage during or following delivery. Studies completed to date do not document an increased risk of any specific birth defect ([Lassen et al. 2016](#)). Venlafaxine and desvenlafaxine are excreted in human breast milk and therefore should not be taken by women who are breast-feeding.

It is well known that abrupt withdrawal of venlafaxine can result in “discontinuation-emergent” symptoms such as dizziness, dry mouth, insomnia, nausea, nervousness, sweating, anorexia, diarrhea, somnolence, and sensory disturbances ([Haddad 2001](#)). Available evidence suggests that desvenlafaxine may have somewhat less problematic discontinuation-emergent symptoms ([Montgomery et al. 2009](#)). To minimize discontinuation symptoms, therapy should be tapered over several weeks when possible, and prescribers should counsel patients not to abruptly stop taking their antidepressant medication.

A number of fatal overdoses of venlafaxine have been reported; there is less clinical experience with overdoses of desvenlafaxine. In nonfatal overdoses of venlafaxine, electrocardiogram changes (e.g., QT interval prolongation, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), serotonin syndrome, and seizures have been reported ([Howell et al. 2007](#); [Whyte et al. 2003](#)).

In a study using pharmacoepidemiological data collected in the United Kingdom, findings suggested that venlafaxine may be more lethal in overdose than the SSRIs, albeit less so than the TCAs ([Buckley and McManus 2002](#); [Hawton et al. 2010](#)). Because the statistical measure used in these studies, the Fatal Toxicity Index ([Henry 1989](#)), is based on the number of overdose deaths per million prescriptions, findings are subject to use biases, in that the patients who are treated with venlafaxine in the current prescribing environment tend to have more severe and resistant psychiatric illnesses compared with patients who are treated with SSRIs, and thus may have greater inherent suicide risk ([Mines et al. 2005](#); [Rubino et al. 2007](#)).



Nevertheless, venlafaxine's apparent excess lethality in overdose might be attributable to adverse effects on the seizure threshold ([Whyte et al. 2003](#)) and on cardiac conduction ([Howell et al. 2007](#)) at extremely high plasma levels.

---

## Drug-Drug Interactions

---

Venlafaxine undergoes extensive metabolism in the liver by the cytochrome P450 (CYP) enzyme system, particularly by the CYP2D6 isoenzyme, which is the pathway for conversion of venlafaxine into *O*-desmethylvenlafaxine. People who are poor metabolizers of CYP2D6 thus have unusually low plasma levels of the metabolite ODV ([Preskorn et al. 2009](#)) and may be less likely to benefit from treatment with the parent drug than patients who are normal or extensive metabolizers ([Lobello et al. 2010](#); [Shams et al. 2006](#)). Such patients therefore could potentially be better candidates for therapy with desvenlafaxine than for therapy with the parent drug.

In vitro and in vivo studies have shown that venlafaxine and ODV are weak inhibitors of CYP2D6 and cause little or no inhibition of other CYP isoenzymes, including 1A2, 2C9, 2C19, and 3A4 ([Ball et al. 1997](#); [Oganesian et al. 2009](#); [Owen and Nemeroff 1998](#)).

Use of venlafaxine or desvenlafaxine is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) because of the risk of serotonin syndrome. As with TCAs and SSRIs, venlafaxine or desvenlafaxine should not be initiated until 2 weeks after discontinuation of an MAOI,

and MAOI therapy should not be initiated until at least 7 days after discontinuation of venlafaxine or desvenlafaxine.

---

## Conclusion

---

Venlafaxine, the first member of the SNRI class in the United States and much of the world, is one of the more effective newer-generation antidepressants, with an overall safety profile that is intermediate between that of the SSRIs and that of the TCAs. There is evidence of an efficacy advantage for venlafaxine over fluoxetine and perhaps over other SSRIs; however, such an advantage has not been specifically demonstrated for all members of the SSRI class, most particularly escitalopram. Venlafaxine's treatment efficacy has also been established in GAD, social anxiety disorder, and panic disorder. Desvenlafaxine, which is approved only for the treatment of MDD, has several advantages relative to venlafaxine, including simpler dosing and metabolism that is not dependent on CYP2D6. Until generic formulations of desvenlafaxine are available, however, it seems likely that it will be more cost-effective to use generic formulations of venlafaxine XR, except for patients who cannot tolerate venlafaxine or who are known to be poor CYP2D6 metabolizers.

---

## References

---

Albert U, Aguglia E, Maina G, et al: Venlafaxine versus clomipramine in the treatment of obsessive-compulsive disorder: a preliminary single-blind, 12-week, controlled

study. J Clin Psychiatry 63(11): 1004-1009, 2002  
12444814

Allgulander C, Mangano R, Zhang J, et al; SAD 388 Study Group: Efficacy of Venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. Hum Psychopharmacol 19(6):387-396, 2004 15303242

Allgulander C, Nutt D, Detke M, et al: A non-inferiority comparison of duloxetine and venlafaxine in the treatment of adult patients with generalized anxiety disorder. J Psychopharmacol 22(4):417-425, 2008  
18635722

Alvarez E, Perez V, Dragheim M, et al: A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol 15(5):589-600, 2012 21767441

Amsterdam JD, Shults J: Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: a randomized open-label study. J Clin Psychopharmacol 28(2):171-181, 2008  
18344727

Amsterdam JD, Lorenzo-Luaces L, Soeller I, et al: Short-term venlafaxine v. lithium monotherapy for bipolar type II major depressive episodes: effectiveness and mood conversion rate. Br J Psychiatry 208(4):359-365, 2016  
26892848

Ball SE, Ahern D, Scatina J, Kao J: Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. Br J Clin Pharmacol 43(6):619-626, 1997 9205822

Benkert O, Szegedi A, Philipp M, et al: Mirtazapine orally disintegrating tablets versus venlafaxine extended release: a double-blind, randomized multicenter trial

- comparing the onset of antidepressant response in patients with major depressive disorder. *J Clin Psychopharmacol* 26(1):75-78, 2006 16415711
- Bitsios P, Szabadi E, Bradshaw CM: Comparison of the effects of venlafaxine, paroxetine and desipramine on the pupillary light reflex in man. *Psychopharmacology (Berl)* 143(3):286-292, 1999 10353432
- Bolden-Watson C, Richelson E: Blockade by newly developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci* 52(12):1023-1029, 1993 8445992
- Bose A, Korotzer A, Gommoll C, Li D: Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of generalized anxiety disorder. *Depress Anxiety* 25(10):854-861, 2008 18050245
- Boyer P, Vialet C, Hwang E, et al: Efficacy of desvenlafaxine 50 mg/d versus placebo in the long-term treatment of major depressive disorder: a randomized, double-blind trial. *Prim Care Companion CNS Disord* 17(4), 2015 26693033
- Bradwejn J, Ahokas A, Stein DJ, et al: Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry* 187:352-359, 2005 16199795
- Brent D, Emslie G, Clarke G, et al: Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA* 299(8):901-913, 2008 18314433
- Buckley NA, McManus PR: Fatal toxicity of serotonergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 325(7376):1332-1333, 2002 12468481
- Cipriani A, Furukawa TA, Salanti G, et al: Comparative efficacy and acceptability of 12 new-generation

- antidepressants: a multiple-treatments meta-analysis. *Lancet* 373(9665):746–758, 2009 19185342
- Clayton AH, Pradko JF, Croft HA, et al: Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 63(4):357–366, 2002 12000211
- Clayton AH, Kornstein SG, Rosas G, et al: An integrated analysis of the safety and tolerability of desvenlafaxine compared with placebo in the treatment of major depressive disorder. *CNS Spectr* 14(4):183–195, 2009 19407730
- Coleman KA, Xavier VY, Palmer TL, et al: An indirect comparison of the efficacy and safety of desvenlafaxine and venlafaxine using placebo as the common comparator. *CNS Spectr* 17(3):131–141, 2012 22883424
- Davari-Tanha F, Soleymani-Farsani M, Asadi M, et al: Comparison of citalopram and venlafaxine's role in treating sleep disturbances in menopausal women, a randomized, double-blind, placebo-controlled trial. *Arch Gynecol Obstet* 293(5):1007–1013, 2016 26437957
- Davidson JR, DuPont RL, Hedges D, et al: Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *J Clin Psychiatry* 60(8):528–535, 1999 10485635
- Davidson J, Watkins L, Owens M, et al: Effects of paroxetine and venlafaxine XR on heart rate variability in depression. *J Clin Psychopharmacol* 25(5):480–484, 2005 16160626
- Davidson J, Baldwin D, Stein DJ, et al: Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry* 63(10):1158–1165, 2006a 17015818
- Davidson J, Rothbaum BO, Tucker P, et al: Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J Clin Psychopharmacol* 26(3):259–267, 2006b 16702890

- Deecher DC, Beyer CE, Johnston G, et al: Desvenlafaxine succinate: A new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther* 318(2):657-665, 2006 16675639
- Einarson TR, Arikian SR, Casciano J, et al: Comparison of extended-release venlafaxine, selective serotonin reuptake inhibitors, and tricyclic antidepressants in the treatment of depression: a meta-analysis of randomized controlled trials. *Clin Ther* 21(2):296-308, 1999 10211533
- Emslie GJ, Findling RL, Yeung PP, et al: Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry* 46(4):479-488, 2007 17420682
- Ensrud KE, Guthrie KA, Hohensee C, et al: Effects of estradiol and venlafaxine on insomnia symptoms and sleep quality in women with hot flashes. *Sleep* 38(1):97-108, 2015 25325454
- Entsuaeh R, Gao B: Global benefit-risk evaluation of antidepressant action: comparison of pooled data for venlafaxine, SSRIs, and placebo. *CNS Spectr* 7(12):882-888, 2002 12766699
- Ferguson JM, Khan A, Mangano R, et al: Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. *J Clin Psychiatry* 68(1):58-68, 2007 17284131
- Findling RL, Groark J, Chiles D, et al: Safety and tolerability of desvenlafaxine in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 24(4):201-209, 2014 24611442
- Freeman EW, Rickels K, Yonkers KA, et al: Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 98(5 Pt 1):737-744, 2001 11704162
- Gahr M, Zeiss R, Lang D, et al: Association between haemorrhages and treatment with selective and non-selective serotonergic antidepressants: Possible

- implications of quantitative signal detection. *Psychiatry Res* 229(1-2):257-263, 2015 26208982
- Guelfi JD, Ansseau M, Timmerman L, et al; Mirtazapine-Venlafaxine Study Group: Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. *J Clin Psychopharmacol* 21(4):425-431, 2001 11476127
- Hackett D, Haudiquet V, Salinas E: A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. *Eur Psychiatry* 18(4): 182-187, 2003 12814852
- Haddad PM: Antidepressant discontinuation syndromes. *Drug Saf* 24(3):183-197, 2001 11347722
- Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56-62, 1960 14399272
- Hanley GE, Smolina K, Mintzes B, et al: Postpartum hemorrhage and use of serotonin reuptake inhibitor antidepressants in pregnancy. *Obstet Gynecol* 127(3):553-561, 2016 26855096
- Harvey AT, Rudolph RL, Preskorn SH: Evidence of the dual mechanisms of action of venlafaxine. *Arch Gen Psychiatry* 57(5): 503-509, 2000 10807491
- Hawton K, Bergen H, Simkin S, et al: Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. *Br J Psychiatry* 196(5):354-358, 2010 20435959
- Henry JA: A fatal toxicity index for antidepressant poisoning. *Acta Psychiatr Scand Suppl* 354:37-45, 1989 2589102
- Hewett K, Gee MD, Krishen A, et al: Double-blind, placebo-controlled comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J Psychopharmacol* 24(8):1209-1216, 2010 19939870
- Howell C, Wilson AD, Waring WS: Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235

- consecutive cases. *Br J Clin Pharmacol* 64(2):192-197, 2007 17298480
- Howell SR, Husbands GE, Scatina JA, et al: Metabolic disposition of <sup>14</sup>C-venlafaxine in mouse, rat, dog, rhesus monkey and man. *Xenobiotica* 23(4):349-359, 1993 8337893
- Huang WL, Liao SC, Kuo TB, et al: The effects of antidepressants and quetiapine on heart rate variability. *Pharmacopsychiatry* 49(5):191-198, 2016 27023265
- Keller MB, Trivedi MH, Thase ME, et al: The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) Study: outcomes from the 2-year and combined maintenance phases. *J Clin Psychiatry* 68(8):1246-1256, 2007 17854250
- Kelsey JE: Dose-response relationship with venlafaxine. *J Clin Psychopharmacol* 16 (3 suppl 2):21S-26S, discussion 26S-28S, 1996 8784645
- Kennedy SH, Eisfeld BS, Dickens SE, et al: Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry* 61(4):276-281, 2000 10830148
- Kennedy SH, Rizvi S, Fulton K, et al: A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol* 28(3):329-333, 2008 18480691
- Kennedy SH, Andersen HF, Thase ME: Escitalopram in the treatment of major depressive disorder: a meta-analysis. *Curr Med Res Opin* 25(1):161-175, 2009 19210149
- Khan A, Upton GV, Rudolph RL, et al; Venlafaxine Investigator Study Group: The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. *J Clin Psychopharmacol* 18(1):19-25, 1998 9472838
- Klamerus KJ, Maloney K, Rudolph RL, et al: Introduction of a composite parameter to the pharmacokinetics of



- venlafaxine and its active O-desmethyl metabolite. *J Clin Pharmacol* 32(8):716-724, 1992 1487561
- Kocsis JH, Thase ME, Trivedi MH, et al: Prevention of recurrent episodes of depression with venlafaxine ER in a 1-year maintenance phase from the PREVENT Study. *J Clin Psychiatry* 68(7):1014-1023, 2007 17685736
- Kornstein SG, McIntyre RS, Thase ME, et al: Desvenlafaxine for the treatment of major depressive disorder. *Expert Opin Pharmacother* 15(10):1449-1463, 2014 24914479
- Lassen D, Ennis ZN, Damkier P: First-trimester pregnancy exposure to venlafaxine or duloxetine and risk of major congenital malformations: a systematic review. *Basic Clin Pharmacol Toxicol* 118(1):32-36, 2016 26435496
- Liebowitz MR, Gelenberg AJ, Munjack D: Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry* 62(2):190-198, 2005 15699296
- Lobello KW, Preskorn SH, Guico-Pabia CJ, et al: Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. *J Clin Psychiatry* 71(11):1482-1487, 2010 20441720
- March JS, Entusah AR, Rynn M, et al: A Randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biol Psychiatry* 62(10):1149-1154, 2007 17553467
- Mines D, Hill D, Yu H, Novelli L: Prevalence of risk factors for suicide in patients prescribed venlafaxine, fluoxetine, and citalopram. *Pharmacoepidemiol Drug Saf* 14(6):367-372, 2005 15883980
- Montejo AL, Llorca G, Izquierdo JA, et al; Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction: Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J Clin Psychiatry* 62 (suppl 3): 10-21, 2001 11229449

- Montgomery SA, Fava M, Padmanabhan SK, et al: Discontinuation symptoms and taper/poststudy-emergent adverse events with desvenlafaxine treatment for major depressive disorder. *Int Clin Psychopharmacol* 24(6):296-305, 2009 19779354
- Muth EA, Haskins JT, Moyer JA, et al: Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ethyl cyclohexanol derivative. *Biochem Pharmacol* 35(24):4493-4497, 1986 3790168
- Nemeroff CB, Entsuah R, Benattia I, et al: Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. *Biol Psychiatry* 63(4):424-434, 2008 17888885
- Oganesian A, Shilling AD, Young-Sciame R, et al: Desvenlafaxine and venlafaxine exert minimal in vitro inhibition of human cytochrome P450 and P-glycoprotein activities. *Psychopharmacol Bull* 42(2):47-63, 2009 19629022
- Owen JR, Nemeroff CB: New antidepressants and the cytochrome P450 system: focus on venlafaxine, nefazodone, and mirtazapine. *Depress Anxiety* 7 (suppl 1):24-32, 1998 9597349
- Owens MJ, Morgan WN, Plott SJ, et al: Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Ther* 283(3):1305-1322, 1997 9400006
- Owens MJ, Krulewicz S, Simon JS, et al: Estimates of serotonin and norepinephrine transporter inhibition in depressed patients treated with paroxetine or venlafaxine. *Neuropsychopharmacology* 33(13): 3201-3212, 2008 18418363
- Palmsten K, Hernández-Díaz S, Huybrechts KF, et al: Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ* 347:f4877, 2013 23965506
- Papakostas GI, Fava M, Thase ME: Treatment of SSRI-resistant depression: a meta-analysis comparing within-

versus across-class switches. *Biol Psychiatry* 63(7):699-704, 2008 17919460

Perahia DG, Pritchett YL, Kajdasz DK, et al: A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res* 42(1):22-34, 2008 17445831

Pollack MH, Lepola U, Koponen H, et al: A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder. *Depress Anxiety* 24(1):1-14, 2007a 16894619

Pollack M, Mangano R, Entsuah R, et al: A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. *Psychopharmacology (Berl)* 194(2):233-242, 2007b 17589833

Post RM, Altshuler LL, Leverich GS, et al: Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 189:124-131, 2006 16880481

Preskorn S, Patroneva A, Silman H, et al: Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. *J Clin Psychopharmacol* 29(1):39-43, 2009 19142106

Ramaswami R, Villarreal MD, Pitta DM, et al: Venlafaxine in management of hot flashes in women with breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 152(2):231-237, 2015 26067931

Rickels K, Etemad B, Khalid-Khan S, et al: Time to relapse after 6 and 12 months' treatment of generalized anxiety disorder with venlafaxine extended release. *Arch Gen Psychiatry* 67(12):1274-1281, 2010a 21135327

Rickels K, Montgomery SA, Tourian KA, et al: Desvenlafaxine for the prevention of relapse in major depressive disorder: results of a randomized trial. *J Clin Psychopharmacol* 30(1):18-24, 2010b 20075643

- Rubino A, Roskell N, Tennis P, et al: Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study. *BMJ* 334(7587):242, 2007 17164297
- Rudolph RL, Fabre LF, Feighner JP, et al: A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. *J Clin Psychiatry* 59(3):116-122, 1998 9541154
- Rynn MA, Riddle MA, Yeung PP, Kunz NR: Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *Am J Psychiatry* 164(2):290-300, 2007 17267793
- Schueler YB, Koesters M, Wieseler B, et al: A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. *Acta Psychiatr Scand* 123(4):247-265, 2011 20831742
- Serretti A, Chiesa A: Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J Clin Psychopharmacol* 29(3):259-266, 2009 19440080
- Shams ME, Arnetz B, Hiemke C, et al: CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. *J Clin Pharm Ther* 31(5):493-502, 2006 16958828
- Siepmann T, Ziemssen T, Mueck-Weymann M, et al: The effects of venlafaxine on autonomic functions in healthy volunteers. *J Clin Psychopharmacol* 27(6):687-691, 2007 18004138
- Simon JS, Aguiar LM, Kunz NR, Lei D: Extended-release venlafaxine in relapse prevention for patients with major depressive disorder. *J Psychiatr Res* 38(3):249-257, 2004 15003430
- Smith D, Dempster C, Glanville J, et al: Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants:

- a meta-analysis. *Br J Psychiatry* 180:396-404, 2002 11983635
- Sun Z, Hao Y, Zhang M: Efficacy and safety of desvenlafaxine treatment for hot flashes associated with menopause: a meta-analysis of randomized controlled trials. *Gynecol Obstet Invest* 75(4):255-262, 2013 23548358
- Takano A, Halldin C, Farde L: SERT and NET occupancy by venlafaxine and milnacipran in nonhuman primates: a PET study. *Psychopharmacology (Berl)* 226(1):147-153, 2013 23090625
- Tella SH, Gallagher JC: Efficacy of desvenlafaxine succinate for menopausal hot flashes. *Expert Opin Pharmacother* 15(16):2407-2418, 2014 25252697
- Thase ME: Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *J Clin Psychiatry* 59(10):502-508, 1998 9818630
- Thase ME, Sloan DME: Venlafaxine, in *Essentials of Clinical Psychopharmacology*, 2nd Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, American Psychiatric Publishing, 2006, pp 159-170
- Thase ME, Friedman ES, Howland RH: Venlafaxine and treatment-resistant depression. *Depress Anxiety* 12 (suppl 1):55-62, 2000 11098415
- Thase ME, Entsuah AR, Rudolph RL: Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 178:234-241, 2001 11230034
- Thase ME, Shelton RC, Khan A: Treatment with venlafaxine extended release after SSRI nonresponse or intolerance: a randomized comparison of standard- and higher-dosing strategies. *J Clin Psychopharmacol* 26(3):250-258, 2006 16702889
- Thase ME, Kornstein SG, Germain JM, et al: An integrated analysis of the efficacy of desvenlafaxine compared with

placebo in patients with major depressive disorder. *CNS Spectr* 14(3):144-154, 2009 19407711

Thase ME, Gelenberg A, Kornstein SG, et al: Comparing venlafaxine extended release and fluoxetine for preventing the recurrence of major depression: results from the PREVENT study. *J Psychiatr Res* 45(3):412-420, 2011 20801464

Thase ME, Fayyad R, Cheng RF, et al: Effects of desvenlafaxine on blood pressure in patients treated for major depressive disorder: a pooled analysis. *Curr Med Res Opin* 31(4):809-820, 2015 25758058

Troy SM, Parker VD, Fruncillo RJ, et al: The pharmacokinetics of venlafaxine when given in a twice-daily regimen. *J Clin Pharmacol* 35(4):404-409, 1995 7650231

Vaishnavi SN, Nemeroff CB, Plott SJ, et al: Milnacipran: a comparative analysis of human monoamine uptake and transporter binding affinity. *Biol Psychiatry* 55(3):320-322, 2004 14744476

Vieta E, Martinez-Arán A, Goikolea JM, et al: A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. *J Clin Psychiatry* 63(6):508-512, 2002 12088162

Voineskos AN, Wilson AA, Boovariwala A, et al: Serotonin transporter occupancy of high-dose selective serotonin reuptake inhibitors during major depressive disorder measured with [11C]DASB positron emission tomography. *Psychopharmacology (Berl)* 193(4):539-545, 2007 17497139

Wang G, Gislum M, Filippov G, Montgomery S: Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study. *Curr Med Res Opin* 31(4):785-794, 2015 25650503

Whyte IM, Dawson AH, Buckley NA: Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM 96(5):369-374, 2003 12702786

## CHAPTER 20

# Duloxetine, Milnacipran, and Levomilnacipran

Sandhaya Norris, M.D.

Pierre Blier, M.D., Ph.D.

---

### History and Discovery

Duloxetine was first synthesized in the late 1980s and subsequently patented in 1991. It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD) and diabetic neuropathy in the third quarter of 2004. This long delay after the initiation of clinical investigations was the result of the drug's initial testing in depressed patients at low dosages of 5–20 mg/day, which were not efficacious. Duloxetine has subsequently received approval almost worldwide.

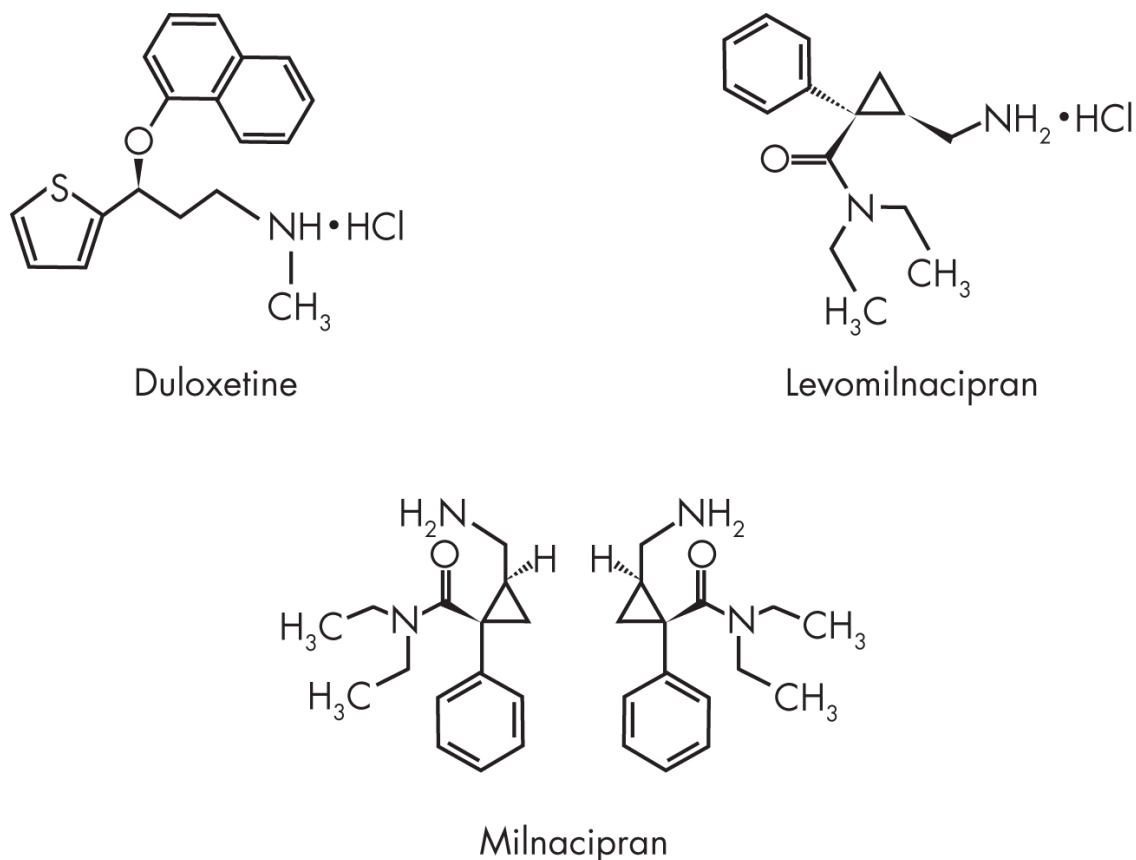
Although milnacipran was approved for the treatment of MDD in France in 1996 and has long been used for that indication in various countries worldwide, it has not received FDA approval for the treatment of MDD. Its sole approved indication in the United States (received in 2009) is for the treatment of fibromyalgia. Levomilnacipran, the active enantiomer of milnacipran, was approved for MDD in the United States in 2013 and in Canada in 2015.

---

### Structure-Activity Relations

Duloxetine, milnacipran, and levomilnacipran ([Figure 20-1](#)), along with venlafaxine, are antidepressant medications that can act as both serotonin (5-hydroxytryptamine; 5-HT) and norepinephrine reuptake inhibitors. Whereas selective serotonin reuptake inhibitors (SSRIs) target only the serotonin transporter (5-HTT), the dual-acting medications have the potential to inhibit both the 5-HTT and the norepinephrine transporter (NET). Collectively, these three medications are referred to as *serotonin-norepinephrine reuptake inhibitors* (SNRIs). Several lines of evidence must be considered, however, to determine at which concentrations SNRIs are indeed effective dual reuptake inhibitors. This is of crucial importance in estimating their potency in clinical settings.





**FIGURE 20-1.** Chemical structures of duloxetine, milnacipran, and levomilnacipran.

## Pharmacological Profile

### In Vitro Assessments

The first data to consider in determining the biochemical profile of reuptake inhibitors are their affinity values for membranal carriers. Finding these values involves determining the concentration of a medication necessary to displace 50% of the specific binding of a standard ligand for a given transporter subtype in a cell lysate preparation. This technique generally provides rough estimates of the potential for drugs to inhibit reuptake. A somewhat more informative approach involves determining the concentration of a drug necessary to inhibit the uptake of a given transmitter in intact cells from either animal brains or human cell lines. These physiological results are more reliable than mere binding data because of the integrity of the tissue. Indeed, data indicate that for some norepinephrine reuptake blockers, binding varies markedly depending on whether they are tested in membrane preparations or in intact cells, whereas for others, such as tricyclic antidepressants (TCAs), binding does not vary ([Mason et al. 2007](#)). As can be seen in [Table 20-1](#), both the absolute potencies and the ratios vary between the two preparations.

**TABLE 20-1. In vitro affinity and inhibition values for milnacipran and duloxetine for human reuptake transporters**

	Serotonin transporter	Norepinephrine transporter	Dopamine transporter
<b>In vitro affinity for uptake transporters, <math>K_i</math> (nM)</b>			
Milnacipran	8.4	22	ND
Duloxetine	0.1	1.2	230
<b>In vitro inhibition for uptake transporters, <math>K_i</math> (nM)</b>			
Milnacipran	151	68	ND
Duloxetine	3.7	20	439

*Note.* ND=not detectable. Values for duloxetine for the dopamine transporter are not physiologically significant.

*Source.* Adapted from [Vaishnavi et al. 2004](#).

## In Vivo Assessments

Ideally, the potency of reuptake inhibitors in animal experiments should be assessed in vivo with the medications administered peripherally. One common technique involves the use of microdialysis studies in which extracellular levels of neurotransmitters are estimated from the perfusion of artificial cerebrospinal fluid. Data generated with duloxetine indicate that it first increases the levels of serotonin in the rat brain, and with escalating dosage it then increases the levels of norepinephrine ([Koch et al. 2003](#)). In the case of milnacipran, the levels of serotonin and norepinephrine are generally increased to the same extent (in guinea pigs; [Moret and Briley 1997](#)), although pronounced regional differences have been observed ([Bel and Artigas 1999](#)). Levomilnacipran increases rat cortical extracellular levels of norepinephrine and serotonin, with a norepinephrine-to-serotonin potency ratio of 2:1 ([Auclair et al. 2013](#)).

Potency ratios also can be assessed in vivo with electrophysiological approaches. Specifically, by determining the capacity of reuptake inhibitors to suppress the firing of norepinephrine and serotonin neurons, reliable potency estimates can be obtained. As reuptake transporters are dose-dependently inhibited from their peripheral injection, there will be an accumulation of serotonin and norepinephrine at the cell-body level of those neurons that will activate their respective autoreceptors, thereby decreasing their firing activity. Use of this technique reveals that duloxetine suppresses the firing rate of serotonin neurons by 50% with an intravenous dose of 0.1 mg/kg and that of norepinephrine neurons with 0.5 mg/kg ([Kasamo et al. 1996](#)). This in vivo ratio of 1:5 is therefore quite different from the in vitro affinity ratio of 1:12 ([Vaishnavi et al. 2004](#); see [Table 20-1](#)). In contrast, use of the same technique reveals that the dose of milnacipran necessary to inhibit the firing rate of serotonin neurons by 50% is 5.7 mg/kg ([Mongeau et al. 1998](#)). The latter results therefore suggest that milnacipran is a much less potent inhibitor of serotonin reuptake than is duloxetine.

## Assessments of Serotonin and Norepinephrine Reuptake in Humans

Reuptake of neurotransmitters cannot be assessed as directly in humans as it can be in the brains of laboratory animals. However, several approaches can provide useful estimates. For instance, serotonin reuptake inhibition can be estimated with blood platelet uptake of radioactive serotonin, because platelets do not synthesize serotonin and they contain a 5-HTT that is nearly identical to the one present on serotonin neurons in the brain. And because more than 90% of the serotonin present in the blood is in platelets, whole-blood serotonin depletion by a reuptake inhibitor is an even simpler measure. With use of a peripheral (platelet) assay, duloxetine produces a dose-dependent depletion of the serotonin level that reaches about 60% with a dosage of 60 mg/day, an effect still significantly inferior to that seen with 100 mg/day of the TCA clomipramine (Turcotte et al. 2001). Milnacipran produces only a 64% inhibition of serotonin uptake with the usual recommended dosage of 100 mg/day (Palmier et al. 1989). By comparison, platelet assays reveal that SSRIs produce greater than 80% inhibition of serotonin uptake at clinically effective dosages (Gilmor et al. 2002).

Occupancy of the 5-HTT in the human brain can be assessed directly through positron emission tomography (PET) studies using carbon 11 ( $^{11}\text{C}$ )-labeled ligands of this transporter. All SSRIs and venlafaxine produce 80% occupancy of the 5-HTT at their minimum effective dosages in depression (Meyer et al. 2004). A duloxetine daily dosage of 60 mg, but not of 40 mg, produces a sustained 80% occupancy (Takano et al. 2006). PET studies show that milnacipran daily dosages of 100 mg and 200 mg produce 5-HTT occupancies of 40% and 60%, respectively (Nogami et al. 2013). To our knowledge, levomilnacipran has not been tested with this approach.

Researchers have attempted to assess occupancy of the NET in the human brain with PET. However, issues remain regarding the specificity of the reboxetine derivative used in several reports (i.e., the lack of a plasma concentration-occupancy relation; Takano et al. 2014). A variety of peripheral measures can, however, be used. In particular, the intravenous tyramine pressor test has produced consistent results. Tyramine penetrates into peripheral norepinephrine terminals through the NET and releases norepinephrine in a calcium-independent manner, thereby transiently elevating the systolic blood pressure. Any drug that effectively blocks the NET attenuates this pressor response in a dose-dependent manner. Whereas the SSRIs paroxetine and sertraline do not affect pressor response, the TCAs desipramine, nortriptyline, and clomipramine attenuate the pressor response, as also do the selective norepinephrine reuptake inhibitors maprotiline, reboxetine, and atomoxetine (Blier et al. 2007; Gobbi et al. 2003; Harvey et al. 2000; Turcotte et al. 2001). Venlafaxine significantly attenuates the tyramine response in depressed patients only at dosages in the range of 225–375 mg/day (Blier et al. 2010; Debonnel et al. 2007). Duloxetine exerts a clear effect starting at 120 mg/day (Vincent et al. 2004), whereas milnacipran and levomilnacipran have not yet been tested in this model. A variety of other peripheral measures suggest that duloxetine may begin to inhibit norepinephrine reuptake at 60 mg/day (Chalon et al. 2003; Vincent et al. 2004).

Taken together, these results obtained in humans indicate that duloxetine is a potent serotonin reuptake inhibitor at 60 mg/day. The exact degree of norepinephrine reuptake inhibition occurring in humans at a duloxetine dosage of 60 mg/day remains unclear, but duloxetine clearly achieves physiologically relevant norepinephrine reuptake inhibition at a dosage of 120 mg/day. A definitive answer regarding the degree of norepinephrine reuptake inhibition produced by duloxetine in the human brain awaits the availability of a specific PET ligand for the NET. Such experiments also will help determine the NET reserve beyond which the overall function of the norepinephrine system is altered, as was determined for the 5-HTT (i.e., 80%; Meyer et al. 2004).

Milnacipran appears to preferentially block norepinephrine reuptake, as has easily been demonstrated in the brains of laboratory animals even at low doses ([Bel and Artigas 1999](#); [Mongeau et al. 1998](#)), whereas blockade of serotonin reuptake can only be documented with high doses. In humans, robust serotonin reuptake inhibition (>80% transporter blockade) appears to be achieved only with supratherapeutic doses (i.e., 300–400 mg; [Palmier et al. 1989](#)). Similar preclinical results have been obtained with levomilnacipran ([Auclair et al. 2013](#)).

---

## Mechanism of Action

---

SNRIs produce rapid inhibition of reuptake transporters in the brain, but their antidepressant effects are generally not seen for at least 2 weeks. Extensive electrophysiological and microdialysis studies in laboratory animals have consistently shown a similar delay before SNRIs produce a net enhancement of serotonin and/or norepinephrine transmission (see [Blier 2006](#) for a review). This delay may occur because, as a result of 5-HTT inhibition, potent serotonin reuptake inhibitors initially suppress the firing of serotonin neurons through activation of serotonin type 1A (5-HT<sub>1A</sub>) autoreceptors on neuron cell bodies. After 2–3 weeks of sustained administration, 5-HT<sub>1A</sub> autoreceptors desensitize, and the serotonin neuronal firing rate returns to normal. At this point, there is a net enhancement of 5-HT transmission in the forebrain ([Blier and De Montigny 1983](#)).

In the case of drugs that inhibit the NET, the firing rate of norepinephrine neurons is promptly diminished through activation of the  $\alpha_2$ -adrenergic autoreceptors on neuron cell bodies. After 2–3 weeks of sustained administration, the firing rate remains attenuated because the cell body  $\alpha_2$ -adrenergic autoreceptors do not become desensitized. In contrast,  $\alpha_2$ -adrenergic autoreceptors on norepinephrine terminals generally become desensitized with sustained administration, leading to a net enhancement of norepinephrine transmission in the forebrain ([Invernizzi and Garattini 2004](#); [Rueter et al. 1998a, 1998b](#); [Szabo and Blier 2001](#)).

---

## Pharmacokinetics and Disposition

---

### Absorption and Distribution

#### Duloxetine

Duloxetine is available in an enteric-coated formulation. It is rapidly absorbed after oral administration, and its absorption is not altered by food. Duloxetine's plasma level is proportional to dose, up to a maximum of 60 mg twice daily. It is highly (about 90%) bound to its plasma proteins. Its plasma elimination half-life is approximately 12 hours ([Sharma et al. 2000](#)). On repeated administration, duloxetine takes approximately 3 days to reach a steady-state level.

#### Milnacipran and Levomilnacipran

Milnacipran and levomilnacipran have low (13% and 22%, respectively) and nonsaturable plasma protein binding. They are rapidly absorbed after oral administration and have high bioavailability, and their absorption is not affected by food intake. They have no active

metabolites, and their elimination half-life is 8 hours. Steady-state levels are thus achieved within 3 days, with no drug accumulation occurring during prolonged dosing, and milnacipran and levomilnacipran are cleared from the body within 3 days of treatment cessation.

## Metabolism and Elimination

### Duloxetine

Duloxetine is extensively metabolized through various pathways ([Skinner et al. 2003](#)). Numerous metabolites are found in circulation, none of which is believed to contribute to duloxetine's therapeutic activity. Duloxetine is metabolized mainly by cytochrome P450 (CYP) 1A2 and 2D6 isoenzymes.

### Milnacipran and Levomilnacipran

The CYP system is not involved in the metabolism of milnacipran or levomilnacipran ([Briley 1998](#); [Chen et al. 2015](#)). Their metabolism is mainly mediated through phase II conjugation. They are eliminated by the kidneys; approximately 50%–60% of the drugs are recovered in the urine as the parent compounds and 20% as their glucuronide conjugates. The remainder of the metabolites are excreted mainly as an *N*-dealkyl metabolite and its glucuronide conjugate and in negligible amounts as an *N*-didealkyl metabolite and a hydroxy metabolite ([Brunner et al. 2015](#); [Chen et al. 2015](#); [Puozzo and Leonard 1996](#); [Puozzo et al. 2002](#)).

---

## Indications and Efficacy

---

Duloxetine is FDA approved for use in the treatment of MDD and diabetic peripheral neuropathic pain; in Europe, it is also approved for the treatment of stress urinary incontinence. The fact that SNRIs are effective in anxiety disorders is consistent with a noradrenergic mechanism ([Montoya et al. 2016](#)).

Although milnacipran is used to treat MDD in various countries, it has not yet received FDA approval for that indication. In the United States, milnacipran is approved only for the treatment of fibromyalgia, and levomilnacipran is approved only for treatment of MDD. Clinical practice has shown us the efficacy of these two molecules in both conditions, despite the lack of controlled studies, because and of fact that levomilnacipran is the active enantiomer of milnacipran.

## Major Depressive Disorder

### Duloxetine

To date, 17 placebo-controlled studies have examined the antidepressant efficacy of duloxetine at dosages of 40–120 mg/day. (These studies and non-placebo-controlled duloxetine trials are summarized in [Tables 20–2](#) and [20–3](#).) Several of these studies had an active drug comparator group. Head-to-head comparisons with SSRIs and SNRIs have yielded mixed results, which appear to be influenced by dosing regimens ([Cipriani et al. 2012](#)). Overall, no statistically significant difference in efficacy was found between duloxetine and other drugs to treat MDD.

**TABLE 20-2. Duloxetine versus placebo/active comparator in acute studies (≤ 12**

Study	Duration (weeks)	Sample size	Duloxetine dosage (mg/day)	Comparator used	Comparator dosage (mg/day)	Placebo?
Goldstein et al. 2002	8	173	120	Fluoxetine	20	Y
Nemeroff et al. 2002 <sup>a</sup>	8	194	120	Fluoxetine	20	Y
Nemeroff et al. 2002 <sup>a</sup>	8	354	40, 80	Paroxetine	20	Y
Goldstein et al. 2004	8	353	40, 80	Paroxetine	20	Y
Detke et al. 2002a	9	245	60	None	N/A	Y
Detke et al. 2002b	9	267	60	None	N/A	Y
Detke et al. 2004	8	354	80, 120	Paroxetine	20	Y
Eli Lilly 2008a	8	323	60	Venlafaxine	150	N
Eli Lilly 2008b	8	491	60	Venlafaxine	150	N
Perahia et al. 2006b	8	392	80, 120	Paroxetine	20	Y
Raskin et al. 2007	8	311	60	None	—	Y
Nierenberg et al. 2007	8	684	60	Escitalopram	10	Y
Khan et al. 2007	8	278	60	Escitalopram	10-20	N
Brecht et al. 2007	8	327	60	None	—	Y
Lee et al. 2007	8	478	60	Paroxetine	20	N
Wade et al. 2007	8	295	60	Escitalopram	20	N
Perahia et al. 2008	12	667	120	Venlafaxine	225	Y
Cutler et al. 2009	6	453	60	Quetiapine	150-300	Y
Katona et al. 2012	6	453	60	Vortioxetine	5	Y
Mahableshwarkar et al. 2015	8	602	60	Vortioxetine	10-20	Y

*Note.* ">" denotes significantly greater effect; "=" denotes no difference.

<sup>a</sup>These failed studies were reported in this review but were not conducted by Dr. Nemeroff.

**TABLE 20-3. Duloxetine versus placebo/active SSRI/SNRI comparator in continuat weeks) of depression**

Study	Duration (weeks)	Sample size	Duloxetine dosage (mg/day)	Comparator used	Comparator dose (mg/day)	Placebo?	Results
-------	---------------------	----------------	----------------------------------	--------------------	--------------------------------	----------	---------

Study	Duration (weeks)	Sample size	Duloxetine dosage (mg/day)	Comparator used	Comparator dose (mg/day)	Placebo?	Results
<a href="#">Pigott et al. 2007</a>	32	684	60–120	Escitalopram	10–20	Y	Duloxetine placebo underpowered length of study
<a href="#">Wade et al. 2007</a>	24	295	60	Escitalopram	20	N	Duloxetine
<a href="#">Perahia et al. 2009</a>	52	288	60–120	—	—	Y	Duloxetine

*Note.* SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; “—” denotes no difference; “>” denotes significantly greater effect.

In a meta-analysis comparing SNRIs and SSRIs in the treatment of MDD, duloxetine 40–120 mg/day was found to be an effective antidepressant with an overall efficacy profile equal to that of fluoxetine and paroxetine at 20 mg/day ([Thase et al. 2007](#)). For patients with more severe symptoms, remission rates with duloxetine were statistically superior to those with the SSRIs. A meta-analysis of nine randomized controlled trials (RCTs) evaluating higher dosages of duloxetine in patients with severe depression concluded that duloxetine 120 mg/day produced significantly greater baseline-to-endpoint improvement versus placebo on several of the 17-item Hamilton Rating Scale for Depression (Ham-D-17) items ([Shelton et al. 2007a, 2007b](#)). These results indicate that for duloxetine, the higher dosage that achieves consistent norepinephrine reuptake inhibition may be more effective than the lower dosage that achieves only serotonin reuptake inhibition ([Chalon et al. 2003](#); [Turcotte et al. 2001](#); [Vincent et al. 2004](#)). This assertion was also made in a large open-label study in which patients who did not respond to 60 mg/day after 4 weeks improved with an up-titration to 120 mg/day ([Sagman et al. 2011](#)).

## Milnacipran

A meta-analysis of three short-term (4- to 8-week) double-blind, acute efficacy multicenter trials in inpatients and outpatients with moderate to severe depression concluded that milnacipran provides a superior antidepressant effect compared with placebo at dosages of 50 mg and 100 mg twice daily but not at a dosage of 25 mg twice daily ([Lecrubier et al. 1996](#); [Macher et al. 1989](#)).

Several studies have compared milnacipran with SSRIs or TCAs ([Table 20-4](#)). Milnacipran was noted to have equal efficacy but superior tolerability relative to the TCA imipramine ([Puech et al. 1997](#)). A meta-analysis concluded that evidence was insufficient to suggest a difference in response rates between milnacipran and any SSRI. Pooling response rates between agents yielded an overall response rate of 62% for milnacipran



and of 58% for the SSRIs (Papakostas and Fava 2007). A 24-week randomized, double-blind study demonstrated the safety, tolerability, and efficacy of flexible dosages of milnacipran and venlafaxine (100–200 mg/day) in MDD (Olié et al. 2010). There is no maximum recommended dosage for milnacipran, but it is important to note that the highest daily dosage tested so far, 300 mg, was tested in only 41 patients and for only 2 weeks (Ansseau et al. 1991). The maximum recommended dosage of milnacipran in fibromyalgia is 200 mg/day.

**TABLE 20-4. Milnacipran versus placebo/active SSRI comparator in acute studies (weeks) of depression**

Study	Duration (weeks)	Sample size	Milnacipran dosage (mg/day)	Comparator used	Comparator dosage (mg/day)	Results
Macher et al. 1989	4	58	100	Placebo	—	Milnacipran>placebo
Ansseau et al. 1991	4	127	150–300	Fluvoxamine	200	Milnacipran=fluvoxamine
Ansseau et al. 1994	6	190	100 <sup>a</sup>	Fluoxetine	20	Fluoxetine>milnacipran
Lecrubier et al. 1996 <sup>b</sup>	6–8	644	50–200	Placebo	—	Milnacipran 100, (but not 50)>placebo
Guelfi et al. 1998	12	289	100–200	Fluoxetine	20	Milnacipran=fluoxetine
Clerc et al. 2001	6	113	100	Fluvoxamine	200	Milnacipran>fluvoxamine
Sechter et al. 2004	6	302	100	Paroxetine	20	Milnacipran=paroxetine
Lee et al. 2005	6	70	100	Fluoxetine	20	Milnacipran=fluoxetine
Kamijima et al. 2013	9	905	100–200	Paroxetine	20–40	Milnacipran=paroxetine

*Note.* SSRI=selective serotonin reuptake inhibitor. “>” denotes significantly greater efficacy; “=” denotes no difference.

<sup>a</sup>Milnacipran was given once daily; this was in contrast to the other studies, in which it was administered on a twice-daily basis.

<sup>b</sup>This was a composite of two positive controlled studies.

### Levomilnacipran

Although it is recommended that levomilnacipran be started at 20 mg/day for the first few days, the minimum effective dosage of 40 mg/day is generally well tolerated as a starting dosage. The dosage can then be increased to 80 mg/day and 120 mg/day, according to tolerability and response. Four of the five controlled studies (involving a total of 3,020 patients) reported effectiveness for the 40–120 mg/day dosage range in patients with MDD ages 18–80 years (Table 20-5). No active comparator study has yet been published.



**TABLE 20-5. Levomilnacipran versus placebo in acute studies ( $\leq 10$  weeks) of depression**

Study	Duration (weeks)	Sample size	Levomilnacipran dosage (mg/day)	Results
<a href="#">Asnis et al. 2013</a>	8	704	40–120	Levomilnacipran>placebo
<a href="#">Montgomery et al. 2013</a>	10	975	75–100	Levomilnacipran>placebo
<a href="#">Bakish et al. 2014</a>	8	557	40–80	Levomilnacipran>placebo
<a href="#">Gommoll et al. 2014</a>	8	355	40–120	Levomilnacipran=placebo
<a href="#">Sambunaris et al. 2014</a>	8	429	40–120	Levomilnacipran>placebo

*Note.* “>” denotes significantly greater effect; “=” denotes no difference.

## Neuropathic and Chronic Pain

### Duloxetine

TCAs and SNRIs clearly produce significant relief of physical symptoms, such as pain in depression and in a variety of pain syndromes ([Stahl et al. 2005](#)). Duloxetine exerts a prompt and substantial analgesic effect over and above its antidepressant action ([Perahia et al. 2006a](#)). Potentiation of the activity of serotonin and norepinephrine is believed to result in central pain inhibition through descending modulatory pathways ([Sussman 2003](#)).

In an 8-week study, duloxetine at a fixed dosage of 60 mg/day significantly reduced pain measures from baseline to endpoint compared with placebo in patients with MDD and at least moderate pain. At 8 weeks, the mean average pain score on the Brief Pain Inventory—Short Form was close to 3, which can be considered a mild level of pain compared with the moderate or higher levels of pain indicated by baseline scores (5.8; [Brecht et al. 2007](#)). Similarly, elderly patients with depression who received duloxetine 60 mg/day for 8 weeks showed significant improvement on back pain scores and amount of time in pain compared with patients who received placebo ([Raskin et al. 2007](#)). In an RCT evaluating the efficacy of duloxetine 60 mg/day in patients with MDD and associated painful physical symptoms, the drug was superior to placebo in reducing overall, shoulder, and back pain, as well as time spent in pain ([Detke et al. 2002a](#)).

### Milnacipran

The capacity of milnacipran to relieve chronic pain has been reported in open trials, but no RCTs have been published to date.

## Fibromyalgia

### Duloxetine

A 12-week RCT of duloxetine 120 mg/day versus placebo in patients with fibromyalgia with or without depression found significant improvement in pain scores and in tender points in duloxetine recipients compared with placebo recipients ([Arnold et al. 2005](#)). Duloxetine 120 mg/day improved fibromyalgia symptoms and pain severity regardless of the extent of the accompanying depressive disorder. This direct effect of duloxetine on painful physical symptoms was later confirmed ([Robinson et al. 2013](#)).

### Milnacipran

An initial placebo-controlled study of milnacipran in fibromyalgia patients found that 37% of those who received 100 mg of milnacipran twice daily experienced a significant reduction (50% or more) in pain intensity compared with 14% of those who received placebo ([Vitton et al. 2004](#)). Subsequent studies led to milnacipran's approval in the United States for fibromyalgia ([Häuser et al. 2011](#)).

## Stress Urinary Incontinence

Duloxetine has been shown to be efficacious in the treatment of stress urinary incontinence, with 40 mg twice daily being the recommended dosage ([Li et al. 2013](#)). Serotonin and norepinephrine increase excitatory glutamate transmission in the Onuf nucleus in the sacral spinal cord, which facilitates urethral sphincter contraction ([Thor 2003](#)). This presumably is the mechanism for duloxetine's beneficial effects in the treatment of this problem.

---

## Side Effects and Toxicology

---

### Duloxetine

The safety and tolerability of duloxetine at a dosage range of 40–120 mg/day have been assessed in a number of clinical trials. In an 8-month study, the most common treatment-emergent adverse events were nausea, dry mouth, vomiting, yawning, and night sweats ([Pigott et al. 2007](#)). Most of these effects emerged early, within the first 8 weeks of treatment. Other studies have reported insomnia, somnolence, headaches, ejaculation disorders, diarrhea, constipation, and dizziness as common adverse events with duloxetine ([Detke et al. 2002a, 2002b](#); [Khan et al. 2007](#); [Nierenberg et al. 2007](#)).

The incidence of nausea associated with duloxetine appears to be comparable to that associated with other SSRIs and SNRIs. Nausea is transient and is usually experienced on treatment initiation. A starting dosage of 60 mg/day appears to provide the best combination of clinical response and tolerability ([Bech et al. 2006](#); [Pritchett et al. 2007](#)). Clinicians may, however, consider starting at a lower dosage (30 mg/day) for patients in whom tolerance is a concern. Compared with a duloxetine dosage of 60 mg/day, a dosage of 30 mg/day was associated with a lower rate of nausea (16%, vs. 33% for 60 mg/day) and was preferred by the majority of female patients ([Dunner et al. 2005](#); [Wilhelm et al. 2012](#)). The initial tolerability of duloxetine at 60 mg/day can be improved if the drug is taken with food; it then has tolerability comparable to an initial dosage of 30 mg/day ([Whitmyer et al. 2007](#)).

Duloxetine has not been associated with weight gain, and in one study it was in fact noted to be associated with a mean weight loss of 1 kg ([Nierenberg et al. 2007](#)). This

decrease was a significant difference compared with the lack of effect that placebo and escitalopram had on weight.

Changes in blood pressure and heart rate associated with duloxetine treatment do not appear to be clinically significant. Pooled data from 735 patients receiving duloxetine 40–120 mg/day showed that 0.7% experienced a 10 mm Hg increase in systolic or diastolic blood pressure, versus 0.4% of patients receiving placebo. Heart rate was increased by less than 1 beat per minute ([Schatzberg 2003](#)).

Rates of sexual dysfunction, including anorgasmia, erectile dysfunction, delayed ejaculation, and decreased libido, appear to be low with duloxetine. Researchers found that after 8 months, categorical outcomes shown on a questionnaire about changes in sexual functioning did not differ significantly between duloxetine- and escitalopram-treated groups ([Pigott et al. 2007](#)). In clinical practice, however, any drug that strongly inhibits serotonin reuptake has the potential to cause problematic sexual dysfunction in a significant proportion of patients.

A significantly higher rate of treatment discontinuation was reported among patients who were randomly assigned to receive duloxetine compared with those who were assigned to receive escitalopram or venlafaxine ([Cipriani et al. 2012](#)). It appears that study participants who discontinue duloxetine because of adverse events often do so during early treatment ([Nierenberg et al. 2007](#); [Perahia et al. 2008](#); [Pigott et al. 2007](#)), which may indicate poorer initial tolerability.

A systematic search of accumulated data for in utero exposure to duloxetine identified 16 major congenital malformations occurring in 668 infants, yielding a relative risk ratio of 0.8 ([Lassen et al. 2016](#)). Infant exposure to duloxetine through breast milk is less than 1% of the maternal weight-adjusted dosage ([Andrade 2014](#)). These figures suggest that duloxetine can be safely used during pregnancy and lactation.

## Milnacipran and Levomilnacipran

Analysis of a database of more than 3,300 patients concluded that the adverse-event profile of milnacipran in MDD was comparable to that of the SSRIs, except that the SSRIs were associated with a higher frequency of nausea and anxiety, whereas milnacipran was associated with a higher incidence of dysuria ([Puech et al. 1997](#)). Weight gain is uncommon, but sedation may be reported. Although data on rates of sexual dysfunction with milnacipran have not been reported, the incidence is estimated to be low compared with that associated with venlafaxine and SSRIs ([Stahl et al. 2005](#)). The lower incidence of nausea and sexual dysfunction with milnacipran relative to the SSRIs may be taken as indirect evidence of milnacipran's lower serotonin reuptake inhibition potential, given that these two treatment-emergent adverse events are classically induced by potent serotonin reuptake inhibitors.

Blood pressure increases with milnacipran are minimal. A 12-week randomized, double-blind study comparing milnacipran dosages of 100 mg/day and 200 mg/day versus fluoxetine 20 mg/day in 289 depressed inpatients found no significant changes in blood pressure in any of the groups ([Guelfi et al. 1998](#)). Tachycardia (defined as a heart rate greater than 100 beats per minute) was seen in 0% of patients receiving fluoxetine, 3% of patients receiving milnacipran 100 mg/day, and 6% of patients receiving milnacipran 200 mg/day. A review of more than 4,000 patients taking milnacipran for MDD showed that the mean increase in blood pressure was less than 1 mm Hg, and the mean increase in heart rate was 4 beats per minute ([Puech et al. 1997](#)). Given that an increase in heart rate is a thumbprint of potent norepinephrine reuptake inhibition, this increase is consistent with

the capacity of milnacipran to effectively block norepinephrine reuptake. No cardiotoxicity has been reported with overdoses of up to 2.8 g/day, which is 28 times the recommended daily dose ([Montgomery et al. 1996](#)).

An analysis of the long-term safety of milnacipran (in 715 patients with MDD receiving milnacipran for >6 months, and 189 for >12 months, as reported by [Puech et al. 1997](#)) concluded that most adverse events appeared within the first 3 months of treatment and that the incidence decreased steadily thereafter. More important, no treatment-emergent adverse events developed during long-term treatment.

The adverse-event profile of levomilnacipran is similar to that of milnacipran and basically relates to noradrenergic mechanisms. Common side effects include hyperhidrosis, increased heart rate, elevation of blood pressure, urinary hesitancy, constipation, and nausea. These effects are generally of low intensity and seldom lead to discontinuation. The QTc interval remains unaltered at all therapeutic dosages (40–120 mg/day) and is not prolonged to a clinically significant extent at a dosage of 300 mg ([Asnis and Henderson 2015](#)).

---

## Drug-Drug Interactions

---

Serotonin syndrome, a serious and potentially lethal pharmacodynamic interaction, can result if milnacipran, levomilnacipran, or duloxetine is taken concomitantly with a monoamine oxidase inhibitor (MAOI). To avoid this catastrophic outcome, an MAOI must not be initiated until at least 5 days after duloxetine, milnacipran, or levomilnacipran has been discontinued. A longer elimination period than that expected from plasma half-life is recommended, because brain elimination generally lags behind plasma elimination. At least a 14-day washout of MAOIs must be respected before starting any SNRI.

## Duloxetine

Inhibitors of CYP1A2, such as ciprofloxacin, increase plasma levels of duloxetine, and concomitant use may require that duloxetine dosages be reduced or that duloxetine be discontinued. When duloxetine is coadministered with a CYP2D6 inhibitor of moderate potency, such as bupropion or diphenhydramine, duloxetine levels may increase. However, such alterations of duloxetine levels are in general not clinically significant.

Duloxetine does not inhibit or induce the activity of the CYP1A2, 2C9, or 3A4 systems. It does, however, moderately inhibit the activity of the CYP2D6 isoenzyme. If duloxetine is coadministered with an agent metabolized by CYP2D6, clinicians should prescribe dosages that are approximately half those usually recommended for the concomitant medication. Duloxetine does not potentiate the psychotropic effects of ethanol or benzodiazepines.

## Milnacipran and Levomilnacipran

Because milnacipran and levomilnacipran are not metabolized by CYP pathways, they do not produce pharmacokinetic drug-drug interactions.

---

## Conclusion

---

At their minimum effective dosages, duloxetine (60 mg/day) and milnacipran (100 mg/day) potentially block the reuptake of serotonin and norepinephrine, respectively. In the case of duloxetine, it is difficult to imagine how an increase from a subtherapeutic dosage of 40 mg/day, at which it does not perform as a weak SSRI, to 60 mg/day could produce marked norepinephrine reuptake inhibition when the in vivo serotonin-to-norepinephrine reuptake potency ratio is 1:5. In the case of milnacipran, a 100-mg daily dosage produces suboptimal platelet serotonin reuptake inhibition. Duloxetine, at its maximum recommended dosage (120 mg/day), and milnacipran, at its upper therapeutic range (200 mg/day), are dual reuptake inhibitors. Consequently, none of the four SNRIs currently available can be considered equal reuptake inhibitors. They all show efficacy in the treatment of depression and pain syndromes, with emerging evidence also suggesting a potential role for duloxetine in the treatment of stress urinary incontinence and generalized anxiety disorder.

These medications are generally well tolerated, with most adverse effects occurring early in treatment, being mild to moderate in severity, and having a tendency to decrease or disappear with continued treatment.

Either duloxetine or milnacipran may be used as a first-line treatment for depression, because these medications are not toxic in overdose, and they can be used at a therapeutic dosage from treatment initiation onward with minimal side effects. Furthermore, data suggest that treatment with a dual reuptake inhibitor may be superior to treatment with an antidepressant with only one mechanism of action, such as an SSRI (Nemeroff et al. 2008; Poirier and Boyer 1999; Sagman et al. 2011; Thase et al. 2007). Consequently, these drugs may be beneficial in patients whose symptoms have been unresponsive to treatment with SSRIs and norepinephrine reuptake inhibitors, provided that they are taken at dosages at the upper end of the therapeutic range.

---

## References

---

- Andrade C: The safety of duloxetine during pregnancy and lactation. *J Clin Psychiatry* 75(12):e1423-e1427, 2014 25551238
- Anseau M, von Freyckell R, Gérard MA, et al: Interest of a loading dose of milnacipran in endogenous depressive inpatients. Comparison with the standard regimen and with fluvoxamine. *Eur Neuropsychopharmacol* 1(2):113-121, 1991 1821700
- Anseau M, Papart P, Troisfontaines B, et al: Controlled comparison of milnacipran and fluoxetine in major depression. *Psychopharmacology (Berl)* 114(1):131-137, 1994 7846195
- Arnold LM, Rosen A, Pritchett YL, et al: A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain* 119(1-3):5-15, 2005 16298061
- Asnis GM, Henderson MA: Levomilnacipran for the treatment of major depressive disorder: a review. *Neuropsychiatr Dis Treat* 11:125-135, 2015 25657584
- Asnis GM, Bose A, Gommoll CP, et al: Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: a phase 3, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 74(3):242-248, 2013 23561229
- Auclair AL, Martel JC, Assié MB, et al: Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology* 70:338-347, 2013 23499664
- Bakish D, Bose A, Gommoll C, et al: Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-

- controlled study. *J Psychiatry Neurosci* 39(1):40-49, 2014 24144196
- Bech P, Kajdasz DK, Porsdal V: Dose-response relationship of duloxetine in placebo-controlled clinical trials in patients with major depressive disorder. *Psychopharmacology (Berl)* 188(3):273-280, 2006 16960699
- Bel N, Artigas F: Modulation of the extracellular 5-hydroxytryptamine brain concentrations by the serotonin and noradrenaline reuptake inhibitor, milnacipran: microdialysis studies in rats. *Neuropsychopharmacology* 21(6):745-754, 1999 10633480
- Blier P: Dual serotonin and noradrenaline reuptake inhibitors: focus on their differences. *Int J Psychiatry Clin Pract* 10 (suppl 2):22-32, 2006 24921679
- Blier P, De Montigny C: Electrophysiological investigations on the effect of repeated zimelidine administration on serotonergic neurotransmission in the rat. *J Neurosci* 3(6):1270-1278, 1983 6304261
- Blier P, Saint-André E, Hébert C, et al: Effects of different doses of venlafaxine on serotonin and norepinephrine reuptake in healthy volunteers. *Int J Neuropsychopharmacol* 10(1):41-50, 2007 16690005
- Blier P, Aldosary F, Tremblay P, et al: Inhibition of norepinephrine and serotonin reuptake by venlafaxine, paroxetine, and atomoxetine in depressed patients (poster P-09.005). *Int J Neuropsychopharmacol* 13 (suppl 1):143S-144S, 2010
- Brecht S, Courtecuisse C, Debieuvre C, et al: Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. *J Clin Psychiatry* 68(11):1707-1716, 2007 18052564
- Briley M: Milnacipran, a well tolerated specific serotonin and norepinephrine reuptake inhibiting antidepressant. *CNS Drug Reviews* 4(2):137-148, 1998
- Brunner V, Maynadier B, Chen L, et al: Disposition and metabolism of [14C]-levomilnacipran, a serotonin and norepinephrine reuptake inhibitor, in humans, monkeys, and rats. *Drug Des Devel Ther* 9:3199-3215, 2015 26150694
- Chalon SA, Granier LA, Vandenhende FR, et al: Duloxetine increases serotonin and norepinephrine availability in healthy subjects: a double-blind, controlled study. *Neuropsychopharmacology* 28(9):1685-1693, 2003 12784100
- Chen L, Greenberg WM, Gommoll C, et al: Levomilnacipran pharmacokinetics in healthy volunteers versus patients with major depressive disorder and implications for norepinephrine and serotonin reuptake inhibition. *Clin Ther* 37(9):2059-2070, 2015 26256429
- Cipriani A, Koesters M, Furukawa TA, et al: Duloxetine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev* 10:CD006533, 2012 23076926
- Clerc G; Milnacipran/Fluvoxamine Study Group: Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine. *Int Clin Psychopharmacol* 16(3):145-151, 2001 11354236
- Cutler AJ, Montgomery SA, Feifel D, et al: Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. *J Clin Psychiatry* 70(4):526-539, 2009 19358790
- Debonnel G, Saint-André E, Hébert C, et al: Differential physiological effects of a low dose and high doses of venlafaxine in major depression. *Int J Neuropsychopharmacol* 10(1):51-61, 2007 16690006
- Detke MJ, Lu Y, Goldstein DJ, et al: Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 63(4):308-315, 2002a 12000204
- Detke MJ, Lu Y, Goldstein DJ, et al: Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J Psychiatr Res* 36(6):383-390, 2002b 12393307
- Detke MJ, Wiltse CG, Mallinckrodt CH, et al: Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur*



- Neuropsychopharmacol 14(6):457-470, 2004 15589385
- Dunner DL, Wohlreich MM, Mallinckrodt CH, et al: Clinical consequences of initial duloxetine dosing strategies: comparison of 30 and 60 mg QD starting doses. *Curr Ther Res Clin Exp* 66(6):522-540, 2005 24678074
- Eli Lilly: Duloxetine versus venlafaxine extended release in the treatment of major depressive disorder: study F1J-MC-HMBU. 2004a. Available at: 2008a. Available at: <http://www.lillytrials.com/results/Cymbalta.pdf>. Accessed September 14, 2016.
- Eli Lilly: Duloxetine versus venlafaxine extended release in the treatment of major depressive disorder: study F1J-MC-HMCQ. 2008b. Available at: <http://www.lillytrials.com/results/Cymbalta.pdf>. Accessed September 14, 2016.
- Gilmor ML, Owens MJ, Nemeroff CB: Inhibition of norepinephrine uptake in patients with major depression treated with paroxetine. *Am J Psychiatry* 159(10):1702-1710, 2002 12359676
- Gobbi G, Slater S, Boucher N, et al: Neurochemical and psychotropic effects of bupropion in healthy male subjects. *J Clin Psychopharmacol* 23(3):233-239, 2003 12826985
- Goldstein DJ, Mallinckrodt C, Lu Y, et al: Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 63(3):225-231, 2002 11926722
- Goldstein DJ, Lu Y, Detke MJ, et al: Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 24(4):389-399, 2004 15232330
- Gommoll C, Greenberg WM, Chen C: A randomized double-blind, placebo-controlled, study of flexible doses of levomilnacipran ER (40-120 mg/day) in patients with major depressive disorder. *J Drug Assess* 3(1):10-19, 2014 27536449
- Guelfi JD, Ansseau M, Corruble E, et al: A double-blind comparison of the efficacy and safety of milnacipran and fluoxetine in depressed inpatients. *Int Clin Psychopharmacol* 13(3):121-128, 1998 9690979
- Harvey AT, Rudolph RL, Preskorn SH: Evidence of the dual mechanisms of action of venlafaxine. *Arch Gen Psychiatry* 57(5):503-509, 2000 10807491
- Häuser W, Petzke F, Üçeyler N, et al: Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology (Oxford)* 50(3):532-543, 2011 21078630
- Invernizzi RW, Garattini S: Role of presynaptic alpha2-adrenoceptors in antidepressant action: recent findings from microdialysis studies. *Prog Neuropsychopharmacol Biol Psychiatry* 28(5):819-827, 2004 15363606
- Kamijima K, Hashimoto S, Nagayoshi E, et al: Double-blind, comparative study of milnacipran and paroxetine in Japanese patients with major depression. *Neuropsychiatr Dis Treat* 9:555-565, 2013 23650446
- Kasamo K, Blier P, De Montigny C: Blockade of the serotonin and norepinephrine uptake processes by duloxetine: in vitro and in vivo studies in the rat brain. *J Pharmacol Exp Ther* 277(1):278-286, 1996 8613930
- Katona C, Hansen T, Olsen CK: A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol* 27(4):215-223, 2012 22572889
- Khan A, Bose A, Alexopoulos GS, et al: Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. *Clin Drug Investig* 27(7):481-492, 2007 17563128
- Koch S, Hemrick-Luecke SK, Thompson LK, et al: Comparison of effects of dual transporter inhibitors on monoamine transporters and extracellular levels in rats. *Neuropharmacology* 45(7):935-944, 2003 14573386
- Lassen D, Ennis ZN, Damkier P: First-trimester pregnancy exposure to venlafaxine or duloxetine and risk of major congenital malformations: a systematic review. *Basic Clin Pharmacol Toxicol* 118(1):32-36, 2016 26435496

- Lecrubier Y, Pletan Y, Solles A, et al: Clinical efficacy of milnacipran: placebo-controlled trials. *Int Clin Psychopharmacol* 11 (suppl 4):29-33, 1996 8923124
- Lee MS, Ham BJ, Kee BS, et al: Comparison of efficacy and safety of milnacipran and fluoxetine in Korean patients with major depression. *Curr Med Res Opin* 21(9): 1369-1375, 2005 16197655
- Lee P, Shu L, Xu X, et al: Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. *Psychiatry Clin Neurosci* 61(3):295-307, 2007 17472599
- Li J, Yang L, Pu C, et al: The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *Int Urol Nephrol* 45(3):679-686, 2013 23504618
- Macher JP, Sichel JP, Serre C, et al: Double-blind placebo-controlled study of milnacipran in hospitalized patients with major depressive disorders. *Neuropsychobiology* 22(2):77-82, 1989 2701744
- Mahableshwarkar AR, Zajecka J, Jacobson W, et al: A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology* 40(8):2025-2037, 2015 25687662
- Mason JN, Deecker DC, Richmond RL, et al: Desvenlafaxine succinate identifies novel antagonist binding determinants in the human norepinephrine transporter. *J Pharmacol Exp Ther* 323(2):720-729, 2007 17673606
- Meyer JH, Wilson AA, Sagrati S, et al: Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [<sup>11</sup>C]DASB positron emission tomography study. *Am J Psychiatry* 161(5):826-835, 2004 15121647
- Mongeau R, Weiss M, de Montigny C, et al: Effect of acute, short- and long-term milnacipran administration on rat locus coeruleus noradrenergic and dorsal raphe serotonergic neurons. *Neuropharmacology* 37(7):905-918, 1998 9776386
- Montgomery SA, Prost JF, Solles A, et al: Efficacy and tolerability of milnacipran: an overview. *Int Clin Psychopharmacol* 11 (suppl 4):47-51, 1996 8923127
- Montgomery SA, Mansuy L, Ruth A, et al: Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry* 74(4):363-369, 2013 23656841
- Montoya A, Bruins R, Katzman MA, et al: The noradrenergic paradox: implications in the management of depression and anxiety. *Neuropsychiatr Dis Treat* 12:541-557, 2016 27042068
- Moret C, Briley M: Effects of milnacipran and pindolol on extracellular noradrenaline and serotonin levels in guinea pig hypothalamus. *J Neurochem* 69(2):815-822, 1997 9231743
- Nemeroff CB, Schatzberg AF, Goldstein DJ, et al: Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull* 36(4):106-132, 2002 12858150
- Nemeroff CB, Entsuah R, Benattia I, et al: Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. *Biol Psychiatry* 63(4):424-434, 2008 17888885
- Nierenberg AA, Greist JH, Mallinckrodt CH, et al: Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Curr Med Res Opin* 23(2):401-416, 2007 17288694
- Nogami T, Takano H, Arakawa R, et al: Occupancy of serotonin and norepinephrine transporter by milnacipran in patients with major depressive disorder: a positron emission tomography study with [(11)C]DASB and (S,S)-[(18)F]FMeNER-D(2). *Int J Neuropsychopharmacol* 16(5): 937-943, 2013 23067569
- Olié JP, Gourion D, Montagne A, et al: Milnacipran and venlafaxine at flexible doses (up to 200 mg/day) in the outpatient treatment of adults with moderate-to-severe major



- depressive disorder: a 24-week randomized, double-blind exploratory study. *Neuropsychiatr Dis Treat* 6:71-79, 2010 20396639
- Palmier C, Puozzo C, Lenehan T, et al: Monoamine uptake inhibition by plasma from healthy volunteers after single oral doses of the antidepressant milnacipran. *Eur J Clin Pharmacol* 37(3):235-238, 1989 2612537
- Papakostas GI, Fava M: A meta-analysis of clinical trials comparing milnacipran, a serotonin-norepinephrine reuptake inhibitor, with a selective serotonin reuptake inhibitor for the treatment of major depressive disorder. *Eur Neuropsychopharmacol* 17(1):32-36, 2007 16762534
- Perahia DG, Gilaberte I, Wang F, et al: Duloxetine in the prevention of relapse of major depressive disorder: double-blind placebo-controlled study. *Br J Psychiatry* 188:346-353, 2006a 16582061
- Perahia DG, Wang F, Mallinckrodt CH, et al: Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Psychiatry* 21(6):367-378, 2006b 16697153
- Perahia DG, Pritchett YL, Kajdasz DK, et al: A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res* 42(1):22-34, 2008 17445831
- Perahia DG, Maina G, Thase ME, et al: Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 70(5):706-716, 2009 19552867
- Pigott TA, Prakash A, Arnold LM, et al: Duloxetine versus escitalopram and placebo: an 8-month, double-blind trial in patients with major depressive disorder. *Curr Med Res Opin* 23(6):1303-1318, 2007 17559729
- Poirier MF, Boyer P: Venlafaxine and paroxetine in treatment-resistant depression: double-blind, randomised comparison. *Br J Psychiatry* 175:12-16, 1999 10621762
- Pritchett YL, Marciniak MD, Corey-Lisle PK, et al: Use of effect size to determine optimal dose of duloxetine in major depressive disorder. *J Psychiatr Res* 41(3-4):311-318, 2007 16934840
- Puech A, Montgomery SA, Prost JF, et al: Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability. *Int Clin Psychopharmacol* 12(2):99-108, 1997 9219045
- Puozzo C, Leonard BE: Pharmacokinetics of milnacipran in comparison with other antidepressants. *Int Clin Psychopharmacol* 11 (suppl 4):15-27, 1996 8923123
- Puozzo C, Panconi E, Deprez D: Pharmacology and pharmacokinetics of milnacipran. *Int Clin Psychopharmacol* 17 (suppl 1):S25-S35, 2002 12369608
- Raskin J, Wiltse CG, Siegal A, et al: Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry* 164(6):900-909, 2007 17541049
- Robinson MJ, Sheehan D, Gaynor PJ, et al: Relationship between major depressive disorder and associated painful physical symptoms: analysis of data from two pooled placebo-controlled, randomized studies of duloxetine. *Int Clin Psychopharmacol* 28(6):330-338, 2013 23873291
- Rueter LE, De Montigny C, Blier P: Electrophysiological characterization of the effect of long-term duloxetine administration on the rat serotonergic and noradrenergic systems. *J Pharmacol Exp Ther* 285(2):404-412, 1998a 9580577
- Rueter LE, Kasamo K, de Montigny C, et al: Effect of long-term administration of duloxetine on the function of serotonin and noradrenaline terminals in the rat brain. *Naunyn-Schmiedeberg's Arch Pharmacol* 357(6):600-610, 1998b 9686935
- Sagman D, McIntosh D, Lee MS, et al: Attributes of response in depressed patients switched to treatment with duloxetine. *Int J Clin Pract* 65(1):73-81, 2011 21078010
- Sambunaris A, Bose A, Gommoll CP, et al: A phase III, double-blind, placebo-controlled, flexible-dose study of levomilnacipran extended-release in patients with major depressive disorder. *J Clin Psychopharmacol* 34(1):47-56, 2014 24172209

- Schatzberg AF: Efficacy and tolerability of duloxetine, a novel dual reuptake inhibitor, in the treatment of major depressive disorder. *J Clin Psychiatry* 64 (suppl 13):30-37, 2003 14552654
- Sechter D, Vandel P, Weiller E, et al: A comparative study of milnacipran and paroxetine in outpatients with major depression. *J Affect Disord* 83(2-3):233-236, 2004 15555719
- Sharma A, Goldberg MJ, Cerimele BJ: Pharmacokinetics and safety of duloxetine, a dual-serotonin and norepinephrine reuptake inhibitor. *J Clin Pharmacol* 40(2):161-167, 2000 10664922
- Shelton RC, Andorn AC, Mallinckrodt CH, et al: Evidence for the efficacy of duloxetine in treating mild, moderate, and severe depression. *Int Clin Psychopharmacol* 22(6):348-355, 2007a 17917553
- Shelton RC, Prakash A, Mallinckrodt CH, et al: Patterns of depressive symptom response in duloxetine-treated outpatients with mild, moderate or more severe depression. *Int J Clin Pract* 61(8):1337-1348, 2007b 17627710
- Skinner MH, Kuan HY, Pan A, et al: Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther* 73(3):170-177, 2003 12621382
- Stahl SM, Grady MM, Moret C, et al: SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS Spectr* 10(9):732-747, 2005 16142213
- Sussman N: SNRI's versus SSRI's: mechanism of action in treating depression and painful physical symptoms. *Prim Care Companion J Clin Psychiatry* 5 (suppl 7):19-26, 2003 15156243
- Szabo ST, Blier P: Effect of the selective noradrenergic reuptake inhibitor reboxetine on the firing activity of noradrenaline and serotonin neurons. *Eur J Neurosci* 13(11):2077-2087, 2001 11422448
- Takano A, Suzuki K, Kosaka J, et al: A dose-finding study of duloxetine based on serotonin transporter occupancy. *Psychopharmacology (Berl)* 185(3):395-399, 2006 16506079
- Takano H, Arakawa R, Nogami T, et al: Norepinephrine transporter occupancy by nortriptyline in patients with depression: a positron emission tomography study with (S,S)-[<sup>18</sup>F]FMeNER-D<sub>2</sub>. *Int J Neuropsychopharmacol* 17(4):553-560, 2014 24345533
- Thase ME, Pritchett YL, Ossanna MJ, et al: Efficacy of duloxetine and selective serotonin reuptake inhibitors: comparisons as assessed by remission rates in patients with major depressive disorder. *J Clin Psychopharmacol* 27(6):672-676, 2007 18004135
- Thor KB: Serotonin and norepinephrine involvement in efferent pathways to the urethral rhabdosphincter: implications for treating stress urinary incontinence. *Urology* 62 (4 suppl 1):3-9, 2003 14550831
- Turcotte JE, Debonnel G, de Montigny C, et al: Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects. *Neuropsychopharmacology* 24(5):511-521, 2001 11282251
- Vaishnavi SN, Nemeroff CB, Plott SJ, et al: Milnacipran: a comparative analysis of human monoamine uptake and transporter binding affinity. *Biol Psychiatry* 55(3):320-322, 2004 14744476
- Vincent S, Bieck PR, Garland EM, et al: Clinical assessment of norepinephrine transporter blockade through biochemical and pharmacological profiles. *Circulation* 109(25):3202-3207, 2004 15184278
- Vitton O, Gendreau M, Gendreau J, et al: A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol* 19 (suppl 1):S27-S35, 2004 15378666
- Wade A, Gembert K, Florea I: A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. *Curr Med Res Opin* 23(7):1605-1614, 2007 17559755

- Whitmyer VG, Dunner DL, Kornstein SG, et al: A comparison of initial duloxetine dosing strategies in patients with major depressive disorder. *J Clin Psychiatry* 68(12):1921-1930, 2007 18162024
- Wilhelm S, Boess FG, Hegerl U, et al: Tolerability aspects in duloxetine-treated patients with depression: Should one use a lower starting dose in clinical practice? *Expert Opin Drug Saf* 11(5):699-711, 2012 22712514

# CHAPTER 21

## Ketamine

David S. Mathai, B.S.  
Sanjay J. Mathew, M.D.

---

### History and Discovery

---

Ketamine emerged from the exploration of phencyclidine (PCP) derivatives suitable for anesthetic use in humans, and its discovery in 1962 is attributed to Parke-Davis Labs and Dr. Calvin Lee Stevens, a professor of organic chemistry at Wayne State University ([Domino et al. 1965](#)). Following approval by the U.S. Food and Drug Administration (FDA) in 1970, the drug was used as a battlefield anesthetic for American soldiers during the Vietnam War ([Jansen 2000](#)). Over the next several decades, as ketamine gained recognition for its dissociative properties, reports of its nonmedical use began to emerge, ultimately resulting in federal government classification of the drug as a Schedule III controlled substance in August 1999 ([Ahmed and Petchkovsky 1980](#); [Graeme 2000](#); [Shomer 1992](#)). Today

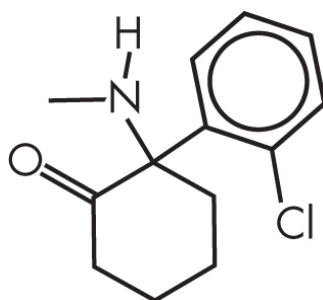
ketamine abuse is prevalent internationally, especially in parts of Asia, where it has been considered a long-standing problem, albeit one that appears to be stabilizing ([United Nations Office on Drugs and Crime 2014](#)). Countries such as the United Kingdom have seen a decrease in ketamine use but an increase in people seeking treatment for ketamine use. Medically, ketamine continues to be widely used as a general anesthetic in specific populations and also as an analgesic for pain unresponsive to standard treatments ([Persson 2013](#)). Psychiatric applications of ketamine are currently an area of intense investigation and encompass its use in treatment-resistant depression, as an antisuicidal agent, as an adjunct to electroconvulsive therapy (ECT), in obsessive-compulsive disorder (OCD), in posttraumatic stress disorder (PTSD), and as a pharmacological model of psychosis.

---

## Structure-Activity Relations

---

Ketamine (2-[2-chlorophenyl]-2-[methylamino]cyclohexanone) is an arylcycloalkylamine compound that is structurally similar to PCP and cyclohexylamine ([Figure 21-1](#)). The free-base form of ketamine is highly lipid soluble and is commercially available as an aqueous preparation of the hydrochloride salt. Ketamine is a chiral compound that exists pharmaceutically as a racemic mixture of (*S*)-ketamine (esketamine) and (*R*)-ketamine (arketamine) enantiomers.



---

**FIGURE 21-1.** Chemical structure of ketamine.

---

## Pharmacological Profile

---

Ketamine has high lipid solubility and low plasma protein binding. It undergoes biotransformation in the liver to norketamine, its primary active metabolite. Approximately 90% of ketamine is excreted in the urine in metabolite form with minimal clearance of unchanged drug, and another 5% undergoes fecal excretion ([Clements et al. 1982](#)). Ketamine has a wide therapeutic index and has been shown to have a low risk of lethal overdose ([Green et al. 1999](#)). Its main pharmacological action is on glutamate as an open-channel, nonselective *N*-methyl-D-aspartate (NMDA) receptor antagonist.

---

## Pharmacokinetics and Disposition

---

Ketamine can be administered by oral, intravenous, intramuscular, subcutaneous, intranasal, epidural, transdermal, intra-articular, and sublingual routes

([Kotlińska-Lemieszek and Luczak 2004](#)). When given orally, ketamine undergoes extensive hepatic biotransformation (via *N*-demethylation by cytochrome P450 [CYP] isoenzymes 3A4, 2C9, and 2B6) into norketamine, the drug's major metabolite. With oral administration of ketamine, norketamine has lower potency than the parent drug but higher plasma levels than those produced when ketamine is given intramuscularly ([Grant et al. 1981](#)). Hydroxynorketamine (HNK), a secondary metabolite also found at high levels soon after administration of ketamine, may play a role in the extended clinical responses that persist after ketamine has been metabolized ([Paul et al. 2014](#); [Singh et al. 2014](#)). Ketamine undergoes renal elimination, and dehydronorketamine (DHNK) is the inactive metabolite that is predominant in urine ([Sinner and Graf 2008](#)). The oral bioavailability of ketamine is 17%–20%; bioavailability for other routes is as follows: 25%–50% for intranasal, 30% for sublingual, 30% for rectal, 93% for intramuscular, and ~99%–100% for intravenous ([Clements et al. 1982](#); [Quibell et al. 2015](#)). Peak plasma concentrations are reached within 30–60 minutes of oral administration, 5–15 minutes of intramuscular injection, and 1 minute of intravenous injection ([Paul et al. 2014](#)). Ketamine is rapidly distributed to highly perfused tissues, including the brain, with a distribution half-life of approximately 10–15 minutes and an elimination half-life of 2–2.5 hours ([Domino et al. 1984](#)). The half-lives of ketamine metabolites are longer than that of the parent drug, measuring 5.3 hours and 6.9 hours for norketamine and DHNK, respectively ([Hijazi et al. 2003](#)).

---

# Mechanism of Action

---

Ketamine is a dissociative anesthetic with analgesic and amnesic properties ([Curran and Morgan 2000](#)). The anesthetic state produced by ketamine was initially termed “dissociative anesthesia” because an electrophysiological unlinking of the thalamoneocortical and limbic systems was thought to be the mechanism by which the drug exerted its primary effect on the central nervous system (CNS); however, the term was later generalized to capture a more psychological sensation of dissociation from self or the surrounding environment, often manifesting as a cataleptic-type state ([Haas and Harper 1992](#); [Jansen 1990](#); [Reich and Silvay 1989](#)). Ketamine has a very complex pharmacological profile, with variable, concentration-dependent affinities for numerous receptors ([Alkire et al. 2008](#); [Oye et al. 1992](#); [Rabiner 2007](#); [Sleigh et al. 2014](#); [Smith et al. 1981, 1987](#)). Off-target interactions at these receptors are responsible for ketamine’s transient cardiovascular, respiratory, and sympathomimetic effects ([Domino 2010](#)). Ketamine exerts its primary effect as a voltage-dependent nonselective NMDA receptor antagonist that inhibits transmembranous flux of calcium and sodium in the presence of the coagonists glutamate and glycine ([Niciu et al. 2014](#)). Of ketamine’s two enantiomers, (*S*)-ketamine has been shown to have a higher affinity for the NMDA receptor and a three- to fourfold greater anesthetic potency relative to (*R*)-ketamine, as well as increased psychotomimetic side effects ([Bergman 1999](#); [Kohrs and Durieux 1998](#)).

At the level of NMDA receptor blockade, ketamine is thought to interfere with multiple processes, including sensory input to higher CNS centers, emotional responses



to those stimuli, and learning and memory consolidation ([Bergman 1999](#)). Previous studies demonstrated that the NMDA receptor channel complex is integral to the central sensitization of dorsal horn neurons that transmit pain signals ([Petrenko et al. 2003](#)). When the channel is unblocked, neuronal hyperexcitability contributes to hyperalgesia, allodynia, and reduced opioid responsiveness; these effects are thought to be mediated by intracellular formation of nitric oxide and cyclic guanosine monophosphate (cGMP), along with interactions between opioid receptors and the NMDA receptor channel ([Mion and Villeveille 2013](#)). Ketamine-induced central antinociception has been shown to be antagonized in a dose-dependent manner by naloxone, clocinnamox, and naltrindole; to be potentiated by bestatin; and to be unaffected by norbinaltorphimine, suggesting the involvement of endogenous mu and delta (but not kappa) opioid receptors in ketamine's antinociceptive effects ([Pacheco et al. 2014](#)). In rodent models, ketamine's antinociceptive effects have also been attributed to stimulation of the L-arginine/nitric oxide/cGMP pathway via neuronal nitric oxide synthase ([Romero et al. 2011](#)).

Other studies have implicated neurotrophic signaling cascades in the antidepressant effects of ketamine ([Autry et al. 2011](#); [Browne and Lucki 2013](#); [Duman et al. 2012](#); [Haile et al. 2014](#); [Hashimoto et al. 2013](#); [Kavalali and Monteggia 2012](#); [Li et al. 2010, 2011](#)). Signaling changes include induction of mammalian target of rapamycin (mTOR) signaling and resultant synaptic remodeling, consistent with existing neuroplasticity-related theories of depression ([Duman 2014](#); [Duman and Li 2012](#); [Duman and Monteggia 2006](#); [Grady and Stahl 2013](#); [Murrough and Charney 2010](#)). Activation of mTOR is also thought to be mediated by

activation of the non-NMDA glutamate  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and upregulation of brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase B (TrkB) signaling ([Duman and Voleti 2012](#)). Both norketamine and HNK have been shown to have significant pharmacological activity and may contribute to the therapeutic effects of subanesthetic doses of ketamine by antagonistic action at the alpha-7 nicotinic acetylcholine receptor ( $\alpha 7$ -nAChR) ([Quibell et al. 2015](#)).

---

## Indications and Efficacy

---

### Anesthesia

Ketamine gained FDA approval in 1970 for the following indications: 1) as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, 2) for induction of anesthesia prior to administration of other general anesthetic agents, and 3) to supplement low-potency anesthetic agents, such as nitrous oxide ([Par Pharmaceutical Companies 2014](#)). Ketamine was an attractive drug for these indications because of its potent anesthetic properties and its safety profile, characterized by a large therapeutic window and low risk of respiratory depression. Recommended dosages for induction of anesthesia are 6.5–13.0 mg/kg intramuscular and 1.0–4.5 mg/kg intravenous, with alternative off-label recommendations for situations that involve administration of adjuvant drugs ([Miller et al. 2010](#)). For maintenance of anesthesia, the manufacturer recommends administering one-half to the full induction dose *or* a continuous infusion

of 0.1–0.5 mg/minute of ketamine; however, clinical studies have suggested that higher dosages may be needed to maintain an adequate concentration for anesthesia ([White et al. 1982](#)). Although only the racemic mixture of ketamine is marketed in the United States, (*S*)-ketamine was approved in Europe in 1998 and is available in a number of European Union countries for induction and maintenance of general anesthesia, supplementation of local anesthesia, and analgesia in emergency medicine.

## Off-Label Applications

### **Sedation, Analgesia, and Reduction of Postsurgical Pain, Nausea, and Vomiting**

In regard to off-label applications, various laboratory and clinical studies support the use of ketamine for sedation, analgesia, and improved postoperative outcomes ([Adam et al. 2005](#); [Green et al. 2011](#); [Hocking and Cousins 2003](#); [Menigaux et al. 2000](#); [Remérand et al. 2009](#); [Zakine et al. 2008](#)). A systematic review of low-dosage ketamine for chronic noncancer pain (e.g., neuropathic, ischemic, fibromyalgia) administered by multiple routes concluded that although ketamine provided relief, its long-term use should be restricted to controlled trials ([Bell 2009](#)). Another review of ketamine as an analgesic for phantom limb pain reached a similar conclusion ([Alviar et al. 2011](#)). Randomized controlled trial (RCT) evidence ([Schwartzman et al. 2009](#); [Sigtermans et al. 2009](#)) pointed to ketamine's benefit in complex regional pain syndrome type 1 at a variety of dosages and routes of administration; however, a larger review ([Azari et al. 2012](#)) suggested that stronger evidence (drawn from larger studies that include data on

unsuccessful trials) is needed before ketamine can be recommended for that indication. Subanesthetic doses of ketamine have also been found to be effective in the management of acute postoperative pain, reducing morphine requirements during the first 24 hours after surgery and additionally improving nausea and vomiting ([Bell et al. 2006](#)).

## **Relief of Acute Depression and Suicidal Ideation**

Multiple meta-analyses have confirmed ketamine's acute antidepressant effects in patients with major depressive episodes associated with major depressive disorder or bipolar disorder, including a reduction in suicidal ideation ([Caddy et al. 2014](#); [Fond et al. 2014](#); [Lee et al. 2015](#); [McGirr et al. 2015](#); [Price and Mathew 2015](#)). Data have shown rapid improvement of depressive symptoms in up to 71% of patients following administration of a single intravenous dose of ketamine (typically 0.5 mg/kg over 40 minutes), with response seen within hours and the peak antidepressant effect occurring at 24 hours ([aan het Rot et al. 2012](#); [Lee et al. 2015](#); [Mathew et al. 2012](#); [Salvadore and Singh 2013](#)). For patients who showed early benefit (within several days) from a single infusion, the mean duration of response was highly variable. In a Cochrane Review meta-analysis of 25 double-blind and single-blind RCT studies (1,242 participants) comparing intravenous administration of 11 different glutamate receptor modulators with placebo, other active psychotropic drugs, or ECT in adults with unipolar major depressive disorder, only ketamine showed a significant effect in reducing the acute symptoms of depression ([Caddy et al. 2015](#)).

Ketamine's antidepressant effects were evident at 1 week after treatment but had disappeared by 2 weeks. Ketamine was found to cause more confusion and emotional blunting than placebo. A systematic review evaluating the use of ketamine and other NMDA antagonists in depression also noted compelling evidence for the rapid, yet transient, antidepressant effects of ketamine infusion but recommended further investigation into ketamine's mechanism of action ([Newport et al. 2015](#)). The reviewers concluded that apart from ketamine, no NMDA antagonists consistently demonstrated antidepressant efficacy, although two partial agonists at the NMDA coagonist site, D-cycloserine and rapastinel, were found to significantly reduce depressive symptoms without causing psychotomimetic or dissociative effects.

In addition to studies on the antidepressant effects of ketamine, there is a need for further exploration of ketamine's effects on cognition, quality of life, and suicidality. Although ketamine has been demonstrated to provide rapid reduction in suicidal ideation in some patients with major depressive disorder, limited controlled data are available on ketamine's effects in patients with a more severe risk of suicide, such as patients who have been hospitalized for suicidal ideation or a suicide attempt ([Price and Mathew 2015](#)). Additional investigation is also needed regarding other modes (besides intravenous) of ketamine administration and the efficacy and safety of repeated administrations of the drug. Four studies of a series of four to six ketamine infusions administered over a 2-week interval reported relapse rates of 55%–89% in the month following treatment, although these studies were limited by small sizes and an open-label design ([van het Rot et al.](#)

2010; Murrough et al. 2013; Rasmussen et al. 2013; Shiroma et al. 2014).

## **Augmentation Agent in Electroconvulsive Therapy**

Ketamine's use in conjunction with ECT has also been explored. A 2015 systematic review and meta-analysis identified five studies ( $N=180$  adults with unipolar or bipolar depression) in which intravenous ketamine (0.5–2.0 mg/kg) was used either in addition to ([Abdallah et al. 2012](#); [Järventausta et al. 2014](#); [Loo et al. 2012](#)) or instead of ([X. Wang et al. 2012](#); [Yoosefi et al. 2014](#)) another agent—propofol, thiopental, or placebo—to induce anesthesia prior to ECT administration ([Newport et al. 2015](#)). Meta-analysis indicated that ketamine was associated with a significantly greater reduction in depressive symptoms after the initial ECT session; however, this advantage had disappeared by the end of the ECT course. Across the studies included within the review, the inclusion of ketamine in the ECT anesthetic regimen was associated with longer seizure durations (prolonged by an average of 11.49 seconds). A retrospective study comparing the effects of pre-ECT administration of ketamine, etomidate, thiopental, or propofol on seizure parameters and quality found that ketamine anesthesia was associated with higher-quality seizures (as defined by seizure duration and degree of central inhibition) than were produced with the other anesthetic agents ([Hoyer et al. 2014](#)). Although ketamine has been used reluctantly at times in ECT because of its potential to provoke dissociative symptoms, these study findings suggest that the drug's psychiatric side effects may be dose-dependent and may be effectively controlled

without relevant distress for patients. Furthermore, ketamine was found to be preferable to other anesthetic agents, with decreased induction of transient cognitive effects ([Hoyer et al. 2014](#)).

## Investigative Applications

Ketamine has been investigated in a number of other psychiatric conditions. Glutamate-modulating agents have been considered as therapeutic candidates in treatment-refractory OCD based on lines of evidence pointing to an underlying role of glutamate dysregulation in this disorder; however, studies examining the benefit of these agents in OCD have been inconclusive ([Pittenger 2015](#)). In a randomized, placebo-controlled crossover trial of ketamine in unmedicated patients with refractory OCD, participants who received ketamine first showed significant and rapid antiobsessional effects during the 0.5 mg/kg infusion that persisted until 1 week postinfusion, compared with participants who received placebo (saline infusion) first ([Rodriguez et al. 2013](#)). A subsequent study of the neurochemical effects of ketamine versus saline infusions using proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS) suggested that the therapeutic effect of ketamine in OCD may in fact occur independently of the glutamate-glutamine activity ([Rodriguez et al. 2015](#)).

In patients with chronic PTSD, preliminary RCT evidence demonstrated that a single intravenous ketamine infusion (0.5 mg/kg) was associated with a significant and rapid reduction in PTSD symptom severity compared with midazolam when assessed 24 hours after administration

([Feder et al. 2014](#)). Ketamine was well tolerated, with no clinically significant or persistent dissociative symptoms.

In regard to substance use disorders, there is evidence that infusions of ketamine at subanesthetic doses improved motivation to quit and reduced cue-induced craving in nondepressed cocaine-dependent volunteers ([Dakwar et al. 2014](#)). Efforts to enhance a patient's motivation for change have been previously recognized as an important aspect of addiction-oriented psychotherapy, but this particular use of ketamine marks one of the first times that the psychological parameter of motivation has been targeted as a focus of pharmacotherapy.

In the realm of experimental psychopharmacology, ketamine has been explored as a safe research tool to transiently induce or provoke multidimensional schizophrenia-like symptoms ([Anticevic et al. 2012](#); [Lahti et al. 1995](#); [Perry et al. 2007](#)). Models of psychosis based on acute or chronic administration of noncompetitive NMDA receptor antagonists in both humans and rats show phenomenological validity with promise for testing new substances with potential antipsychotic effects ([Bubeníková-Valesová et al. 2008](#)). It is important to note that these uses are investigational as of the time of this writing (2015).

---

## Side Effects and Toxicology

---

Ketamine has a wide margin of safety but may be associated with various adverse reactions. At anesthetic doses of the drug (1–3 mg/kg), emergence reactions—characterized by a range of psychological manifestations including



hallucinations, confusion, delirium, vivid imagery, and a prolonged dreamlike state—have occurred in approximately 12% of patients recovering from anesthesia ([Green et al. 2011](#)). Other common side effects ( $\leq 10\%$ ) include transient nystagmus, diplopia, hypertension, tachycardia, respiratory stimulation, nausea, vomiting, and skin inflammation or rash. Less common side effects ( $\leq 1\%$ ) include anorexia, bradycardia, cardiac arrhythmia, hypotension, and respiratory depression. In rare cases ( $\leq 0.1\%$ ), anaphylaxis, sialorrhea, laryngospasm, and cystitis have been reported. Ketamine-induced renal dysfunction, ulcerative cystitis, and abdominal pain seem to be more prevalent in frequent, high-dose users ([Morgan and Curran 2012](#)).

At the subanesthetic doses (0.1–1 mg/kg) used in studies investigating ketamine's analgesic and antidepressant properties, cardiovascular and respiratory effects, including stimulation of the cardiovascular system and mild respiratory depression, have been demonstrated; therefore, adequate monitoring and medical support must be provided during administration. There is also evidence for mild, acute neuropsychiatric effects—such as neurocognitive disturbance, sensory-motor disturbance, and dissociation—that should be considered alongside preclinical data suggesting that ketamine may be neurotoxic in certain contexts, based on timing of administration, dosage given, and extent of exposure ([Krystal et al. 1994](#); [Malhotra et al. 1996](#); [Morgan et al. 2004](#); [Newcomer et al. 1999](#); [Soriano 2012](#)). It is significant that longer-term follow-up data do not report the persistent dissociative or psychotomimetic sequelae that previously were a concern regarding ketamine's use in depression, but further study of chronic-use outcomes is warranted, especially in the context of repeated medical use of ketamine ([Green and Li 2000](#); [Wan](#)

[et al. 2015](#)). For example, although studies of ketamine in mood disorder patients indicate that repeated infusions are largely well tolerated, studies in ketamine abusers and rodent models have pointed to adverse effects on brain structure and function under certain conditions of chronic exposure ([Liao et al. 2011](#); [Schobel et al. 2013](#); [C. Wang et al. 2013](#)).

Ketamine dependence has also been reported in the scientific literature, and the drug's potential for misuse and addiction may be related to its agonist activity at mu opioid receptors and/or to its dopaminergic effects ([Lindefors et al. 1997](#); [Liu et al. 2015](#); [Sanacora and Schatzberg 2015](#); [Xu and Lipsky 2015](#)). A valuable case report from *American Journal of Psychiatry* described the misuse and unintended consequences of ketamine prescribed for depression in a patient with a history of substance abuse before an optimized treatment plan and system of monitoring were put into place ([Schak et al. 2016](#)). Taken together, these initial findings suggest that although subanesthetic doses of ketamine administered to unipolar depressed patients in a controlled research setting present a low and acceptable level of risk, great emphasis must be placed on ongoing investigation regarding the abuse potential of ketamine, carefully regulated prescribing of ketamine for off-label use, and close follow-up and outcome reporting.

---

## Drug-Drug Interactions

---

Drugs such as rifampin and St. John's wort (which are potent inducers of CYP3A4) increase the metabolism and clearance of ketamine—and, to a much greater extent, of

norketamine ([Mion and Villevieille 2013](#)). Enzyme-inhibiting substances have the opposite effect and include clarithromycin and grapefruit juice (CYP3A4 inhibitors) and ticlopidine (a potent CYP2C19 inhibitor and a weak CYP2B6 inhibitor) ([Domino et al. 1984](#)). Several studies have also reported ketamine's synergistic effects when administered with other sedatives ([Akhavanakbari et al. 2014](#); [Eker et al. 2011](#); [Hui et al. 1995](#); [Lo and Cumming 1975](#)). The clinical relevance of these interactions remains unclear.

---

## Conclusion

---

Whereas much is known about the pharmacological profile of ketamine from its long history of use as an anesthetic and analgesic agent, far less is known about the mechanisms associated with ketamine's antidepressant efficacy at subanesthetic doses. Early studies implicated a number of pathways that may be involved in the therapeutic effects of ketamine, including pathways mediated by BDNF, TrkB, mTOR, and AMPA. Further investigations of NMDA receptor activity and the efficacy of other potential glutamate-modulating agents are ongoing. Therefore, as the use of ketamine in clinical practice becomes increasingly more common in U.S. hospital and clinic-based settings, it is imperative that the field develop standard operating procedures to guide clinical use. Despite the promise shown in initial trials of ketamine, it is important to recognize that ketamine therapy is still an experimental approach. The transient nature of ketamine's antidepressant activity and its potential for abuse suggest that routine adoption of this drug in psychiatric practice settings may be premature at

this time. Future research will need to work toward improving our understanding of ketamine's mechanism of action, developing administration strategies that offer sustained therapeutic benefit, and providing continued longitudinal assessment of safety and tolerability.

---

## References

---

- aan het Rot M, Collins KA, Murrough JW, et al: Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 67(2):139-145, 2010 19897179
- aan het Rot M, Zarate CA Jr, Charney DS, et al: Ketamine for depression: where do we go from here? *Biol Psychiatry* 72(7):537-547, 2012 22705040
- Abdallah CG, Fasula M, Kelmendi B, et al: Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting. *J ECT* 28(3):157-161, 2012 22847373
- Adam F, Chauvin M, Du Manoir B, et al: Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. *Anesth Analg* 100(2):475-480, 2005 15673878
- Ahmed SN, Petchkovsky L: Abuse of ketamine. *Br J Psychiatry* 137:303, 1980 7437669
- Akhavanakbari G, Mohamadian A, Entezariasl M: Evaluation the effects of adding ketamine to morphine in intravenous patient-controlled analgesia after orthopedic surgery. *Perspect Clin Res* 5(2):85-87, 2014 24741486
- Alkire MT, Hudetz AG, Tononi G: Consciousness and anesthesia. *Science* 322(5903): 876-880, 2008 18988836

- Alviar MJM, Hale T, Dungca M: Pharmacologic interventions for treating phantom limb pain. *Cochrane Database Syst Rev* (12):CD006380, 2011 22161403
- Anticevic A, Gancsos M, Murray JD, et al: NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. *Proc Natl Acad Sci U S A* 109(41):16720-16725, 2012 23012427
- Autry AE, Adachi M, Nosyreva E, et al: NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 475(7354):91-95, 2011 21677641
- Azari P, Lindsay DR, Briones D, et al: Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. *CNS Drugs* 26(3):215-228, 2012 22136149
- Bell RF: Ketamine for chronic non-cancer pain. *Pain* 141(3):210-214, 2009 19128879
- Bell RF, Dahl JB, Moore RA, et al: Perioperative ketamine for acute postoperative pain. *Cochrane Database Syst Rev* (1): CD004603, 2006 16437490
- Bergman SA: Ketamine: review of its pharmacology and its use in pediatric anesthesia. *Anesth Prog* 46(1):10-20, 1999 10551055
- Browne CA, Lucki I: Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants. *Front Pharmacol* 4:161, 2013 24409146
- Bubeníková-Valesová V, Horáček J, Vraiová M, et al: Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. *Neurosci Biobehav Rev* 32(5):1014-1023, 2008 18471877
- Caddy C, Giaroli G, White TP, et al: Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and

- meta-analysis of efficacy. *Ther Adv Psychopharmacol* 4(2):75-99, 2014 24688759
- Caddy C, Amit BH, McCloud TL, et al: Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database Syst Rev* (9):CD011612, 2015 26395901
- Clements JA, Nimmo WS, Grant IS: Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *J Pharm Sci* 71(5):539-542, 1982 7097501
- Curran HV, Morgan C: Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction* 95(4):575-590, 2000 10829333
- Dakwar E, Levin F, Foltin RW, et al: The effects of subanesthetic ketamine infusions on motivation to quit and cue-induced craving in cocaine-dependent research volunteers. *Biol Psychiatry* 76(1):40-46, 2014 24035344
- Domino EF: Taming the ketamine tiger. 1965. *Anesthesiology* 113(3):678-684, 2010 20693870
- Domino EF, Chodoff P, Corssen G: Pharmacologic Effects of CI-581, A New Dissociative Anesthetic, in Man. *Clin Pharmacol Ther* 6:279-291, 1965 14296024
- Domino EF, Domino SE, Smith RE, et al: Ketamine kinetics in unmedicated and diazepam-premedicated subjects. *Clin Pharmacol Ther* 36(5):645-653, 1984 6488686
- Duman RS: Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues Clin Neurosci* 16(1):11-27, 2014 24733968
- Duman RS, Li N: A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. *Philos Trans R Soc Lond B Biol Sci* 367(1601):2475-2484, 2012 22826346
- Duman RS, Monteggia LM: A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 59(12):1116-1127, 2006 16631126

- Duman RS, Voleti B: Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. *Trends Neurosci* 35(1):47-56, 2012 22217452
- Duman RS, Li N, Liu RJ, et al: Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology* 62(1):35-41, 2012 21907221
- Eker HE, Yalcin Cok O, Aribogan A, et al: Children on phenobarbital monotherapy requires more sedatives during MRI. *Paediatr Anaesth* 21(10):998-1002, 2011 21564387
- Feder A, Parides MK, Murrough JW, et al: Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry* 71(6):681-688, 2014 24740528
- Fond G, Loundou A, Rabu C, et al: Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology (Berl)* 231(18):3663-3676, 2014 25038867
- Grady MM, Stahl SM: Novel agents in development for the treatment of depression. *CNS Spectr* 18 (suppl 1):37-40, quiz 41, 2013 24252548
- Graeme KA: New drugs of abuse. *Emerg Med Clin North Am* 18(4):625-636, 2000 11130930
- Grant IS, Nimmo WS, Clements JA: Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *Br J Anaesth* 53(8):805-810, 1981 7272143
- Green SM, Li J: Ketamine in adults: what emergency physicians need to know about patient selection and emergence reactions. *Acad Emerg Med* 7(3):278-281, 2000 10730837
- Green SM, Clark R, Hostetler MA, et al: Inadvertent ketamine overdose in children: clinical manifestations and outcome. *Ann Emerg Med* 34(4 Pt 1):492-497, 1999 10499950

- Green SM, Roback MG, Kennedy RM, et al: Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med* 57(5):449-461, 2011 21256625
- Haas DA, Harper DG: Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. *Anesth Prog* 39(3):61-68, 1992 1308374
- Haile CN, Murrough JW, Iosifescu DV, et al: Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol* 17(2):331-336, 2014 24103211
- Hashimoto K, Malchow B, Falkai P, et al: Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. *Eur Arch Psychiatry Clin Neurosci* 263(5):367-377, 2013 23455590
- Hijazi Y, Bodonian C, Bolon M, et al: Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. *Br J Anaesth* 90(2):155-160, 2003 12538370
- Hocking G, Cousins MJ: Ketamine in chronic pain management: an evidence-based review. *Anesth Analg* 97(6):1730-1739, 2003 14633551
- Hoyer C, Kranaster L, Janke C, et al: Impact of the anesthetic agents ketamine, etomidate, thiopental, and propofol on seizure parameters and seizure quality in electroconvulsive therapy: a retrospective study. *Eur Arch Psychiatry Clin Neurosci* 264(3):255-261, 2014 23835527
- Hui TW, Short TG, Hong W, et al: Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. *Anesthesiology* 82(3):641-648, 1995 7879932
- Jansen KL: Ketamine—can chronic use impair memory? *Int J Addict* 25(2):133-139, 1990 2228329



- Jansen KL: A review of the nonmedical use of ketamine: use, users and consequences. *J Psychoactive Drugs* 32(4):419-433, 2000 11210204
- Järventausta K, Chrapek W, Kampman O, et al: Effects of S-ketamine as an anesthetic adjuvant to propofol on treatment response to electroconvulsive therapy in treatment-resistant depression: a randomized pilot study. *J ECT* 29(3):158-161, 2013 23475029
- Kavalali ET, Monteggia LM: Synaptic mechanisms underlying rapid antidepressant action of ketamine. *Am J Psychiatry* 169(11):1150-1156, 2012 23534055
- Kohrs R, Durieux ME: Ketamine: teaching an old drug new tricks. *Anesth Analg* 87(5): 1186-1193, 1998 9806706
- Kotlińska-Lemieszek A, Luczak J: Subanesthetic ketamine: an essential adjuvant for intractable cancer pain. *J Pain Symptom Manage* 28(2):100-102, 2004 15276189
- Krystal JH, Karper LP, Seibyl JP, et al: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51(3):199-214, 1994 8122957
- Lahti AC, Koffel B, LaPorte D, et al: Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology* 13(1):9-19, 1995 8526975
- Lee EE, Della Selva MP, Liu A, Himelhoch S: Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. *Gen Hosp Psychiatry* 37(2):178-184, 2015 25698228
- Li N, Lee B, Liu RJ, et al: mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329(5994):959-964, 2010 20724638
- Li N, Liu RJ, Dwyer JM, et al: Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress

- exposure. *Biol Psychiatry* 69(8):754-761, 2011 21292242
- Liao Y, Tang J, Corlett PR, et al: Reduced dorsal prefrontal gray matter after chronic ketamine use. *Biol Psychiatry* 69(1):42-48, 2011 21035788
- Lindefors N, Barati S, O'Connor WT: Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. *Brain Res* 759(2): 205-212, 1997 9221938
- Liu JX, Zerbo E, Ross S: Intensive ketamine use for multiple years: a case report. *Am J Addict* 24(1):7-9, 2015 25823629
- Lo JN, Cumming JF: Interaction between sedative premedicants and ketamine in man in isolated perfused rat livers. *Anesthesiology* 43(3):307-312, 1975 1163830
- Loo CK, Katalinic N, Garfield JB, et al: Neuropsychological and mood effects of ketamine in electroconvulsive therapy: a randomised controlled trial. *J Affect Disord* 142(1-3):233-240, 2012 22858219
- Malhotra AK, Pinals DA, Weingartner H, et al: NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 14(5):301-307, 1996 8703299
- Mathew SJ, Shah A, Lapidus K, et al: Ketamine for treatment-resistant unipolar depression: current evidence. *CNS Drugs* 26(3):189-204, 2012 22303887
- McGirr A, Berlim MT, Bond DJ, et al: A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med* 45(4):693-704, 2015 25010396
- Menigaux C, Fletcher D, Dupont X, et al: The benefits of intraoperative small-dose ketamine on postoperative

- pain after anterior cruciate ligament repair. *Anesth Analg* 90(1):129-135, 2000 10624993
- Miller RD, Eriksson LI, Fleisher LA, et al: *Miller's Anesthesia*, 7th Edition. Philadelphia, PA, Churchill Livingstone/Elsevier, 2010
- Mion G, Villevieille T: Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther* 19(6):370-380, 2013 23575437
- Morgan CJA, Curran HV; Independent Scientific Committee on Drugs: Ketamine use: a review. *Addiction* 107(1):27-38, 2012 21777321
- Morgan CJA, Mofeez A, Brandner B, et al: Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology* 29(1):208-218, 2004 14603267
- Murrough JW, Charney DS: Cracking the moody brain: lifting the mood with ketamine. *Nat Med* 16(12):1384-1385, 2010 21135850
- Murrough JW, Perez AM, Pillemer S, et al: Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* 74(4):250-256, 2013 22840761
- Newcomer JW, Farber NB, Jevtovic-Todorovic V, et al: Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology* 20(2):106-118, 1999 9885791
- Newport DJ, Carpenter LL, McDonald WM, et al; APA Council of Research Task Force on Novel Biomarkers and Treatments: Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry* 172(10):950-966, 2015 26423481
- Niciu MJ, Henter ID, Luckenbaugh DA, et al: Glutamate receptor antagonists as fast-acting therapeutic

- alternatives for the treatment of depression: ketamine and other compounds. *Annu Rev Pharmacol Toxicol* 54:119–139, 2014 24392693
- Oye I, Paulsen O, Maurset A: Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. *J Pharmacol Exp Ther* 260(3):1209–1213, 1992 1312163
- Pacheco DdaF, Romero TRL, Duarte IDG: Central antinociception induced by ketamine is mediated by endogenous opioids and mu- and delta-opioid receptors. *Brain Res* 1562:69–75, 2014 24675031
- Par Pharmaceutical Companies: Ketalar (ketamine hydrochloride) injection, USP [package insert]. Spring Valley, NY, Par Pharmaceutical Companies, September 2014. Available at: <http://www.parsterileproducts.com/products/products/ketalar.php>. Accessed May 1, 2016.
- Paul RK, Singh NS, Khadeer M, et al: (R,S)-Ketamine metabolites (R,S)-norketamine and (2S,6S)-hydroxynorketamine increase the mammalian target of rapamycin function. *Anesthesiology* 121(1):149–159, 2014 24936922
- Perry EB Jr, Cramer JA, Cho HS, et al; Yale Ketamine Study Group: Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology (Berl)* 192(2):253–260, 2007 17458544
- Persson J: Ketamine in pain management. *CNS Neurosci Ther* 19(6):396–402, 2013 23663314
- Petrenko AB, Yamakura T, Baba H, Shimoji K: The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 97(4):1108–1116, 2003 14500166
- Pittenger C: Glutamate modulators in the treatment of obsessive-compulsive disorder. *Psychiatr Ann* 45(6):308–315, 2015 26236057
- Price RB, Mathew SJ: Does ketamine have anti-suicidal properties? Current status and future directions. *CNS*

- Drugs 29(3):181-188, 2015 25715884
- Quibell R, Fallon M, Mihalyo M, et al: Ketamine. J Pain Symptom Manage 50(2):268-278, 2015 26096492
- Rabiner EA: Imaging of striatal dopamine release elicited with NMDA antagonists: is there anything there to be seen? J Psychopharmacol 21(3):253-258, 2007 17591653
- Rasmussen KG, Lineberry TW, Galardy CW, et al: Serial infusions of low-dose ketamine for major depression. J Psychopharmacol 27(5):444-450, 2013 23428794
- Reich DL, Silvay G: Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 36(2):186-197, 1989 2650898
- Remérand F, Le Tendre C, Baud A, et al: The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesth Analg 109(6): 1963-1971, 2009 19923527
- Rodriguez CI, Kegeles LS, Levinson A, et al: Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology 38(12):2475-2483, 2013 23783065
- Rodriguez CI, Kegeles LS, Levinson A, et al: In vivo effects of ketamine on glutamate-glutamine and gamma-aminobutyric acid in obsessive-compulsive disorder: proof of concept. Psychiatry Res 233(2):141-147, 2015 26104826
- Romero TRL, Galdino GS, Silva GC, et al: Ketamine activates the L-arginine/nitric oxide/cyclic guanosine monophosphate pathway to induce peripheral antinociception in rats. Anesth Analg 113(5):1254-1259, 2011 21788321
- Salvadore G, Singh JB: Ketamine as a fast acting antidepressant: current knowledge and open questions. CNS Neurosci Ther 19(6):428-436, 2013 23578128

- Sanacora G, Schatzberg AF: Ketamine: promising path or false prophecy in the development of novel therapeutics for mood disorders? *Neuropsychopharmacology* 40(5):259-267, 2015 25767082
- Schak KM, Vande Voort JL, Johnson EK, et al: Potential risks of poorly monitored ketamine use in depression treatment. *Am J Psychiatry* 173(3):215-218, 2016 26926127
- Schobel SA, Chaudhury NH, Khan UA, et al: Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. *Neuron* 78(1):81-93, 2013 23583108
- Schwartzman RJ, Alexander GM, Grothusen JR, et al: Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain* 147(1-3):107-115, 2009 19783371
- Shiroma PR, Johns B, Kuskowski M, et al: Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord* 155:123-129, 2014 24268616
- Shomer RR: Misuse of ketamine. *J Am Vet Med Assoc* 200(3):256-257, 1992 1548151
- Sigtermans MJ, van Hilten JJ, Bauer MCR, et al: Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain* 145(3):304-311, 2009 19604642
- Singh NS, Zarate CA Jr, Moaddel R, et al: What is hydroxynorketamine and what can it bring to neurotherapeutics? *Expert Rev Neurother* 14(11):1239-1242, 2014 25331415
- Sinner B, Graf BM: Ketamine. *Handb Exp Pharmacol* (182):313-333, 2008 18175098

- Sleigh J, Martyn H, Voss L, Denny B: Ketamine—more mechanisms of action than just NMDA blockade. *Trends in Anaesthesia and Critical Care* 4(2-3):76-81, 2014
- Smith DJ, Azzaro AJ, Zaldivar SB, et al: Properties of the optical isomers and metabolites of ketamine on the high affinity transport and catabolism of monoamines. *Neuropharmacology* 20(4):391-396, 1981 7290352
- Smith DJ, Bouchal RL, deSanctis CA, et al: Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* 26(9):1253-1260, 1987 2823161
- Soriano SG: Neurotoxicity of ketamine: known unknowns. *Crit Care Med* 40(8):2518-2519, 2012 22809932
- United Nations Office on Drugs and Crime: World Drug Report 2014. United Nations, 2014. Available at: [https://www.unodc.org/documents/wdr2014/World\\_Drug\\_Report\\_2014\\_web.pdf](https://www.unodc.org/documents/wdr2014/World_Drug_Report_2014_web.pdf). Accessed April 19, 2016.
- Wan LB, Levitch CF, Perez AM, et al: Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry* 76(3):247-252, 2015 25271445
- Wang C, Zheng D, Xu J, et al: Brain damages in ketamine addicts as revealed by magnetic resonance imaging. *Front Neuroanat* 7:23, 2013 23882190
- Wang X, Chen Y, Zhou X, et al: Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patients with depressive disorder. *J ECT* 28(2):128-132, 2012 22622291
- White PF, Way WL, Trevor AJ: Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 56(2):119-136, 1982 6892475
- Xu K, Lipsky RH: Repeated ketamine administration alters N-methyl-D-aspartic acid receptor subunit gene expression: implication of genetic vulnerability for ketamine abuse and ketamine psychosis in humans. *Exp Biol Med (Maywood)* 240(2):145-155, 2015 25245072

- Yoosefi A, Sepehri AS, Kargar M, et al: Comparing effects of ketamine and thiopental administration during electroconvulsive therapy in patients with major depressive disorder: a randomized, double-blind study. J ECT 30(1):15-21, 2014 24091902
- Zakine J, Samarcq D, Lorne E, et al: Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg 106(6):1856-1861, 2008 18499623



## CHAPTER 22

# Benzodiazepines

David V. Sheehan, M.D., M.B.A.

---

### History and Discovery

---

In spite of adverse publicity and a problematic public image, the most widely prescribed psychiatric medication in the United States over the past two decades is not an antidepressant, an atypical antipsychotic, or a mood stabilizer, but the benzodiazepine alprazolam, with more than 48 million prescriptions issued in 2013 (see [Grohol 2015](#); [Stahl 2002](#)).

The first benzodiazepine, chlordiazepoxide, was patented in 1959. Diazepam was introduced in 1963, and numerous derivatives of this drug have since been introduced into the market. The triazolobenzodiazepine alprazolam was introduced in 1981 and revolutionized the treatment of anxiety disorders when it was shown to be effective in the treatment of panic disorder ([Chouinard et al. 1982](#); [Sheehan et al. 1982](#)). It was the first benzodiazepine to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of panic disorder. Since then, clonazepam, another high-potency benzodiazepine, also has received approval from the FDA for the treatment of panic disorder.

Benzodiazepines were widely prescribed in the 1960s, 1970s, and 1980s for pathological anxiety by psychiatrists, family practitioners, and internists who knew the drugs were effective and relatively safe when compared with prior anxiolytic medications such as the barbiturates and meprobamate. However, since the 1990s, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have displaced benzodiazepines as the clinician's first choice for the treatment of anxiety disorders ([Kramer 1993](#)). The SSRIs and SNRIs are safer and better tolerated than the tricyclic antidepressants and have been shown to be efficacious in a number of different anxiety disorders. In addition, they do not have the dependence, withdrawal, alcohol interaction, and abuse liability of the benzodiazepines.

Despite these drawbacks, benzodiazepines are often used as an adjunctive treatment with an SSRI or SNRI or as the primary treatment for the patient with no response or only a partial response to the SSRI or SNRI. The net result is only a small decline in the recommendation for a benzodiazepine ([Uhlenhuth et al. 1999](#)). One user in four uses the benzodiazepine for a year or longer. Among those using it as a hypnotic, 14% reported long-term use ([Balter 1991](#)). Rates of use increase with age, from 2.6% among

those 18-35 years to 8.7% among those 65-80 years ([Olson et al. 2015](#)). In recent years, there has been a shift to the use of short-half-life benzodiazepines.

---

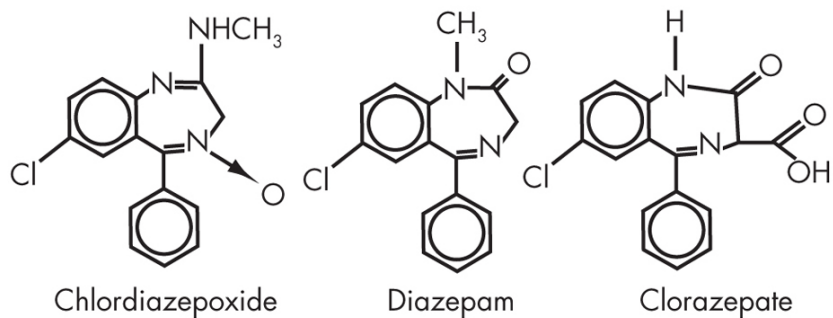
## Structure-Activity Relations

---

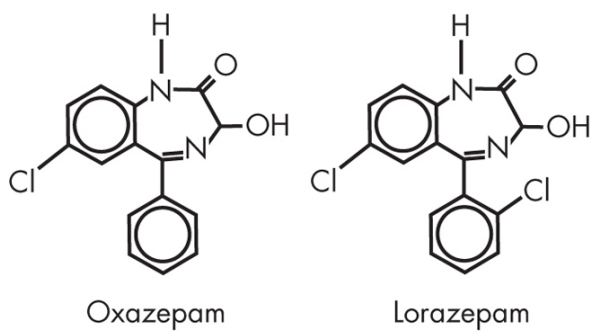
Currently marketed benzodiazepines are similar in that they have the 1,4-benzodiazepine ring system. Modification of this ring system results in benzodiazepines with somewhat different properties ([Figure 22-1](#)).

**(A)**

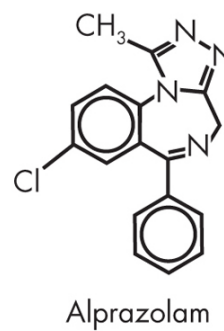
**2-Keto**



**3-Hydroxy**

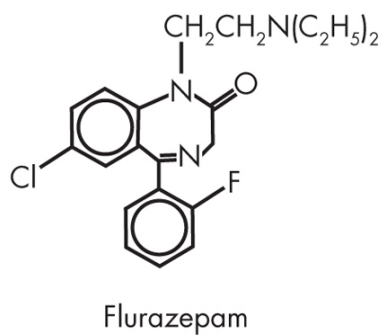


**Triazolo**

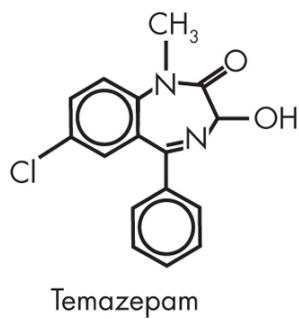


**(B)**

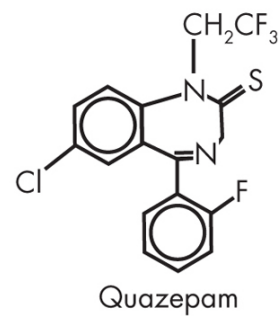
**2-Keto**



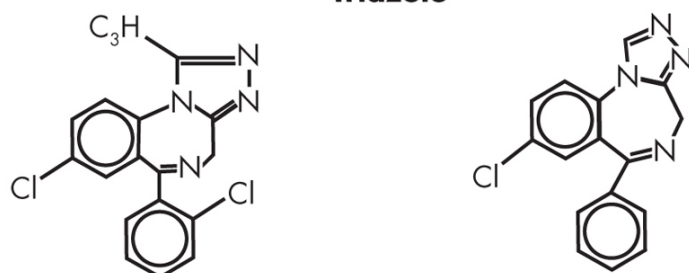
**3-Hydroxy**



**Trifluoroethyl**



**Triazolo**



**FIGURE 22-1.** Chemical structures of commonly used benzodiazepine anxiolytics (A) and hypnotics (B).

## Pharmacokinetics and Disposition

Knowledge of benzodiazepine pharmacokinetics helps the clinician choose the most appropriate benzodiazepine for the patient and also guides its correct use. Benzodiazepines differ in their pharmacokinetic properties, such as absorption, distribution, and elimination (Table 22-1). On the other hand, all benzodiazepines are similar in that to some degree they all possess anxiolytic, muscle-relaxant, sedative-hypnotic, and anticonvulsant properties. The belief that one benzodiazepine is primarily anxiolytic while another is primarily hypnotic is not based on scientific evidence (Greenblatt et al. 1983a, 1983b). The preferential selection of a benzodiazepine for one market over another is usually dictated by its pharmacokinetic properties.

**TABLE 22-1. Pharmacokinetics of benzodiazepines**

Group	Medication	Metabolism	CYP enzyme(s)	t <sub>1/2</sub> , hours	K <sub>i</sub>
Desmethyldiazepam	Diazepam	Oxidation	2C19, 3A4	26–50	9.6
	Bromazepam	Oxidation	3A4	1–5	NA
	Prazepam	Oxidation		>21	NA
	Chlordiazepoxide	Oxidation	3A4	>21	NA
Desalkylflurazepam	Flurazepam	Oxidation		40–120	NA
	Clonazepam	Oxidation		24–56	0.5
Triazolobenzodiazepine	Triazolam	Oxidation	3A4	2–4	0.4
	Alprazolam	Oxidation	3A4	10–15	4.8
Imidazobenzodiazepine	Midazolam	Oxidation	3A4	1–3	0.4
Thienodiazepine	Brotizolam	Oxidation	3A4	4–8	0.9
	Nitrazepam	Reduction	3A4, 2D6	20–50	11.5
	Flunitrazepam	Reduction		10–25	3.8

*Note.* CYP=cytochrome P450; K<sub>i</sub>=kinetic inhibition constant value (nM); NA=not available; t<sub>1/2</sub>=half-life.

Group	Medication	Metabolism	CYP enzyme(s)	t <sub>1/2</sub> , hours	K <sub>i</sub>
Oxazolobenzodiazepine	Oxazepam	Glucuronidation		5–15	17.2
	Lorazepam	Glucuronidation		10–20	3.8
	Temazepam	Glucuronidation		6–16	23.0

*Note.* CYP=cytochrome P450; K<sub>i</sub>=kinetic inhibition constant value (nM); NA=not available; t<sub>1/2</sub>=half-life.

## Rate of Absorption

Benzodiazepines that are rapidly absorbed from the gastrointestinal tract enter and peak in the circulation quickly and have a quicker onset of action than those that are absorbed more slowly. Diazepam and clorazepate are rapidly absorbed and act quickly, chlordiazepoxide and lorazepam have intermediate rates of absorption and onset of action, and prazepam is slowly absorbed and has a slower onset of action.

Gastrointestinal absorption of benzodiazepines is dictated by intrinsic physiochemical properties of the drug and characteristics of the formulation such as particle size (Greenblatt et al. 1983a, 1983b). Benzodiazepine absorption when given intramuscularly is dictated by other factors. For example, chlordiazepoxide and lorazepam, when given orally, are absorbed at similar rates in the gastrointestinal tract. When given intramuscularly, lorazepam is more reliably, rapidly, and completely absorbed than chlordiazepoxide (Greenblatt et al. 1979, 1982b, 1983a, 1983b).

## Lipophilicity

The lipid solubility (lipophilicity) of a benzodiazepine at physiological pH influences the rate at which it crosses the blood-brain barrier by passive diffusion from the circulation, and this, in turn, determines the rapidity of onset of action and intensity of effect (Greenblatt et al. 1983a, 1983b). Highly lipophilic drugs cross the blood-brain barrier rapidly, and although all benzodiazepines are highly lipophilic, they differ in their degree of lipophilicity. Because diazepam is more lipophilic than lorazepam or chlordiazepoxide, it provides more rapid anxiety reduction and onset of side effects.

## Duration of Action

With benzodiazepines, the duration of therapeutic action is determined mainly by the rate and extent of drug distribution rather than by the rate of elimination. Benzodiazepine distribution is largely determined by its lipophilicity. Diazepam, which has a longer half-life than lorazepam, has a shorter duration of clinical action after a single dose. The reason for this is that diazepam, because of its greater lipid solubility, is more extensively distributed to peripheral sites, particularly to fat tissue. Consequently, it is more rapidly moved out of the blood and brain into inactive storage sites, and its

central nervous system (CNS) effects end more rapidly. Conversely, less lipophilic benzodiazepines maintain their effective brain concentrations longer because they are less extensively distributed to the periphery ([Greenblatt et al. 1983a, 1983b](#)).

## Rate of Elimination

The rate of elimination (elimination half-life) influences the speed and extent of accumulation and the time to reach a steady state. It also influences the time for drug washout after termination of multiple doses. Accumulation is slow and extensive when the half-life is long. When the rate of metabolic removal equals the rate of ingestion, the drug is said to have reached steady state. A useful rule of thumb is that when treatment has been in progress for at least four to five times as long as the elimination half-life, then the accumulation process is more than 90% complete ([Greenblatt et al. 1983a, 1983b](#)). When drugs with long elimination half-lives are stopped, they are washed out slowly, and the symptoms recur gradually over a period of days, with less intense or sudden rebound phenomena ([Greenblatt et al. 1981, 1982a; Kales et al. 1982](#)). Side effects from long-term treatment with long-half-life benzodiazepines last longer than with short-half-life benzodiazepines. Because of greater drug accumulation with long-half-life benzodiazepines, frequent drowsiness and sedation are a theoretical concern ([Greenblatt et al. 1981](#)). Tolerance to sedation occurs with long-term use, even though the plasma drug level remains the same. However, as a matter of caution, it is prudent to choose a benzodiazepine with a shorter or intermediate half-life for the elderly ([Greenblatt et al. 1982c](#)), individuals operating heavy machinery, and those engaging in high-level intellectual tasks.

## Biotransformation Pathway

Benzodiazepines are metabolized in the liver by microsomal oxidation or by glucuronide conjugation. Hepatic disease, age, several medical illnesses, and a number of drugs that impair oxidizing capacity, such as cimetidine, estrogens, and the hydrazine monoamine oxidase inhibitors (MAOIs), all influence the oxidation pathway. These factors usually magnify the side effects of the benzodiazepine. Consequently, in the elderly and in individuals with liver disease, benzodiazepines that are conjugated (e.g., temazepam, oxazepam, and lorazepam) are safer than benzodiazepines that are metabolized by oxidation (e.g., diazepam and alprazolam).

## Dosing: Sustained-Release Formulations

Dosing schedules of benzodiazepines should be dictated by knowledge about the rate of distribution rather than by information about elimination half-life. Sustained-release formulations of several benzodiazepines have been introduced to provide 24 hours of anxiolysis. In our experience, the sustained-release forms of alprazolam, clorazepate, diazepam, and adinazolam have a duration of therapeutic action of approximately 12 hours, not 24 hours. Standard alprazolam has a duration of action of 4–6 hours, clonazepam has a duration of action of 7 hours, and other standard-formulation benzodiazepines are within this 4- to 7-hour range.

---

## Mechanism of Action

---

Benzodiazepines produce anxiolysis by their effect on the  $\gamma$ -aminobutyric acid (GABA)-benzodiazepine receptor complex. GABA is synthesized from glutamic acid, which is also the most abundant free amino acid in the CNS. Like serotonin, norepinephrine, and dopamine neurons, the presynaptic GABA neuron has a reuptake pump that transports GABA from the synapse for storage or destruction by GABA transaminase. GABA has three target receptors: GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>. The chloride ion channel is controlled by GABA<sub>A</sub>.

Four distinct pharmacological properties have been described for the benzodiazepine receptor: anxiolytic, hypnotic, anticonvulsant, and muscle relaxation effects. GABA<sub>A</sub> receptors with  $\alpha_2$  (and/or  $\alpha_3$ ) subunits mediate the anxiolytic effects, whereas GABA<sub>A</sub> receptors with an  $\alpha_1$  subunit mediate the sedative-hypnotic actions. Most benzodiazepines interact with both these receptor subtypes. Typically, when GABA occupies the GABA<sub>A</sub> receptor site, opening and closing of the chloride channel occur more frequently, and this effect is inhibitory. If at the same time a benzodiazepine binds to the nearby benzodiazepine receptor, the GABA<sub>A</sub> receptor is allosterically modulated, and GABA exerts a greater effect (greater frequency of opening and closing) on the chloride channel and conductance. Although GABA works alone at the GABA receptor, the action of GABA is stronger in the presence of a benzodiazepine. The benzodiazepine in the absence of GABA cannot influence the chloride channel by itself.

---

## Therapeutic Uses

---

Because of their multiple pharmacological actions, benzodiazepines are useful in many areas of medical practice, such as induction of anesthesia, use as a muscle relaxant, and control of seizures. It is beyond the scope of this chapter to elaborate on these nonpsychiatric uses. In psychiatry, benzodiazepines are used to control anxiety, to treat insomnia, and to acutely manage agitation and withdrawal syndromes.

In the treatment of anxiety disorders, benzodiazepines have a greater effect in some disorders than in others. In panic disorder, they have a significant effect on all dimensions of the illness, with the exception of depression. Alprazolam, for example, has been shown to be effective in panic disorder at a mean dosage of 5.7 mg/day (range=1–10 mg/day) ([Ballenger et al. 1988](#); [Chouinard et al. 1982](#); [Cross National Collaborative Panic Study 1992](#); [Sheehan et al. 1982, 1984, 1993](#)). Rapid improvement was seen within the first week in the form of decreased panic attacks, phobic fears and avoidance, anticipatory anxiety, and disability. These benefits were shown to persist during a follow-up period of 8 months ([Schweizer et al. 1993](#)). Efficacy also has been established for lorazepam ([Rickels and Schweizer 1986](#)) and clonazepam ([Pollack et al. 1993](#); [Tesar et al. 1991](#)). In the latter studies, clonazepam 2.5 mg/day was as effective and well tolerated as alprazolam 5.3 mg/day.

Despite the well-documented efficacy of benzodiazepines in panic disorder, they have been displaced in clinical practice by the SSRIs and SNRIs. However, some clinicians initiate treatment with both classes of drug simultaneously and then withdraw the benzodiazepine after 6 weeks. The benefits and practicality of this approach to treating

panic disorder are reinforced by the findings from two studies ([Goddard et al. 2001, 2008](#)). The [American Psychiatric Association \(1998\)](#) guidelines for the treatment of panic disorder recommending SSRI monotherapy as the treatment of first choice have failed to achieve traction, because more than two-thirds of the SSRI prescriptions were accompanied by a concomitant benzodiazepine ([Keller and Craske 2008](#)). The study by [Goddard et al. \(2008\)](#) lends justification to the rationale for using the combination treatment more frequently and blessing it as a reasonable alternative first-line treatment for many patients with panic disorder.

Three double-blind studies have shown efficacy for benzodiazepines in the treatment of social phobia ([Davidson et al. 1993](#); [Gelernter et al. 1991](#); [Versiani et al. 1997](#)).

In a double-blind, placebo-controlled study, [Rickels et al. \(1993\)](#) found that the tricyclic antidepressant imipramine was better than diazepam in the treatment of generalized anxiety disorder (GAD) without depression over 8 weeks. Imipramine showed a trend of being significantly better on the primary outcome measure scale (the Hamilton Anxiety Scale [Ham-A]) and was statistically superior to diazepam on the Psychic Anxiety factor of the Ham-A. Psychic anxiety includes the items of worry, anxious mood, tension, fears, and concentration problems. Diazepam and imipramine had identical endpoint Ham-A Somatic Anxiety factor scores, suggesting that they are equally effective against the somatic anxiety symptoms in GAD. This suggests that imipramine is a better “anti-worry” medication than the benzodiazepine. Patients taking diazepam had an earlier response than those taking imipramine.

Generally, benzodiazepines are thought to be ineffective in the treatment of obsessive-compulsive disorder (OCD).

The strongest evidence for effective pharmacotherapy in posttraumatic stress disorder (PTSD) is with SSRIs. A meta-analysis of medications in treating PTSD found effect sizes of 0.49 and 1.38 for benzodiazepines and SSRIs, respectively ([Van Etten and Taylor 1998](#)).

Intramuscular clonazepam has been compared with intramuscular haloperidol in the management of acute psychotic agitation. Clonazepam use reduced agitation, but haloperidol use had a more rapid onset ([Chouinard et al. 1993](#)). Individuals with schizophrenia have high levels of anxiety and frequently experience panic attacks. Overall, it appears that benzodiazepines have a role in the acute management of agitation, and their use can reduce the need for or the dose of antipsychotics used.

---

## Side Effects and Toxicology

---

Benzodiazepines are among the safest of drugs, but unwanted effects do occur. The first 1,4-benzodiazepines, such as diazepam and flurazepam, had slow rates of elimination and low receptor-binding affinities. Their main side effect was excessive daytime sleepiness. The late 1970s saw the introduction of the 1,4-benzodiazepines flunitrazepam and lorazepam, which had shorter half-lives and were more potent. These drugs were associated with enhanced efficacy but also with more rapid development of tolerance and significant withdrawal problems. The triazolobenzodiazepines were introduced in the 1980s and were even more potent and had even shorter half-lives. They also have been found to be associated with amnesia, daytime anxiety, early-morning insomnia, and withdrawal problems such as rebound insomnia, anxiety, and seizures ([Noyes et al. 1986](#)).



Sedation and drowsiness are common, occurring in 4%–9% of patients taking benzodiazepines. Ataxia occurs in up to 2%. The drowsiness tends to disappear with time or a reduction in dose ([Greenblatt et al. 1982b](#); [Miller 1973](#); [Svenson and Hamilton 1966](#)). Benzodiazepines may impair psychomotor performance. Most benzodiazepines, shortly after administration at their peak concentration, cause anterograde amnesia ([Lister et al. 1988](#)). These effects are dependent on potency and route of administration ([Bixler et al. 1979](#)). Overall, this memory impairment does appear to be independent of the degree of sedation produced by the drug ([Scharf et al. 1988](#)). Benzodiazepine-treated subjects are often unaware of or underestimate the extent of their memory impairment ([Roache and Griffiths 1985, 1987](#)).

Hyperexcitability phenomena such as early-morning awakening and rebound anxiety and nervousness are more likely with the short-half-life, high-potency benzodiazepines such as triazolam, alprazolam, lorazepam, and brotizolam ([Kales et al. 1983, 1986, 1987](#); [Vela-Bueno et al. 1983](#)). Treatment-emergent hostility ([Rosenbaum et al. 1984](#)) may be seen in up to 10% of the patients receiving benzodiazepines. This is most likely to happen early in treatment, is unrelated to pretreatment impulsivity, and has been reported with all benzodiazepines with the exception of oxazepam. Treatment-emergent mania has been reported with alprazolam ([Goodman and Charney 1987](#); [Pecknold and Fleury 1986](#); [Strahan et al. 1985](#)).

Since the 1960s, benzodiazepines have been known to produce anterograde amnesia, even with oral dosing ([Lister 1985](#)). The deficit is one of disrupted consolidation and not impairment of memory retrieval. The degree of amnesia can range from minimal inability to retain isolated pieces of information to total inability to recall any activities that occurred during a specific period. Whether some benzodiazepines are more likely than others to produce amnesia remains an unresolved question.

## Cognitive Impairment and Risk of Alzheimer's Disease

Some publications have raised concerns that the long-term use of benzodiazepines may lead to cognitive and other impairments that persist long after the drugs have been discontinued. Abnormal computed tomography (CT) scans were reported in long-term users of benzodiazepines in one study ([Lader et al. 1984](#)) but not in others ([Poser et al. 1983](#); [Rickels 1985](#)). [Busto et al. \(2000\)](#) found no difference in the CT brain scans of patients taking benzodiazepines compared with control subjects. Long-term benzodiazepine users have been compared with control subjects and found to have cognitive impairments that reversed on reexamination after taper ([Golombok et al. 1988](#); [Lucki et al. 1986](#); [Rickels et al. 1999](#); [Sakol and Power 1988](#)). Another study found that after long-term use, if the benzodiazepine was stopped, there was only partial recovery even after 6 months ([Tata et al. 1994](#)).

[Billioti de Gage et al. \(2014\)](#) reported inferential evidence suggesting that the use of benzodiazepines for longer than 3 months may be associated with an increased risk for Alzheimer's disease. They used a case-control design to minimize sampling bias and sampled subjects 6 years before the official diagnosis of Alzheimer's disease in an attempt to control for "reverse bias" (the possibility that Alzheimer's disease resulted in benzodiazepines being used before the onset of the dementia). [Salzman and Shader \(2015\)](#) wrote a rejoinder to this study highlighting its methodological limitations and offering alternative interpretations for the findings. They pointed out that the results "could be interpreted to suggest that benzodiazepine use does not cause increased

Alzheimer's disease, but Alzheimer's disease causes an increased need for benzodiazepine treatment in some patients" (p. 2), notably for the prodromal anxiety and insomnia so frequently associated with this illness. In their editorial, [Balon et al. \(2015\)](#) urged caution in the interpretation of the results and noted that it was "premature to conclude that benzodiazepines are a causative factor in a multidimensional disorder such as Alzheimer's disease" ([Balon et al. 2015](#), p. 244).

[Pariente et al. \(2016\)](#) reviewed the literature on the association between benzodiazepine use and the risk of dementia disorders. Nine of the 11 studies reported a harmful effect; 1 study reported a protective effect; and the most recent, largest, best-controlled, and most prospectively designed study found no effect. The problem in interpreting a finding of any such association in an inadequately controlled meta-analytic study is that both anxiety and sleep disturbances are common prodromal symptoms in dementia. A lack of adequate controls confounds the interpretation of results in these studies.

The most recent *BMJ* study ([Gray et al. 2016](#)) followed 3,434 adults ages 65 years and older for 7 years. None had dementia at study initiation; 23% developed dementia by the end of the study. Gray and colleagues used computerized pharmacy data to assess benzodiazepine use. They found no link between the highest level of benzodiazepine use (on average, 1 year of daily use) and dementia or cognitive decline. A small increased risk for dementia was seen in people with moderate (1–4 months) and low (up to 1 month) levels of benzodiazepine use but not in those using benzodiazepines for longer than 4 months. The authors concluded that the pattern of findings "does not support the theory that cumulative benzodiazepine use at the levels observed in our population is causally related to an increased risk for dementia or cognitive decline" ([Gray et al. 2016](#)).

Practice guidelines recommend that benzodiazepines be avoided in Alzheimer's disease and restricted to short-term, as-needed use in elderly persons ([Madhusoodanan and Bogunovic 2004](#); [Salzman 1990](#)). That said, others may agree with the comment by [Salzman and Shader \(2015\)](#), both very seasoned and knowledgeable psychopharmacologists, that

experienced geriatric clinicians often find that judicious use of low-dose, short half-life BZs reduces stress, promotes daytime functioning, and assists in sleep onset; elderly patients themselves report that they would gladly forgo short-term memory reduction in exchange for a calmer daytime and reliable sleep onset.  
(p. 2)

---

## Drug-Drug Interactions

---

Antacids slow benzodiazepine absorption, because aluminum delays gastric emptying ([Greenblatt et al. 1983a](#), 1983b). An acid medium is needed for conversion of clorazepate to desmethyldiazepam, the active metabolite, which is then absorbed ([Shader et al. 1978](#)).

In the liver, benzodiazepines are metabolized by oxidation, reduction, or conjugation. Alprazolam, diazepam, clorazepate, prazepam, chlordiazepoxide, bromazepam, and halazepam are metabolized by oxidation; nitrazepam by reduction; and lorazepam, oxazepam, and temazepam by conjugation. Inhibitors of the oxidase system prolong the half-life of benzodiazepines that are metabolized by this system. This accentuates the

side effects, notably the sedation, ataxia, slurred speech, and imbalance. A decrease in dosage may solve this problem, or a switch to a benzodiazepine that is metabolized by conjugation may be needed. MAOIs, cimetidine ([Greenblatt et al. 1984](#)), and oral contraceptives inhibit the oxidative system. A decline in this system occurs with age or liver disease. In the elderly, there is a 50% decrease in clearance, with a four- to ninefold increase in half-life and a two- to fourfold increase in the volume of distribution ([Peppers 1996](#)). Heparinized patients ([Routledge et al. 1980](#)) should have partial thromboplastin time (PTT) monitored more closely, because PTT is prolonged by benzodiazepines. Because antidepressants such as fluoxetine, paroxetine, and nefazodone and protease inhibitors such as indinavir sulfate inhibit the cytochrome P450 enzyme 3A4, they inhibit the metabolism of triazolobenzodiazepines such as midazolam, alprazolam, and triazolam.

---

## Clinical Issues

---

Despite decades of research, the optimal extent and duration of appropriate benzodiazepine use in the treatment of anxiety and related disorders remain unresolved. This is primarily because of concerns expressed by prescribers, regulators, and the public about issues such as tolerance, dependence, and abuse liability of this class of medications.

### Tolerance

In a study of persistent users of alprazolam and lorazepam, [Romach et al. \(1995\)](#) found that most were not abusing these benzodiazepines, nor were they addicted to them; rather, they were using them appropriately for a chronic disorder and at a constant or a decreasing dose. [Soumerai et al. \(2003\)](#) found no relation between long-term use of benzodiazepines and escalation to high doses in 2,440 long-term (at least 2 years) users of benzodiazepines and noted that escalation to a high dose was very rare.

The cross-tolerance between the benzodiazepines, although good, is not perfect, and it is preferable to switch patients gradually from one benzodiazepine to another and to use comparable doses of each during the switch. One milligram of alprazolam is approximately equivalent to 0.7 mg of clonazepam, 10 mg of diazepam, or 1 mg of lorazepam.

### Withdrawal

A withdrawal syndrome is defined as a predictable constellation of signs and symptoms involving altered CNS activity (e.g., tremor, convulsions, or delirium) after the abrupt discontinuation of, or a rapid decrease in, dosing of the drug ([Rinaldi et al. 1988](#)). Typically, a withdrawal syndrome from short-half-life benzodiazepines will intensify by the second day, will usually have peaked by day 5, and will begin to decrease and taper off by day 10. After 2 weeks, withdrawal symptoms usually have become minimal or are absent. Drug factors associated with withdrawal symptoms include length of use, dose, potency, and rate of discontinuation. The most common are anxiety, restlessness, irritability, insomnia, agitation, muscle tension, weakness, aches and pains, blurred

vision, and racing heart, in that order (O'Brien 2005). Nausea, sweating, runny nose, hypersensitivity to stimuli, and tremor are less frequent. Severe withdrawal symptoms, such as psychosis, seizures, hallucinations, paranoid delusions, and persistent tinnitus, are relatively rare and are more likely to occur in abrupt withdrawal from high doses of high-potency benzodiazepines and in the elderly (American Psychiatric Association 1990; Lader 1990; Petursson and Lader 1981).

The minimum duration of use after which clinically significant withdrawal symptoms can be expected has not been definitively determined. At the end of any course of treatment with therapeutic doses and of duration greater than 3–6 weeks, withdrawal of the benzodiazepine should be done as a very slow taper. This reduces the risk of unpleasant withdrawal symptoms and the danger of withdrawal seizures and minimizes rebound reactivation of the underlying anxiety disorder (Fontaine et al. 1984; Pecknold et al. 1988; Power et al. 1985).

In a 3-year follow-up of patients who tapered successfully in a benzodiazepine taper program, 73% remained benzodiazepine free. Among those who were able to reduce intake by 50%, only 39% were benzodiazepine free at the end of 3 years. In the group that could not tolerate taper at all, only 14% were benzodiazepine free (Rickels et al. 1991).

## Addiction Potential

In our zeal to heal an anxiety disorder, are we creating a population of addicted individuals? Much misinformation and concern are generated because terms like *addiction* are used without precise definition and pejoratively. Terms such as *addiction*, *physical dependency*, and *withdrawal syndrome* are often used interchangeably. Some presume that a medicine's being associated with a withdrawal syndrome is evidence that the medicine is addicting. Some clinicians believe that benzodiazepines that require frequent dosing during the day are more addicting than those that require less frequent dosing. In reality, frequency of dosing is a function of the duration of therapeutic action of the drug rather than of any innate addiction potential of the drug.

Most of the literature discussing benzodiazepine dependence liability uses older terminology. *Substance dependence* is defined as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by the presence of three (or more) of seven criteria, occurring at any time in the same 12-month period (American Psychiatric Association 2000). *Addiction*, by contrast, is defined as a chronic disorder associated with compulsive use of a drug, resulting in physical, psychological, or social harm to the user and continued use despite that harm (Rinaldi et al. 1988). Addiction involves both intense drug-seeking behavior and difficulty in stopping the drug use. If these criteria are used, benzodiazepines are not addictive drugs. *Physical dependence* is different from addiction and is defined as a physiological state of adaptation to a drug, with the development of tolerance to the drug's effects and the emergence of a withdrawal syndrome during prolonged abstinence. During withdrawal after chronic use, biochemical, physiological, or behavioral problems may be triggered. When used on a regular schedule, benzodiazepines are associated with physical dependence and have a withdrawal syndrome.

In DSM-5 (American Psychiatric Association 2013), the terms *abuse* and *dependence* are no longer used in relation to substances. Instead, DSM-5 uses the more neutral term *substance use disorder* to capture the wider range of disorders previously

subsumed under *substance dependence* and *substance abuse*. DSM-5 also uses the terms *substance intoxication* and *substance withdrawal*. *Substance use disorder* is defined as a problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by the presence of 2 (or more) of either 10 or 11 criteria, occurring within a 12-month period. At this time, no large epidemiological studies have used these new criteria in relation to benzodiazepines.

## Abuse

Studies of abuse use four criteria for benzodiazepine abuse. A benzodiazepine is being abused if it is used 1) to get high, 2) to promote psychological regression, 3) at doses higher than prescribed, and 4) after the medical indication has passed ([Dietch 1983](#)). On the basis of this definition, the data suggest that the incidence of benzodiazepine abuse in clinical practice is low.

The incidence of benzodiazepine dependence in the therapeutic setting (among those for whom the drug is medically correctly prescribed) was estimated to be 1 case in 50 million patient-months ([Marks 1978](#)). Of these cases, 92% were associated with alcohol or other drugs of abuse. This estimate is probably on the low side because it is based on the number of published cases of dependence from 1961 to 1977.

In Basel, Switzerland, with a catchment area of 300,000 people, physicians were surveyed on the prevalence of benzodiazepine abuse in their patients. Only 31 patients were identified—a prevalence of 0.01%, or 1 in 10,000. An additional 88 polysubstance abusers were identified ([Ladewig and Grossenbacher 1988](#)). In a random sample of all psychiatric hospitalizations over 15 years (1967–1983) in Sweden ( $N=32,679$ ), [Allgulander \(1989\)](#) found only 38 admissions for substance dependence on sedative-hypnotics. Twenty-one of the 38 had polysubstance abuse, and 17 had sedative-hypnotic abuse.

In another study of all medical and psychiatric hospitalizations ( $N=1.6$  million) in Stockholm County, Sweden, [Allgulander \(1996\)](#) found that 0.04% of “prescribed medication” users (including benzodiazepines) were ever admitted for medical problems relating to their drug use. In a study of 5,426 U.S. physicians randomly selected from the American Medical Association Physician Masterfile database, [Hughes et al. \(1992\)](#) found that although 11.9% had used benzodiazepines in the past year, only 0.6% met DSM-III-R ([American Psychiatric Association 1987](#)) criteria for benzodiazepine abuse, and 0.5% met criteria for benzodiazepine dependence. In 1990, the American Psychiatric Association task force concluded that benzodiazepines were not normally drugs of abuse but noted that people who abused alcohol, cocaine, and opiates were at increased risk for benzodiazepine abuse ([Salzman 1991](#)).

A number of studies have noted no increase in dosage with chronic therapy of duration from 1 to 2.5 years, even though many of the patients had residual symptoms that would have benefited from a dose increase or more intensive or additional treatment strategies ([Pollack et al. 1986](#); [Sheehan 1987](#)). Nonanxious subjects and those with low anxiety levels find benzodiazepines dysphoric ([Reed et al. 1965](#)), prefer placebo to diazepam ([Johanson and Uhlenhuth 1978, 1980](#)), or rate their mood as less happy and pleasant after they were given 10 mg of diazepam ([Svensson et al. 1980](#)).

Although the data suggest that the prevalence of benzodiazepine abuse or dependence is generally low, this is not true among those who abuse alcohol and other drugs. In a study of chronic alcoholic individuals who were high consumers of

benzodiazepines, 17% got their benzodiazepines from nonmedical sources ([Busto et al. 1983](#)). In a study of 1,000 admissions to an alcohol treatment unit, 35% of the patients used benzodiazepines, but only 10% of the total sample were considered abusers or misusers ([Ashley et al. 1978](#)). A study of 427 patients seeking treatment in Toronto, Ontario, who met DSM-III ([American Psychiatric Association 1980](#)) criteria for alcohol abuse or dependence found that 40% were recent benzodiazepine users, and 20% had a lifetime history of benzodiazepine abuse or dependence. By contrast, only 5% of 108 alcoholic patients treated for a year with benzodiazepines for anxiety and tension showed evidence of abuse, and 94% believed that the medication helped them function and remain out of the hospital ([Rothstein et al. 1976](#)).

Benzodiazepines were the primary drug of abuse in one-third of polydrug abusers ([Busto et al. 1986](#)), in 29% of 113 drug abusers admitting to the street purchase of diazepam in the previous month ([Woody et al. 1975b](#)), and in 40% of patients at a methadone maintenance clinic ([Woody et al. 1975a](#)). The principal reasons for benzodiazepine use among drug-addicted persons are self-treatment of withdrawal symptoms, relief from rebound dysphoria, or potentiation of alcohol or street drug effects ([Perera et al. 1987](#)). In one study at an addiction treatment center, 100% of urine samples tested were positive for benzodiazepines, and 44% were positive for multiple nonprescribed benzodiazepines ([Iguchi et al. 1993](#)). A survey of patients at three different methadone maintenance clinics found that 78%–94% admitted to a lifetime use of benzodiazepines, and 44%–66% admitted to use in the prior 6 months. Snorting of benzodiazepines by individuals addicted to cocaine has been reported ([Sheehan et al. 1991](#)), primarily as a means of blunting the anxiogenic effect of cocaine and allowing for a more pleasant and “less edgy” high from that drug. Overall, the existing evidence suggests that the prevalence of benzodiazepine abuse is uncommon, except among those individuals who abuse alcohol and/or other drugs.

Despite extensive data and discussion on this topic, the issue remains and will continue to be controversial, with strong opinions held by opposing camps. Klerman characterized these camps as “pharmacological Calvinism” and “psychotropic hedonism,” respectively ([Klerman 1972](#); [Rosenbaum 2005](#)). The middle ground suggests that we should not hesitate to prescribe benzodiazepines when it is reasonable, but that we should exercise restraint in using them when we see any evidence of abuse ([Pomeranz 2007](#)).

---

## Medicolegal Issues

---

In addition to issues of dependence and withdrawal described in the previous section, use of benzodiazepines is associated with several potential medicolegal pitfalls. These include issues of teratogenicity, injury, and interaction with substances.

## Benzodiazepines and Pregnancy

Because anxiety disorders have their highest incidence in women during their childbearing years, the clinician may have to advise patients who are planning a pregnancy or who become pregnant while taking a benzodiazepine.



## First and Second Trimesters

An important concern in the first and second trimesters is the possibility of teratogenic effects. Diazepam and desmethyldiazepam cross the placental barrier easily, and concentrations are higher in fetal blood than in maternal blood ([Idänpään-Heikkilä et al. 1971](#)). Early concern over benzodiazepine exposure in pregnancy arose because benzodiazepines act on GABA receptors, and GABA is involved in palate shelf reorientation ([Wee and Zimmerman 1983](#); [Zimmerman and Wee 1984](#)). The teratogenic effects of benzodiazepines, however, are a matter of controversy. Exposure to benzodiazepines has been associated with teratogenic effects, including facial clefts and skeletal anomalies in the newborn in some animal studies ([Miller and Becker 1975](#); [Walker and Patterson 1974](#); [Wee and Zimmerman 1983](#); [Zimmerman 1984](#); [Zimmerman and Wee 1984](#)) but not in others ([Beall 1972](#); [Chesley et al. 1991](#)). Early studies in humans, including retrospective and case-control studies, reported an increased risk of oral clefts associated with diazepam ([Aarskog 1975](#); [Livezey et al. 1986](#); [Safra and Oakley 1975](#); [Saxén 1975](#); [Saxén and Lahti 1974](#)). These results, however, have been criticized on methodological grounds and are contradicted by more recent prospective studies, case-control studies, and meta-analyses that show no increased risk of oral clefts related to benzodiazepine use in pregnancy ([Altshuler et al. 1996](#); [Bracken 1986](#); [Czeizel 1987–1988](#); [Dolovich et al. 1998](#); [Ornoy et al. 1998](#); [Pastuszak et al. 1996](#); [Rosenberg et al. 1983](#); [Shiono and Mills 1984](#)).

Pooled data from seven cohort studies, however, do not support an association between fetal exposure to benzodiazepines and major malformations ([Dolovich et al. 1998](#)).

## Third Trimester and Labor

Two concerns associated with benzodiazepine use in the last trimester and through delivery are the possibilities of CNS depression and a withdrawal syndrome. Signs of CNS depression may include hypotonia, lethargy, sucking difficulties, decreased fetal movements, loss of cardiac beat-to-beat variability, respiratory depression, and thermogenesis. These symptoms in the neonate are more likely with higher doses and longer duration of benzodiazepine use by the mother. There have been numerous reports of “floppy infant syndrome” in babies born to women taking diazepam long term during pregnancy ([Gillberg 1977](#); [Haram 1977](#); [Rowlatt 1978](#); [Speight 1977](#)). Neonatal withdrawal symptoms may include hyperactivity and irritability. The occurrence of neonatal withdrawal symptoms is well documented ([Barry and St Clair 1987](#); [Briggs et al. 1998](#); [Cree et al. 1973](#); [Fisher et al. 1985](#); [Gillberg 1977](#); [Haram 1977](#)). Symptoms may be present at birth or appear weeks later and may continue for a period of time ([Schardein 1993](#)).

Diazepam in isolated doses is safe during labor ([Briggs et al. 1998](#)). There are conflicting reports on the effect of benzodiazepines on Apgar scores. Lowered Apgar scores have been reported with benzodiazepine use in some studies ([Berdowitz et al. 1981](#); [McElhatton 1994](#)). One study found that diazepam reduced Apgar scores only when doses greater than 30 mg were administered during labor ([Cree et al. 1973](#)).

## Breast Feeding

Neonates have only limited capacity to metabolize diazepam ([Morselli et al. 1973](#)). Benzodiazepines are excreted in breast milk ([Llewellyn and Stowe 1998](#)). Because of

the neonate's limited capacity to metabolize these drugs, they can potentially accumulate and cause sedation, lethargy, and loss of weight in the nursing infant. Although the extent to which benzodiazepines actually accumulate in the serum of breast-feeding infants is a matter of debate ([Birnbaum et al. 1999](#)), and three decades of studies support a low incidence of toxicity and adverse effects ([Birnbaum et al. 1999](#); [Llewellyn and Stowe 1998](#)), caution taking benzodiazepines while breast feeding is advised.

## Psychomotor Impairment

Another area of risk of benzodiazepine use relates to issues of psychomotor impairment resulting in injury. An examination of the medical records of a group of benzodiazepine users and nonusers found that the benzodiazepine users were more likely to experience at least one episode of accident-related health care and a greater number of accident-related inpatient days and also utilized significantly more non-accident-related health care services than did nonusers. Accident-related utilization of health care was more likely in the first month after the drug was prescribed ([Oster et al. 1987](#)). In the elderly, the issue of benzodiazepine use increasing the risk for falls and fractures is of great concern because hip fractures are associated with increased morbidity and mortality. A number of studies ([Boston Collaborative Drug Surveillance Program 1973](#); [Cummings et al. 1995](#); [Greenblatt et al. 1977](#); [Hemmelgarn et al. 1997](#); [Ray et al. 1992](#); [Roth et al. 1980](#)) have found a greater risk for falls with the use of long-half-life benzodiazepines, and others ([Cumming and Klineberg 1993](#); [Herings et al. 1995](#); [Leipzig et al. 1999](#)) have found the risk to be greater with short-half-life drugs. A more recent study ([Wang et al. 2001](#)) found the risk for hip fracture in the elderly to be the same with the use of short- or long-half-life benzodiazepines. The researchers did find that the risk increased when benzodiazepine dosages were greater than 3 mg/day in diazepam equivalents. They also found the greatest risk to be shortly after initiation of therapy and after 1 month of continuous use. A 5-year prospective cohort study followed a large group of elderly people newly exposed to benzodiazepines ([Tamblyn et al. 2005](#)). Elderly persons using benzodiazepines were at greater risk for a motor vehicle accident ([Hemmelgarn et al. 1997](#)). On the other hand, a study of the effect of New York State requiring triplicate forms for prescribing benzodiazepines showed that despite a 50% decrease in the number of prescriptions written, no significant change was seen in age-adjusted risk for hip fractures ([Wagner et al. 2007](#)).

Patients receiving benzodiazepines are nearly five times more likely than nonusers to experience a serious motor vehicle accident ([Skegg et al. 1979](#)). In the first 2 weeks after persons start using benzodiazepines, there is a several-fold increased risk for hospitalization related to accidental injury compared with persons using antidepressants or antipsychotics ([Neutel 1995](#)).

The best protection is a discussion of these issues with the patient before prescribing a benzodiazepine. This discussion, including cautionary statements about driving or operating dangerous machinery, should be documented in the chart at the start of therapy. The patient should be educated about potentiation by alcohol or other sedating drugs. He or she should be strongly advised never to abruptly discontinue the medicine because of a risk of seizures ([Noyes et al. 1986](#)), and this should be documented. Prescribing benzodiazepines for patients with a current or lifetime history of substance abuse or dependence should be done infrequently and only after documenting a risk-



benefit discussion in the chart. It is good practice to routinely screen for substance abuse before prescribing a benzodiazepine and to document that this was done.

---

## Conclusion

---

Benzodiazepines, if given in adequate doses, are effective in the treatment of anxiety. They have a lower mortality and morbidity per million prescriptions than some of the alternatives (Girdwood 1974), including atypical antipsychotics. Benzodiazepines are quicker in onset of action, easier for the clinician to use, associated with better compliance, and less subjectively disruptive for the patient than any of the other medication alternatives. Until benzodiazepines are replaced by another class of medicine that is safer, better tolerated, and as rapidly effective, it is likely that they will continue to be prescribed to a significant proportion of patients.

---

## References

---

- Aarskog D: Letter: Association between maternal intake of diazepam and oral clefts. *Lancet* 2(7941):921, 1975 53396
- Allgulander C: Psychoactive drug use in a general population sample, Sweden: correlates with perceived health, psychiatric diagnoses, and mortality in an automated record-linkage study. *Am J Public Health* 79(8):1006–1010, 1989 2751014
- Allgulander C: Addiction on prescribed sedative-hypnotics (Presented at Milford Symposium V—Addiction as Behaviour, London, Royal Society, 9 June 1995). *Human Psychopharmacology: Clinical and Experimental* 119(S1):S49–S54, 1996
- Altshuler LL, Cohen L, Szuba MP, et al: Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 153(5):592–606, 1996 8615404
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition. Washington, DC, American Psychiatric Association, 1980
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987
- American Psychiatric Association: *Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force Report of the American Psychiatric Association*. Washington, DC, American Psychiatric Association, 1990
- American Psychiatric Association: Practice guideline for the treatment of patients with panic disorder. Work Group on Panic Disorder. American Psychiatric Association. *Am J Psychiatry* 155 (suppl 5): 1–34, 1998 9585731
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Ashley MJ, le Riche WH, Hatcher J, et al: “Mixed” (drug abusing) and “pure” alcoholics: a socio-medical comparison. *Br J Addict Alcohol Other Drugs* 73(1):19–34, 1978 272901
- Ballenger JC, Burrows G, Dupont RL, et al: Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. I. Efficacy in short-term treatment. *Arch Gen Psychiatry* 45(5):413–422, 1988 3282478
- Balon R, Fava GA, Rickels K: Need for a realistic appraisal of benzodiazepines. *World Psychiatry* 14(2):243–244, 2015 26043345

- Balter MB: Prevalence of medical use of prescription drugs. Paper presented at Evaluation of the Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care: Possible Implications for Future Research (NIDA Technical Review), Bethesda, MD, 1991
- Barry WS, St Clair SM: Exposure to benzodiazepines in utero. *Lancet* 1(8547):1436-1437, 1987 2884529
- Beall JR: Study of the teratogenic potential of diazepam and SCH 12041. *Can Med Assoc J* 106(10):1061, 1972 5032135
- Berdowitz RL, Coustan DR, Mochizuke T (eds): *Handbook for Prescribing Medications During Pregnancy*. Boston, MA, Little, Brown, 1981
- Billioti de Gage S, Moride Y, Ducruet T, et al: Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ* 349:g5205, 2014 25208536
- Birnbaum CS, Cohen LS, Bailey JW, et al: Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. *Pediatrics* 104(1):e11, 1999 10390297
- Bixler EO, Scharf MB, Soldatos CR, et al: Effects of hypnotic drugs on memory. *Life Sci* 25(16):1379-1388, 1979 522606
- Boston Collaborative Drug Surveillance Program: Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N Engl J Med* 288(6): 277-280, 1973 4682666
- Bracken MB: Drug use in pregnancy and congenital heart disease in offspring (letter). *N Engl J Med* 314(17):1120, 1986 3960086
- Briggs GG, Yaffe SJ, Freeman RK: *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*, 5th Edition. Baltimore, MD, Williams & Wilkins, 1998
- Busto U, Simpkins J, Sellers EM, et al: Objective determination of benzodiazepine use and abuse in alcoholics. *Br J Addict* 78(4):429-435, 1983 6140937
- Busto U, Sellers EM, Naranjo CA, et al: Patterns of benzodiazepine abuse and dependence. *Br J Addict* 81(1):87-94, 1986 2870731
- Busto UE, Bremner KE, Knight K, et al: Long-term benzodiazepine therapy does not result in brain abnormalities. *J Clin Psychopharmacol* 20(1):2-6, 2000 10653201
- Chesley S, Lumpkin M, Schatzki A, et al: Prenatal exposure to benzodiazepine, I: prenatal exposure to lorazepam in mice alters open-field activity and GABAA receptor function. *Neuropharmacology* 30(1):53-58, 1991 1646419
- Chouinard G, Annable L, Fontaine R, et al: Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study. *Psychopharmacology (Berl)* 77(3):229-233, 1982 6126907
- Chouinard G, Annable L, Turnier L, et al: A double-blind randomized clinical trial of rapid tranquilization with I.M. clonazepam and I.M. haloperidol in agitated psychotic patients with manic symptoms. *Can J Psychiatry* 38(suppl 4):S114-S121, 1993 8306241
- Cree JE, Meyer J, Hailey DM: Diazepam in labour: its metabolism and effect on the clinical condition and thermogenesis of the newborn. *BMJ* 4(5887):251-255, 1973 4753234
- Cross National Collaborative Panic Study, Second Phase Investigators: Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 160:191-201, 1992 1540759
- Cumming RG, Klineberg RJ: Psychotropics, thiazide diuretics and hip fractures in the elderly. *Med J Aust* 158(6):414-417, 1993 8479356
- Cummings SR, Nevitt MC, Browner WS, et al; Study of Osteoporotic Fractures Research Group: Risk factors for hip fracture in white women. *N Engl J Med* 332(12):767-773, 1995 7862179

- Czeizel A: Lack of evidence of teratogenicity of benzodiazepine drugs in Hungary. *Reprod Toxicol* 1(3):183-188, 1987-1988 2980381
- Davidson JRT, Potts N, Richichi E, et al: Treatment of social phobia with clonazepam and placebo. *J Clin Psychopharmacol* 13(6):423-428, 1993 8120156
- Dietch J: The nature and extent of benzodiazepine abuse: an overview of recent literature. *Hosp Community Psychiatry* 34(12): 1139-1145, 1983 6139334
- Dolovich LR, Addis A, Vaillancourt JM, et al: Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 317(7162):839-843, 1998 9748174
- Fisher JB, Edgren BE, Mammel MC, et al: Neonatal apnea associated with maternal clonazepam therapy: a case report. *Obstet Gynecol* 66 (3 suppl):34S-35S, 1985 4022513
- Fontaine R, Chouinard G, Annable L: Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. *Am J Psychiatry* 141(7):848-852, 1984 6145363
- Gelernter CS, Uhde TW, Cimbalic P, et al: Cognitive-behavioral and pharmacological treatments of social phobia. A controlled study. *Arch Gen Psychiatry* 48(10):938-945, 1991 1929764
- Gillberg C: "Floppy infant syndrome" and maternal diazepam (letter). *Lancet* 2(8031): 244, 1977 69847
- Girdwood RH: Death after taking medicaments. *BMJ* 1(5906):501-504, 1974 4817164
- Goddard AW, Brouette T, Almai A, et al: Early coadministration of clonazepam with sertraline for panic disorder. *Arch Gen Psychiatry* 58(7):681-686, 2001 11448376
- Goddard AW, Sheehan DV, Rickels K: A double blind placebo controlled study comparing sertraline plus placebo and sertraline plus alprazolam XR in the treatment of panic disorder. Paper presented at Anxiety Disorders Association of America annual meeting, Savannah, GA, March 2008
- Golombok S, Moodley P, Lader M: Cognitive impairment in long-term benzodiazepine users. *Psychol Med* 18(2):365-374, 1988 2899898
- Goodman WK, Charney DS: A case of alprazolam, but not lorazepam, inducing manic symptoms. *J Clin Psychiatry* 48(3): 117-118, 1987 3818553
- Gray SL, Dublin S, Yu O, et al: Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ* 352:i90, 2016 26837813
- Greenblatt DJ, Allen MD, Shader RI: Toxicity of high-dose flurazepam in the elderly. *Clin Pharmacol Ther* 21(3):355-361, 1977 13961
- Greenblatt DJ, Shader RI, Franke K, et al: Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. *J Pharm Sci* 68(1):57-63, 1979 31453
- Greenblatt DJ, Divoll M, Harmatz JS, et al: Kinetics and clinical effects of flurazepam in young and elderly noninsomniacs. *Clin Pharmacol Ther* 30(4):475-486, 1981 7285482
- Greenblatt DJ, Divoll M, Abernethy DR, et al: Benzodiazepine hypnotics: kinetic and therapeutic options. *Sleep* 5 (suppl 1):S18-S27, 1982a
- Greenblatt DJ, Divoll M, Harmatz JS, et al: Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. *J Pharm Sci* 71(2):248-252, 1982b 6121043
- Greenblatt DJ, Sellers EM, Shader RI: Drug therapy: drug disposition in old age. *N Engl J Med* 306(18):1081-1088, 1982c 7040951
- Greenblatt DJ, Shader RI, Abernethy DR: Drug therapy: current status of benzodiazepines. *N Engl J Med* 309(6):354-358, 1983a 6135156
- Greenblatt DJ, Shader RI, Abernethy DR: Drug therapy. Current status of benzodiazepines. *N Engl J Med* 309(7):410-416, 1983b 6135990

- Greenblatt DJ, Abernethy DR, Morse DS, et al: Clinical importance of the interaction of diazepam and cimetidine. *N Engl J Med* 310(25):1639-1643, 1984 6427609
- Grohol JM: Top 25 psychiatric medication prescriptions for 2013. November 2015. Available at: <http://psychcentral.com/lib/top-25-psychiatric-medication-prescriptions-for-2013/>. Accessed May 2, 2016.
- Haram K: "Floppy infant syndrome" and maternal diazepam. *Lancet* 2(8038):612-613, 1977 71430
- Hemmelgarn B, Suissa S, Huang A, et al: Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA* 278(1):27-31, 1997 9207334
- Herings RM, Stricker BH, de Boer A, et al: Benzodiazepines and the risk of falling leading to femur fractures: dosage more important than elimination half-life. *Arch Intern Med* 155(16):1801-1807, 1995 7654115
- Hughes PH, Brandenburg N, Baldwin DC Jr, et al: Prevalence of substance use among US physicians. *JAMA* 267(17):2333-2339, 1992 1348789
- Idänpään-Heikkilä JE, Jouppila PI, Puolakka JO, et al: Placental transfer and fetal metabolism of diazepam in early human pregnancy. *Am J Obstet Gynecol* 109(7):1011-1016, 1971 5549341
- Iguchi MY, Handelsman L, Bickel WK, et al: Benzodiazepine and sedative use/abuse by methadone maintenance clients. *Drug Alcohol Depend* 32(3):257-266, 1993 8102331
- IMS America: National Disease and Therapeutic Index (NDTI). Plymouth Meeting, PA, IMS America, 1991
- Johanson CE, Uhlenhuth EH: Drug self-administration in humans. *NIDA Res Monogr* (20):68-85, 1978 101861
- Johanson CE, Uhlenhuth EH: Drug preference and mood in humans: diazepam. *Psychopharmacology (Berl)* 71(3):269-273, 1980 6779334
- Kales A, Bixler EO, Soldatos CR, et al: Quazepam and flurazepam: long-term use and extended withdrawal. *Clin Pharmacol Ther* 32(6):781-788, 1982 7140142
- Kales A, Soldatos CR, Bixler EO, et al: Early morning insomnia with rapidly eliminated benzodiazepines. *Science* 220(4592): 95-97, 1983 6131538
- Kales A, Bixler EO, Soldatos CR, et al: Lorazepam: effects on sleep and withdrawal phenomena. *Pharmacology* 32(3):121-130, 1986 3960963
- Kales A, Bixler EO, Vela-Bueno A, et al: Alprazolam: effects on sleep and withdrawal phenomena. *J Clin Pharmacol* 27(7):508-515, 1987 3655003
- Keller ML, Craske MG: Panic disorder and agoraphobia, in *A Guide to Assessments That Work*. Edited by Hunsley J, Mash EJ. New York, Oxford University Press, 2008, pp 229-253
- Klerman GL: Psychotropic hedonism vs. pharmacological Calvinism. *Hastings Cent Rep* 2(4):1-3, 1972 4679711
- Kramer PD: *Listening to Prozac*. New York, Penguin Books, 1993
- Lader M: Benzodiazepine withdrawal, in *Handbook of Anxiety*, Vol 4. Edited by Noyer R, Roth M, Burrows GD. Amsterdam, Elsevier, 1990, pp 57-71
- Lader MH, Ron M, Petursson H: Computed axial brain tomography in long-term benzodiazepine users. *Psychol Med* 14(1): 203-206, 1984 6143338
- Ladewig D, Grossenbacher H: Benzodiazepine abuse in patients of doctors in domiciliary practice in the Basle area. *Pharmacopsychiatry* 21(2):104-108, 1988 2899328
- Leipzig RM, Cumming RG, Tinetti ME: Drugs and falls in older people: a systematic review and meta-analysis, I: psychotropic drugs. *J Am Geriatr Soc* 47(1):30-39, 1999 9920227
- Lister RG: The amnesic action of benzodiazepines in man. *Neurosci Biobehav Rev* 9(1):87-94, 1985 2858084

- Lister RG, Weingartner H, Eckardt MJ, et al: Clinical relevance of effects of benzodiazepines on learning and memory. *Psychopharmacol Ser* 6:117-127, 1988 2905802
- Livezey GT, Marczyński TJ, McGrew EA, et al: Prenatal exposure to diazepam: late postnatal teratogenic effect. *Neurobehav Toxicol Teratol* 8(5):433-440, 1986 3785505
- Llewellyn A, Stowe ZN: Psychotropic medications in lactation. *J Clin Psychiatry* 59 (suppl 2):41-52, 1998 9559759
- Lucki I, Rickels K, Geller AM: Chronic use of benzodiazepines and psychomotor and cognitive test performance. *Psychopharmacology (Berl)* 88(4):426-433, 1986 2871579
- Madhusoodanan S, Bogunovic OJ: Safety of benzodiazepines in the geriatric population. *Expert Opin Drug Saf* 3(5):485-493, 2004 15335303
- Marks J: *The Benzodiazepines*. Lancaster, UK, MTP Press, 1978
- McElhatton PR: The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 8(6):461-475, 1994 7881198
- Miller RP, Becker BA: Teratogenicity of oral diazepam and diphenylhydantoin in mice. *Toxicol Appl Pharmacol* 32(1):53-61, 1975 1135879
- Miller RR: Drug surveillance utilizing epidemiologic methods: a report from the Boston Collaborative Drug Surveillance Program. *Am J Hosp Pharm* 30(7):584-592, 1973 4715101
- Morselli PL, Principi N, Tognoni G, et al: Diazepam elimination in premature and full term infants, and children. *J Perinat Med* 1(2):133-141, 1973 4806567
- Neutel CI: Risk of traffic accident injury after a prescription for a benzodiazepine. *Ann Epidemiol* 5(3):239-244, 1995 7606314
- Noyes RJr, Perry PJ, Crowe RR, et al: Seizures following the withdrawal of alprazolam. *J Nerv Ment Dis* 174(1):50-52, 1986 2867122
- O'Brien CP: Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry* 66 (suppl 2):28-33, 2005 15762817
- Olfson M, King M, Schoenbaum M: Benzodiazepine use in the United States. *JAMA Psychiatry* 72(2):136-142, 2015 25517224
- Ornoy A, Arnon J, Shechtman S, et al: Is benzodiazepine use during pregnancy really teratogenic? *Reprod Toxicol* 12(5):511-515, 1998 9763242
- Oster G, Russell MW, Huse DM, et al: Accident- and injury-related health-care utilization among benzodiazepine users and nonusers. *J Clin Psychiatry* 48(12, suppl):17-21, 1987 2891685
- Pariente A, de Gage SB, Moore N, et al: The benzodiazepine-dementia disorders link: current state of knowledge. *CNS Drugs* 30(1):1-7, 2016 26715389
- Pastuszek A, Milich V, Chan S, et al: Prospective assessment of pregnancy outcome following first trimester exposure to benzodiazepines. *Can J Clin Pharmacol* 3(4):167-171, 1996
- Pecknold JC, Fleury D: Alprazolam-induced manic episode in two patients with panic disorder. *Am J Psychiatry* 143(5):652-653, 1986 2870649
- Pecknold JC, Swinson RP, Kuch K, et al: Alprazolam in panic disorder and agoraphobia: results from a multicenter trial, III: discontinuation effects. *Arch Gen Psychiatry* 45(5):429-436, 1988 3282479
- Peppers MP: Benzodiazepines for alcohol withdrawal in the elderly and in patients with liver disease. *Pharmacotherapy* 16(1):49-57, 1996 8700792
- Perera KM, Tulley M, Jenner FA: The use of benzodiazepines among drug addicts. *Br J Addict* 82(5):511-515, 1987 2885020
- Petursson H, Lader MH: Withdrawal from long-term benzodiazepine treatment. *Br Med J (Clin Res Ed)* 283(6292):643-645, 1981 6114776

- Pollack MH, Tesar GE, Rosenbaum JF, et al: Clonazepam in the treatment of panic disorder and agoraphobia: a one-year follow-up. *J Clin Psychopharmacol* 6(5): 302-304, 1986 3771814
- Pollack MH, Otto MW, Tesar GE, et al: Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol* 13(4):257-263, 1993 8376613
- Pomeranz JM: Risk versus benefit of benzodiazepines. *Psychiatric Times*, August 1, 2007, pp 22-26
- Poser W, Poser S, Roscher D, et al: Do benzodiazepines cause cerebral atrophy? (letter). *Lancet* 1(8326 pt 1):715, 1983 6132076
- Power KG, Jerrom DWA, Simpson RJ, et al: Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety. *Br Med J (Clin Res Ed)* 290(6477): 1246-1248, 1985 3921173
- Ray WA, Fought RL, Decker MD: Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *Am J Epidemiol* 136(7):873-883, 1992 1442753
- Reed CF, Witt PN, Peakall DB: Freehand copying of a geometric pattern as a test for sensory-motor disturbance. *Percept Mot Skills* 20:941-951, 1965 14314018
- Rickels K: Clinical management of benzodiazepine dependence (letter). *Br Med J (Clin Res Ed)* 291(6509):1649, 1985 3935227
- Rickels K, Schweizer EE: Benzodiazepines for treatment of panic attacks: a new look. *Psychopharmacol Bull* 22(1):93-99, 1986 2873621
- Rickels K, Case WG, Schweizer E, et al: Long-term benzodiazepine users 3 years after participation in a discontinuation program. *Am J Psychiatry* 148(6):757-761, 1991 2035717
- Rickels K, Downing R, Schweizer E, et al: Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 50(11):884-895, 1993 8215814
- Rickels K, Lucki I, Schweizer E, et al: Psychomotor performance of long-term benzodiazepine users before, during, and after benzodiazepine discontinuation. *J Clin Psychopharmacol* 19(2):107-113, 1999 10211911
- Rinaldi RC, Steindler EM, Wilford BB, et al: Clarification and standardization of substance abuse terminology. *JAMA* 259(4):555-557, 1988 3275816
- Roache JD, Griffiths RR: Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. *J Pharmacol Exp Ther* 234(1): 120-133, 1985 2861282
- Roache JD, Griffiths RR: Lorazepam and meprobamate dose effects in humans: behavioral effects and abuse liability. *J Pharmacol Exp Ther* 243(3):978-988, 1987 3694540
- Romach M, Busto U, Somer G, et al: Clinical aspects of chronic use of alprazolam and lorazepam. *Am J Psychiatry* 152(8):1161-1167, 1995 7625464
- Rosenbaum JF: Attitudes toward benzodiazepines over the years. *J Clin Psychiatry* 66(suppl 2):4-8, 2005 15762813
- Rosenbaum JF, Woods SW, Groves JE, et al: Emergence of hostility during alprazolam treatment. *Am J Psychiatry* 141(6):792-793, 1984 6145358
- Rosenberg L, Mitchell AA, Parsells JL, et al: Lack of relation of oral clefts to diazepam use during pregnancy. *N Engl J Med* 309(21):1282-1285, 1983 6633586
- Roth T, Hartse KM, Saab PG, et al: The effects of flurazepam, lorazepam, and triazolam on sleep and memory. *Psychopharmacology (Berl)* 70(3):231-237, 1980 6108588
- Rothstein E, Cobble JC, Sampson N: Chlordiazepoxide: long-term use in alcoholism. *Ann N Y Acad Sci* 273:381-384, 1976 829397
- Routledge PA, Kitchell BB, Bjornsson TD, et al: Diazepam and N-desmethyldiazepam redistribution after heparin. *Clin Pharmacol Ther* 27(4):528-532, 1980 6766834

- Rowlatt RJ: Effect of maternal diazepam on the newborn (letter). *BMJ* 1(6118):985, 1978 638557
- Safra MJ, Oakley GP Jr: Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. *Lancet* 2(7933):478-480, 1975 51287
- Sakol MS, Power KG: The effects of long-term benzodiazepine treatment and graded withdrawal on psychometric performance. *Psychopharmacology (Berl)* 95(1):35-138, 1988 3133693
- Salzman C: Anxiety in the elderly: treatment strategies. *J Clin Psychiatry* 51(suppl):18-21, discussion 29-32, 1990 1976620
- Salzman C: The APA Task Force report on benzodiazepine dependence, toxicity, and abuse. *Am J Psychiatry* 148(2):151-152, 1991 1987812
- Salzman C, Shader RI: Benzodiazepine use and risk for Alzheimer disease. *J Clin Psychopharmacol* 35(1):1-3, 2015 25407694
- Saxén I: Associations between oral clefts and drugs taken during pregnancy. *Int J Epidemiol* 4(1):37-44, 1975 1116890
- Saxén I, Lahti A: Cleft lip and palate in Finland: incidence, secular, seasonal, and geographical variations. *Teratology* 9(2): 217-223, 1974 4824752
- Schardein JL (ed): *Chemically Induced Birth Defects*, 2nd Edition. New York, Marcel Dekker, 1993
- Scharf MB, Fletcher K, Graham JP: Comparative amnestic effects of benzodiazepine hypnotic agents. *J Clin Psychiatry* 49(4): 134-137, 1988 2895761
- Schweizer E, Rickels K, Weiss S, et al: Maintenance drug treatment of panic disorder. I. Results of a prospective, placebo-controlled comparison of alprazolam and imipramine. *Arch Gen Psychiatry* 50(1):51-60, 1993 8422222
- Shader RI, Georgotas A, Greenblatt DJ, et al: Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther* 24(3):308-315, 1978 28870
- Sheehan DV: Benzodiazepines in panic disorder and agoraphobia. *J Affect Disord* 13(2):169-181, 1987 2890678
- Sheehan DV, Uzogara E, Coleman JH, et al: The treatment of panic attacks with agoraphobia with alprazolam and ibuprofen: a controlled study. Paper presented at the annual meeting of the American Psychiatric Association, Toronto, Canada, May 1982
- Sheehan DV, Coleman JH, Greenblatt DJ, et al: Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J Clin Psychopharmacol* 4(2):66-75, 1984 6142907
- Sheehan DV, Raj AB, Harnett-Sheehan K, et al: The relative efficacy of high-dose buspirone and alprazolam in the treatment of panic disorder: a double-blind placebo-controlled study. *Acta Psychiatr Scand* 88(1):1-11, 1993 8372689
- Sheehan MF, Sheehan DV, Torres A, et al: Snorting benzodiazepines. *Am J Drug Alcohol Abuse* 17(4):457-468, 1991 1684083
- Shiono PH, Mills JL: Oral clefts and diazepam use during pregnancy. *N Engl J Med* 311(14):919-920, 1984 6472406
- Skegg DCG, Richards SM, Doll R: Minor tranquillisers and road accidents. *BMJ* 1(6168):917-919, 1979 35267
- Soumerai SB, Simoni-Wastila L, Singer C, et al: Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv* 54(7):1006-1011, 2003 12851438
- Speight AN: Floppy-infant syndrome and maternal diazepam and/or nitrazepam (letter). *Lancet* 2(8043):878, 1977 72227
- Stahl SM: Don't ask, don't tell, but benzodiazepines are still the leading treatments for anxiety disorder. *J Clin Psychiatry* 63(9):756-757, 2002 12363113

- Strahan A, Rosenthal J, Kaswan M, et al: Three case reports of acute paroxysmal excitement associated with alprazolam treatment. *Am J Psychiatry* 142(7):859-861, 1985 2861755
- Svenson SE, Hamilton RG: A critique of overemphasis on side effects with the psychotropic drugs: an analysis of 18,000 chlordiazepoxide-treated cases. *Curr Ther Res Clin Exp* 8(10):455-464, 1966 4961021
- Svensson E, Persson LO, Sjöberg L: Mood effects of diazepam and caffeine. *Psychopharmacology (Berl)* 67(1):73-80, 1980 6768081
- Tamblyn R, Abrahamowicz M, du Berger R, et al: A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. *J Am Geriatr Soc* 53(2):233-241, 2005 15673346
- Tata PR, Rollings J, Collins M, et al: Lack of cognitive recovery following withdrawal from long-term benzodiazepine use. *Psychol Med* 24(1):203-213, 1994 8208885
- Tesar GE, Rosenbaum JF, Pollack MH, et al: Double-blind, placebo-controlled comparison of clonazepam and alprazolam for panic disorder. *J Clin Psychiatry* 52(2): 69-76, 1991 1993639
- Uhlenhuth EH, Balter MB, Ban TA, et al: International study of expert judgment on therapeutic use of benzodiazepines and other psychotherapeutic medications, VI: trends in recommendations for the pharmacotherapy of anxiety disorders, 1992-1997. *Depress Anxiety* 9(3):107-116, 1999 10356648
- Van Etten ML, Taylor S: Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. *Clin Psychol Psychother* 5(3):126-144, 1998
- Vela-Bueno A, Oliveros JC, Dobladez-Blanco B, et al: Brotizolam: a sleep laboratory evaluation. *Eur J Clin Pharmacol* 25(1): 53-56, 1983 6617724
- Versiani M, Nardi AE, Figueira I, et al: Double blind placebo controlled trial with bromazepam in social phobia (in Portuguese). *J Bras Psiquiatr* 46(3):167-171, 1997
- Wagner AK, Ross-Degnan D, Gurwitz JH, et al: Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. *Ann Intern Med* 146(2):96-103, 2007 17227933
- Walker BE, Patterson A: Induction of cleft palate in mice by tranquilizers and barbiturates. *Teratology* 10(2):159-163, 1974 4428425
- Wang PS, Bohn RL, Glynn RJ, et al: Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. *Am J Psychiatry* 158(6):892-898, 2001 11384896
- Wee EL, Zimmerman EF: Involvement of GABA in palate morphogenesis and its relation to diazepam teratogenesis in two mouse strains. *Teratology* 28(1):15-22, 1983 6635994
- Woody GE, Mintz G, O'Hare K, et al: Diazepam use by patients in a methadone program: how serious a problem? *J Psychedelic Drugs* 7(4):373-379, 1975a
- Woody GE, O'Brien CP, Greenstein R: Misuse and abuse of diazepam: an increasingly common medical problem. *Int J Addict* 10(5):843-848, 1975b 1176235
- Zimmerman EF: Neuropharmacologic teratogenesis and neurotransmitter regulation of palate development. *Am J Ment Defic* 88(5):548-558, 1984 6145355
- Zimmerman EF, Wee EL: Role of neurotransmitters in palate development. *Curr Top Dev Biol* 19:37-63, 1984 6149892



# CHAPTER 23

## Buspirone

Donald S. Robinson, M.D.

Karl Rickels, M.D.

**Altered** central serotonergic function is implicated in several psychiatric disorders, especially mood and anxiety disorders. Discovery of the serotonin-1A (5-HT<sub>1A</sub>) receptor linked modulation of serotonin (5-hydroxytryptamine [5-HT]) neurotransmission to anxiety symptoms. Similarly, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) linked serotonin to the pathophysiology and treatment of depression.

The notion of a role for serotonin in the treatment of anxiety arose from the finding that benzodiazepines reduce brain 5-HT turnover and that para-chlorophenylalanine (pCPA), an inhibitor of serotonin synthesis, mimics the effects of benzodiazepines in behavioral models of anxiety ([Wise et al. 1972](#)). Discovery of the 5-HT<sub>1A</sub> receptor partial agonist buspirone confirmed that serotonin plays a key role in anxiolysis ([Eison and Eison 1994](#)). Because both

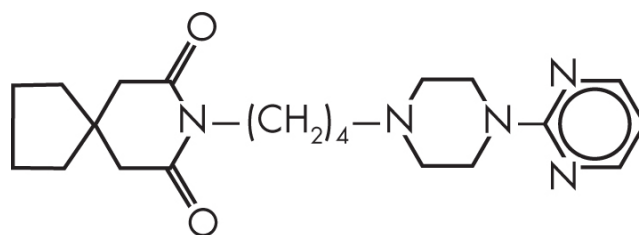
benzodiazepines and buspirone reduce 5-HT impulse flow, albeit by different mechanisms, altered serotonergic tone was postulated to be an underlying factor in the etiology of anxiety disorders.

---

## The 5-HT<sub>1A</sub> Receptor

---

Identification of multiple serotonin receptors ([Hoyer et al. 2002](#); [Pierce et al. 2002](#)) and discovery of the role of the 5-HT<sub>1A</sub> receptor, which couples negatively to adenylyl cyclase ([De Vivo and Maayani 1986](#); [Savitz et al. 2009](#)), led to pharmacological characterization of this receptor utilizing selective agonists ([Hamon et al. 1984](#)); selective partial agonist azapirones, such as buspirone ([Figure 23-1](#)); and specific antagonists ([Fletcher et al. 1996](#)). Clinical development of 5-HT<sub>1A</sub> partial agonists, which were active in models of both anxiety and depression, ensued when it became apparent that this receptor plays a central role in neuropsychiatric disorders ([Robinson et al. 1989a](#)).



---

**FIGURE 23-1.** Chemical structure of buspirone.

## Pharmacological and Clinical Implications

High regional density of 5-HT<sub>1A</sub> receptors in midbrain, hippocampus, and limbic areas of the brain comports with the notion that 5-HT neurotransmission modulates mood and anxiety. Brain regions with high densities of 5-HT<sub>1A</sub> receptors control thermoregulation, endocrine function, appetite, aggressive and sexual behavior, and mood. Mice lacking the 5-HT<sub>1A</sub> receptor gene exhibit manifestations of anxious behavior ([Parks et al. 1998](#); [Pattij et al. 2002](#)).

5-HT<sub>1A</sub> receptors on 5-HT neurons in midbrain raphe regions modulate release of 5-HT at synapses in forebrain. These somatodendritic autoreceptors control synthesis and impulse flow ([Yocca 1990](#)) and release ([Sharp et al. 1989](#)) of neurotransmitter from ascending 5-HT-containing neurons. Using the receptor-specific, tritiated ligand 8-hydroxy-2-[*N*-dipropylamino]-tetralin (8-OH-DPAT), [Stockmeier et al. \(1998\)](#) reported enhanced binding of the ligand to inhibitory 5-HT<sub>1A</sub> autoreceptors in the dorsal raphe of suicide victims, in support of the hypothesis that these individuals had diminished 5-HT neuronal activity. Imaging studies of brain regions using OH-DPAT or the receptor-specific radioligand [carbonyl-<sup>11</sup>C]WAY100635 confirmed diminished function (reduced binding potential) of serotonin 5-HT<sub>1A</sub> receptors in the brains of both suicide victims and patients with major depressive disorder (MDD) compared with matched controls ([Boldrini et al. 2008](#); [Drevets et al. 2007](#); [Hirvonen et al. 2008](#); [Meltzer et al. 2004](#)), indicative of diminished activity of 5-HT neurons in mood disorders. Blunted 5-HT<sub>1A</sub> receptor-mediated response to corticosteroids is present in patients with MDD, suggesting desensitization of these receptors in patients with anxiety and depression ([Lesch 1992](#); [Rausch et al. 2006](#); [Stahl 1992](#)).

# 5-HT Receptors and Partial Agonists

Given the evidence implicating 5-HT in mood disorders and the role of the 5-HT<sub>1A</sub> receptor in 5-HT neurotransmission, drugs targeting this receptor hold interest for the treatment of mood and anxiety disorders. Partial agonists of this receptor act in part by signal attenuation at one or more target receptors ([Yocca and Altar 2006](#)). The partial agonist buspirone produces therapeutic response with an excellent safety profile and was developed for the treatment of anxiety and associated depression.

Although the selective 5-HT<sub>1A</sub> receptor partial agonist gepirone recently (May 2016) received U.S. Food and Drug Administration (FDA) approval for the treatment of MDD, no other selective 5-HT<sub>1A</sub> agonists have obtained FDA approval for a generalized anxiety disorder (GAD) indication. An appropriate degree of agonism at both pre- and postsynaptic 5-HT<sub>1A</sub> receptors may be essential for anxiolytic efficacy. There is a region-dependent difference in responses to 5-HT<sub>1A</sub> agonists at pre- and postsynaptic 5-HT<sub>1A</sub> receptors, possibly attributable to differences in regional receptor reserve ([Meller et al. 1990](#); [Yocca et al. 1992](#)).

---

## History and Development

---

Buspirone hydrochloride, an azaspirodecanedione derivative ([Wu et al. 1969](#)), was originally studied as a putative antipsychotic agent but was not efficacious ([Sathananthan et al. 1975](#)). Buspirone was found to produce a marked taming effect in aggressive monkeys

([Tompkins et al. 1980](#)). In behavioral rodent models of anxiety, buspirone inhibited footshock-induced fighting and prevented shock-induced suppression of drinking behavior, tests predictive of anxiolytic effects ([Riblet et al. 1982](#)). At that time, minimal data were available on the molecular pharmacology of buspirone, although it had been reported to displace [<sup>3</sup>H]spiperone from dopamine D<sub>2</sub> receptors in rat striatal membranes and to produce a right shift in binding activity in the presence of guanosine triphosphate (GTP), both characteristics of a D<sub>2</sub> agonist ([Riblet et al. 1982](#)). Until subsequent discovery of buspirone's high-affinity binding to the newly discovered 5-HT<sub>1A</sub> receptor, the anxiolytic activity of buspirone was presumed to be dopaminergic.

A Phase II proof-of-concept study in patients with DSM-II ([American Psychiatric Association 1968](#)) anxiety disorder showed significant anxiolytic efficacy of buspirone compared with placebo ([Goldberg and Finnerty 1979](#)), which fostered its clinical development as an antianxiety agent ([Robinson 1991](#)). Recently, buspirone was found to bind to dopamine D<sub>3</sub> and D<sub>4</sub> receptors, suggesting its possible utility in treatment of drug addiction ([Bergman et al. 2013](#); [Le Foll and Boileau 2013](#)).

---

## Pharmacological Profile

---

Buspirone has low affinity in vitro for noradrenergic, cholinergic, and histaminergic receptors and does not displace [<sup>3</sup>H]diazepam or [<sup>3</sup>H]nitrazepam from the benzodiazepine receptor complex ([Riblet et al. 1982](#)). Although buspirone displaces [<sup>3</sup>H]spiperone from rat

striatal membranes at high concentrations ([Mennini et al. 1986, 1987](#)), dopamine receptor binding appears to play no role in either the therapeutic effects or the side effects of buspirone ([Eison et al. 1991](#)). In the frontal cortex of freely moving rats, buspirone produces dose-dependent decreases in dialysate levels of 5-HT and increases in levels of dopamine and norepinephrine, findings indicative of multiple mechanisms by which buspirone may modify monoaminergic neurotransmission ([Gobert et al. 1999](#)).

The discovery that nanomolar quantities of buspirone displaced [<sup>3</sup>H]5-HT from hippocampal membranes ([Glaser and Traber 1983](#)) led to elucidation of buspirone's actions on specific central 5-HT receptors. Buspirone inhibits [<sup>3</sup>H]5-HT binding to cortical and hippocampal membranes ([Skolnick et al. 1985](#)) and selectively displaces [<sup>3</sup>H]8-OH-DPAT from 5-HT<sub>1A</sub> receptor-binding sites in rat hippocampal membranes with high affinity (24 nM) ([Yocca 1990](#)).

The antianxiety properties of buspirone reflect its actions at both pre- and postsynaptic 5-HT<sub>1A</sub> receptors ([Eison and Eison 1994](#); [Yocca 1990](#)). At presynaptic 5-HT<sub>1A</sub> receptors in the dorsal raphe, buspirone acts as a full agonist, inhibiting neuronal 5-HT synthesis and firing, whereas at postsynaptic receptors in hippocampus and cortex, it functions as a partial agonist. It is postulated that the anxiolytic effect of buspirone is mediated by serotonergic actions in the presence of a pre-existing deficiency of this neurotransmitter.

Buspirone differs from benzodiazepines in that it does not inhibit motor coordination or spontaneous motor activity but can produce serotonin syndrome in rats ([Barrett and Witkin 1991](#); [Eison et al. 1991](#)). Unlike benzodiazepines,

buspirone lacks abuse potential and does not impair psychomotor performance alone or in combination with ethanol ([Griffith et al. 1986](#); [Smiley 1987](#); [Sussman and Chow 1988](#)). The behavioral effects of buspirone and benzodiazepines differ somewhat in animal models of anxiety ([Barrett and Witkin 1991](#)) in that buspirone does not uniformly increase punished or conflict responding in rats and monkeys. In pigeons, by contrast, buspirone enhances punished response equivalently to benzodiazepines, a characteristic of 5-HT<sub>1A</sub> receptor agonists such as 8-OH-DPAT, whereas TCAs, SSRIs, opioids, antipsychotics, and psychomotor stimulants do not. Buspirone enhances exploratory and social interaction behavior in rodents, similar to benzodiazepines.

5-HT<sub>1A</sub> agonists are active in animal models of depression. Similar to TCAs and SSRIs, 5-HT<sub>1A</sub> agonists such as 8-OH-DPAT and the azapirones produce antidepressant-like behavior in the forced-swim test in rats ([Wieland and Lucki 1990](#)). This effect occurs in the absence of changes in locomotor activity and is not diminished by pretreatment with the 5-HT synthesis inhibitor pCPA, suggesting that 5-HT<sub>1A</sub> agonists produce an antidepressant response through postsynaptic effects on 5-HT<sub>1A</sub> receptors. Buspirone's activity in preclinical models of depression comports with findings in placebo-controlled trials of buspirone indicative of its antidepressant properties ([Rickels et al. 1991](#); [Robinson et al. 1989a](#)). The buspirone metabolite 1-(2-pyrimidinyl)piperazine (1-PP) is devoid of such activity.

---

# Pharmacokinetics and Mechanism of Action

---

With oral administration, buspirone undergoes extensive first-pass metabolism by cytochrome P450 (CYP) 3A4 enzymes, with a mean elimination half-life of 3–4 hours ([Gammans and Johnston 1991](#)). Food prolongs the elimination half-life of buspirone, as does hepatic or renal impairment. The pharmacokinetics of buspirone in elderly patients and young adults do not differ ([Gammans et al. 1989](#)).

Buspirone has several metabolites with differing pharmacological activity: 6-hydroxybuspirone (6-OH-Bu), 5-hydroxybuspirone (5-OH-Bu), 8-hydroxybuspirone (8-OH-Bu), and 1-PP. Noradrenergic properties of 1-PP may induce unwanted side effects in patients who have panic attacks or are undergoing benzodiazepine withdrawal. Conversion of buspirone to 6-OH-Bu is the major metabolic pathway in the hepatic clearance of buspirone ([Dockens et al. 2006](#); [Zhu et al. 2005](#)), and bioavailability of 6-OH-Bu is greater than that of the parent drug (19% vs. 1.4% for buspirone; [Wong et al. 2007](#)), significantly contributing to buspirone's therapeutic activity ([Dockens et al. 2006](#)). In vitro, 6-OH-Bu exhibits high affinity (25 nM) and partial agonist activity for the 5-HT<sub>1A</sub> receptor ([Wong et al. 2007](#)).

The anxiolytic effects of buspirone appear to be mediated by its actions on 5-HT receptors in the limbic system ([Eison and Eison 1994](#); [Yocca 1990](#)). In addition to being a 5-HT<sub>1A</sub> agonist, buspirone acts as both a D<sub>2</sub> agonist and a D<sub>2</sub> antagonist in the anterior pituitary, regulating prolactin levels. Buspirone has significant neuroendocrine effects



beyond those related to dopamine receptors. 5-HT<sub>1A</sub> receptors regulate the neuroendocrine hormones, including growth hormone, adrenocorticotrophic hormone, corticosterone, and oxytocin ([Gilbert et al. 1988](#); [Pan and Gilbert 1992](#); [Van de Kar et al. 1985](#); [Vicentic et al. 1998](#)). Buspirone produces dose-dependent increases in rat plasma prolactin levels ([Meltzer and Fleming 1982](#)). Buspirone antagonizes the inhibitory effects of dopamine on prolactin release from the rat pituitary gland in vitro, illustrative of its partial agonist activity at D<sub>2</sub> receptors ([Meltzer et al. 1991](#)). All azapirones decrease body temperature ([Cowen et al. 1990](#); [Meltzer et al. 1991](#)). Buspirone stimulation of prolactin and corticosterone secretion in the rat is enhanced by pCPA, whereas spiperone inhibits buspirone-induced increases in corticosterone secretion ([Meltzer et al. 1991](#)). Pindolol, a 5-HT<sub>1A</sub> antagonist, does not block the buspirone-induced increase in prolactin ([Meltzer et al. 1991](#)). The neuroendocrine effects of buspirone are complex, reflecting properties of both dopamine antagonism and 5-HT<sub>1A</sub> partial agonism.

---

## Indications and Efficacy

---

### Approved Clinical Indications

#### Generalized Anxiety Disorder

Clinical development of buspirone began after positive findings were reported in a placebo-controlled, proof-of-concept study in anxious patients ([Goldberg and Finnerty](#)

1979). In Phase III placebo-controlled trials comparing buspirone and diazepam, the two anxiolytics had comparable efficacy in patients meeting diagnostic criteria for DSM-II anxiety neurosis (Böhm et al. 1990a; Goldberg and Finnerty 1982; Rickels et al. 1982). In these double-blind, variable-dose titration studies, buspirone or diazepam was given thrice daily at a mean dosage of 20–25 mg/day over 4 weeks.

When the FDA granted marketing approval for buspirone in 1986, a newer DSM classification system, DSM-III (American Psychiatric Association 1980), had replaced anxiety neurosis with the diagnostic category generalized anxiety disorder. Analyses of Hamilton Anxiety Scale (Ham-A; Hamilton 1959) and other symptom ratings were consistent with a diagnosis of DSM-III GAD, and buspirone received FDA approval for the indication of GAD, including anxiety with coexisting depressive symptoms.

Buspirone has a slower onset of therapeutic effect relative to the benzodiazepines (Enkelmann 1991; Pecknold et al. 1989; Rickels 1990). This slower onset is attributable to differences between buspirone and benzodiazepines in relief of somatic anxiety, whereas the two drugs are similar in rate of alleviation of psychic anxiety. Lack of sedation with buspirone also contributes to the perception of a more gradual onset of anxiolysis, similar to that with imipramine (Rickels et al. 1993) and SSRIs (Rickels et al. 2003). With buspirone, relief of somatic anxiety (particularly insomnia) occurs only after psychic anxiety symptoms abate, whereas the immediate-sedating properties of benzodiazepines give the perception of a faster onset of therapeutic benefit.

A longer-term 6-month double-blind comparative trial of buspirone and benzodiazepines confirmed that onset of anxiolytic effects was slower with buspirone than with

clorazepate during the first 4 weeks of treatment ([Rickels et al. 1988](#)). With ongoing treatment, however, the therapeutic response to the two drugs was equivalent. Clinical improvement was maintained over the 6-month study period, and therapeutic tolerance did not develop with either drug. On double-blind termination of treatment at 6 months, several patients who stopped clorazepate abruptly experienced relapse, whereas none relapsed in the buspirone group. The finding that symptom relapse did not occur with abrupt discontinuation of buspirone confirmed conclusions from other investigators ([Fontaine et al. 1984](#); [Noyes et al. 1988](#)) that the rapid return of symptoms after discontinuation of clorazepate was attributable to benzodiazepine withdrawal rather than to a recrudescence of the underlying anxiety disorder.

A benzodiazepine may be indicated as initial therapy for chronically anxious patients; however, longer-term benzodiazepine treatment can lead to physical dependence. Benzodiazepine treatment may be inappropriate for some patients because of the risk of substance abuse or cognitive impairment. When starting a patient on buspirone treatment, one should inform the patient that the drug is less sedating and has a gradual onset of action. Patients can be reassured that buspirone lacks physical dependence liability and does not impair cognition or acquisition of coping skills ([Rickels and Schweizer 1990](#)).

Possible clinical benefit of buspirone on the benzodiazepine withdrawal syndrome was assessed in 15 patients with chronic anxiety who had previously attempted both abrupt and gradual withdrawal of benzodiazepine treatment without success ([Schweizer and Rickels 1986](#)). In this study, addition of buspirone overlapping with tapering of the benzodiazepine dosage did not ameliorate the

symptoms of benzodiazepine withdrawal, and none of the patients could be maintained on buspirone monotherapy after complete withdrawal of benzodiazepine treatment. In other studies, buspirone showed only modest beneficial effects on the benzodiazepine withdrawal syndrome ([Delle Chiaie et al. 1995](#); [DeMartinis et al. 2000](#); [Udelman and Udelman 1990](#)).

Following buspirone's approval by the FDA, several well-controlled efficacy trials in GAD confirmed the drug's significant anxiolytic efficacy ([Enkelmann 1991](#); [Laakmann et al. 1998](#); [Lader and Scotto 1998](#); [Murphy et al. 1989](#); [Pecknold et al. 1989](#); [Scheibe 1996](#)). In a 3-week placebo-controlled comparison trial in 60 patients with anxiety disorder in a general medical setting, [Böhm et al. \(1990a\)](#) found buspirone and the benzodiazepine clobazam to be equally effective and superior to placebo in relieving anxiety.

Long-term follow-up at 40 months of patients who previously completed a 6-month controlled trial comparing buspirone and clorazepate revealed that none of the buspirone-treated patients needed anxiolytic medication, whereas more than 50% of the patients treated with clorazepate required continuation anxiolytic therapy ([Rickels and Schweizer 1990](#)).

Buspirone was evaluated in elderly patients with anxiety symptoms in a double-blind, placebo-controlled trial and was found to be both safe and effective ([Böhm et al. 1990b](#)). Buspirone's lack of sedation and sparing of cognition and memory were a strong therapeutic advantage in this population. Meta-analyses of several multicenter trials of buspirone in elderly patients also showed buspirone to be safe and well tolerated ([Ritchie and Cox 1993](#); [Robinson et al. 1988](#)).

Buspirone treatment also was assessed in patients with panic disorder in placebo-controlled trials ([Pohl et al. 1989](#); [Sheehan et al. 1990](#)). Buspirone does not diminish panic attacks. However, a meta-analysis of double-blind three-arm multicenter trials in panic disorder comparing buspirone, imipramine, and placebo treatment found that both imipramine and buspirone improved anxiety symptoms ([Robinson et al. 1989b](#)). Buspirone's lack of effect on number of panic attacks is unsurprising in light of preclinical evidence that buspirone increases firing rates in the locus coeruleus ([Eison and Temple 1986](#)) and causes noradrenergic hyperactivity ([Sanghera et al. 1982](#)), both manifestations of panic disorder.

### **Mixed Anxiety-Depression**

In initial trials of patients with anxiety disorder and subsyndromal depression, depressive symptoms improved significantly with buspirone treatment ([Feighner et al. 1982](#); [Goldberg and Finnerty 1979](#)). This finding fostered interest in the potential antidepressant properties of buspirone because of the high comorbidity of GAD and MDD ([Brown and Barlow 1992](#)) and led to the speculation that GAD and MDD may represent differing clinical manifestations of a single underlying diathesis. Genetic studies in patients with MDD and GAD suggest that genetic vulnerability for the two disorders is largely shared ([Kendler et al. 1992](#)). The relationship of MDD and GAD and their clinical treatment have been reviewed ([Kendler et al. 1992](#); [Roy-Byrne 2008](#)).

Buspirone treatment of patients with MDD associated with significant anxiety symptoms was assessed in placebo-controlled trials ([Rickels et al. 1991](#); [Robinson et al. 1989a, 1990](#)). Patients with MDD were eligible for inclusion in

these studies if their Hamilton Rating Scale for Depression (Ham-D; [Hamilton 1960](#)) and Ham-A scores were  $\geq 18$  and  $\geq 15$ , respectively. The daily dosage ranged up to a maximum of buspirone 90 mg/day (mean  $\sim 50$  mg/day). Buspirone treatment was superior to placebo treatment, with a global response rate (based on Clinical Global Impressions-Improvement [CGI-I] scale scores) of 70% for buspirone and 35% for placebo ([Rickels et al. 1991](#)). In a subsequent placebo-controlled study involving 177 geriatric depressed outpatients, [Schweizer et al. \(1998\)](#) compared buspirone and imipramine treatment for 8 weeks. There was a statistically significant treatment effect for both buspirone (mean daily dosage,  $\sim 50$  mg) and imipramine (mean daily dosage,  $\sim 90$  mg) compared with placebo treatment.

Buspirone augmentation of SSRI treatment of partially responding depressed patients leads to further improvement ([Dimitriou and Dimitriou 1998](#); [Gonul et al. 1999](#); [Jacobsen 1991](#); [Landén et al. 1998](#)). These findings were confirmed in a report of the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) program. Patients who initially did not respond to an adequate therapeutic trial with an SSRI responded when their medication was augmented with either buspirone or bupropion ([Trivedi et al. 2006](#)). In an exploratory double-blind, placebo-controlled study in patients with an MDD diagnosis, [Fava et al. \(2012\)](#) reported significant antidepressant efficacy for combined buspirone 15 mg and melatonin slow release (SR) 3 mg. This preliminary finding is mentioned only to indicate persisting interest in buspirone as a potential augmentor of other antidepressants, not as a treatment recommendation.

We speculate that had buspirone's sponsor pursued a depression rather than a GAD indication, buspirone might well have become the first 5-HT<sub>1A</sub> partial agonist developed as an antidepressant. At present, however, buspirone exists in the shadow of numerous approved antidepressant drugs with high clinical exposure and promotion. The fact that the product life cycle of buspirone (BuSpar) was relatively short, whereas SSRIs with longer patent lives had already received a clinical indication for GAD, served to restrain buspirone's sponsor from seeking an approved indication for MDD and limited the drug's approved indication to treatment of anxiety and anxiety with associated depression.

## Nonapproved Clinical Indications

Potential clinical indications for buspirone treatment unapproved by the FDA were reviewed by [Rickels et al. \(2003\)](#); selected studies are mentioned here.

### **Substance-Related Disorders**

Several placebo-controlled trials have demonstrated the usefulness of buspirone in facilitating smoking cessation ([Hilleman et al. 1992](#); [West et al. 1991](#)), although its main effect was in smokers who were also highly anxious ([Cinciripini et al. 1995](#)).

Buspirone has been assessed in several double-blind, placebo-controlled trials involving anxious outpatients with coexisting alcohol use disorder and found to be efficacious ([Rickels et al. 2003](#)). Buspirone's lack of abuse potential and negligible additive effects on psychomotor and cognitive functions when coadministered with alcohol

([Mattila et al. 1982](#)) make it a useful addition to pharmacotherapies for alcohol-related disorders.

Buspirone was found to ameliorate symptoms of opioid withdrawal in a placebo-controlled trial ([Buydens-Branchey et al. 2005](#)).

Although elevations in synaptic dopamine levels have been demonstrated to play a pivotal role in the reinforcing effects of cocaine, neither D<sub>1</sub> nor D<sub>2</sub> receptor antagonists have proved clinically effective in cocaine addiction. Speculating that dopamine D<sub>3</sub> and D<sub>4</sub> receptors might be possible targets for pharmacotherapy, [Bergman et al. \(2013\)](#) undertook an investigation of buspirone, which has been found to bind with high affinity to these receptors, to evaluate its functional effects in animal models. On the basis of their finding that buspirone produced a downward shift in the dose–effect function for cocaine-maintained behavior, Bergman and colleagues proposed that buspirone be evaluated for its utility in the management of cocaine addiction. However, in a 16-week double-blind multicenter pilot trial, [Winhusen et al. \(2014\)](#) found that buspirone at dosages titrated up to 60 mg/day was not beneficial in preventing relapse to cocaine use.

A small placebo-controlled pilot trial originally found buspirone to be significantly superior to placebo on several measures in the treatment of DSM-IV ([American Psychiatric Association 1994](#)) marijuana dependence ([McRae-Clark et al. 2009](#)). However, a 12-week trial with a larger sample size found no advantage for buspirone (titrated to 60 mg/day) over placebo in reducing cannabis use ([McRae-Clark et al. 2015](#)).

## **Adjunctive Use in Schizophrenia**



Several studies have evaluated the adjunctive use of buspirone in patients with chronic schizophrenia being treated with typical and atypical antipsychotic drugs. In a 6-month placebo-controlled trial of adjunctive buspirone 30 mg/day in patients being maintained on an atypical antipsychotic drug, Sumiyoshi [et al. \(2007\)](#) observed no improvement in Brief Psychiatric Rating Scale scores, although they noted improved recall on one secondary outcome measure, the Verbal Learning subscale. Two placebo-controlled pilot trials of limited size by an Iranian group found that adjunctive treatment with buspirone was beneficial in improving negative symptoms in patients with chronic schizophrenia maintained on antipsychotic drugs ([Ghaleiha et al. 2010](#); [Sheikhmoonesi et al. 2015](#)), a finding warranting further study.

### **Adjunctive Use in Autism Spectrum Disorder**

Buspirone treatment has been assessed in autistic patients. In an 8-week placebo-controlled trial of adjunctive buspirone during risperidone maintenance treatment of 40 children and adolescents with autism spectrum disorder, [Ghanizadeh and Ayoobzadehshirazi \(2015\)](#) observed a 30% decline in Aberrant Behavior Checklist-Community Rating Scale irritability subscale scores in 13 of the 16 buspirone patients versus 7 of the 18 placebo patients, a significant treatment effect. In a three-arm, 24-week placebo-controlled trial ( $n=166$ ), [Chugani et al. \(2016\)](#) assessed the safety and efficacy of low-dosage buspirone in children with autism spectrum disorder. The buspirone 2.5 mg bid group showed significant improvement in irritability ratings, whereas the 5.0 mg bid group did not differ from the placebo group. This finding warrants further investigation.

## Other Disorders

Buspirone's utility has been explored in a variety of other disorders. Two small double-blind clinical trials indicated modest efficacy for buspirone over placebo in the symptomatic treatment of premenstrual syndrome ([Brown et al. 1990](#); [Rickels et al. 1989](#)). [Lee et al. \(2005\)](#), in a placebo-controlled study, showed beneficial effects of buspirone in migraine patients with anxiety symptoms. Buspirone was evaluated under double-blind conditions in Alzheimer's patients with aggressive behavior and agitation ([Cantillon et al. 1996](#)) and was found to be superior to haloperidol. In a randomized double-blind study, buspirone was as effective as methylphenidate in treating aggressive behavior in attention-deficit/hyperactivity disorder ([Davari-Ashtiani et al. 2010](#)). Studies in animal models and clinical trials indicate that buspirone may be useful in treating tardive dyskinesia ([Howland 2011](#)) as well as L-dopa-induced and graft-induced dyskinesias of Parkinson's disease ([Loane and Politis 2012](#)).

---

## Dosage and Administration

---

The recommended buspirone dosage for treatment of GAD is 15–20 mg/day initially, prescribed in divided doses, with increases to 30 mg/day if indicated and a maximum dosage of 60 mg/day. It should be mentioned that in the double-blind, placebo-controlled MDD trials described earlier (see the section “Mixed Anxiety-Depression”), the maximum dosage was 90 mg/day ([Rickels et al. 1991](#); [Robinson et al. 1989a, 1990](#)). Therefore, higher buspirone dosages than those prescribed for anxiety disorders may be required in

the treatment of MDD, either as monotherapy or as augmentation of an SSRI.

Therapeutic response to buspirone differs in anxious patients naïve to benzodiazepine treatment compared with patients recently treated with a benzodiazepine ([DeMartinis et al. 2000](#); [Schweizer and Rickels 1986](#)). Findings of placebo-controlled efficacy trials showed that GAD patients with either no prior benzodiazepine treatment or temporally remote benzodiazepine treatment (>6 months previously) experienced greater improvement with buspirone therapy than did patients who either were currently receiving or had recently completed treatment with a benzodiazepine. This diminished therapeutic response may reflect a subclinical benzodiazepine withdrawal syndrome (possibly exacerbated by buspirone's 1-PP metabolite). Directly switching from SSRI treatment to buspirone is not problematic.

---

## Side Effects and Toxicology

---

[Newton et al. \(1986\)](#), summarizing data from 17 clinical trials, noted the incidence of frequently reported adverse effects experienced during buspirone treatment: dizziness (12%), drowsiness (10%), nausea (8%), headache (6%), nervousness (5%), fatigue (4%), insomnia (3%), light-headedness (3%), dry mouth (3%), and excitement (2%). Buspirone lacks abuse potential, unlike alcohol and the benzodiazepines ([Balster 1991](#)). Psychomotor function studies, including evaluation of complex motor driving skills and memory tasks, have documented buspirone's absence of impairment liability in these domains ([Boulenger et al.](#)

1989; Greenblatt et al. 1994; Lucki et al. 1987; Smiley and Moskowitz 1986). Buspirone does not inhibit CYP enzymes, although it does cause modest elevations of haloperidol and cyclosporin A levels. Buspirone has few significant pharmacodynamic interactions with other psychotropic drugs, apart from a potential risk of serotonin syndrome in combination with monoamine oxidase inhibitors. Since buspirone's introduction into clinical medicine, no deaths attributable solely to buspirone overdose have been reported. Buspirone remains an unusually safe and well-tolerated anxiolytic with no abuse liability.

---

## Conclusion

---

Discovery of the 5-HT<sub>1A</sub> receptor was instrumental in linking modulation of 5-HT neurotransmission with anxiety disorders. Buspirone, a selective partial agonist of the 5-HT<sub>1A</sub> receptor, is the only drug in this class of antianxiety agents approved for the treatment of GAD and anxiety with associated depressive symptoms.

---

## References

---

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 2nd Edition. Washington, DC, American Psychiatric Association, 1968
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Balster RL: Preclinical studies of the abuse potential of buspirone, in *Buspirone: Mechanisms and Clinical Aspects*. Edited by Tunnicliff G, Eison AS, Taylor DP. New York, Academic Press, 1991, pp 97-107
- Barrett JE, Witkin JM: Buspirone in animal models of anxiety, in *Buspirone: Mechanisms and Clinical Aspects*. Edited by Tunnicliff G, Eison AS, Taylor DP. New York, Academic Press, 1991, pp 37-79
- Bergman J, Roof RA, Furman CA, et al: Modification of cocaine self-administration by buspirone (buspar®): potential involvement of D3 and D4 dopamine receptors. *Int J Neuropsychopharmacol* 16(2):445-458, 2013 22827916
- Böhm C, Placchi M, Stallone F, et al: A double-blind comparison of buspirone, clobazam, and placebo in patients with anxiety treated in a general practice setting. *J Clin Psychopharmacol* 10 (3 suppl):38S-42S, 1990a 1973939
- Böhm C, Robinson DS, Gammans RE, et al: Buspirone therapy in anxious elderly patients: a controlled clinical trial. *J Clin Psychopharmacol* 10 (3 suppl):47S-51S, 1990b 2198301
- Boldrini M, Underwood MD, Mann JJ, et al: Serotonin-1A autoreceptor binding in the dorsal raphe nucleus of depressed suicides. *J Psychiatr Res* 42(6):433-442, 2008 17574270
- Boulenger JP, Gram LF, Jolicouer FB, Zarifian E: Repeated administration of buspirone: absence of pharmacodynamic or pharmacokinetic interaction with triazolam. *Human Psychopharmacology: Clinical and Experimental* 8(2):117-124, 1989
- Brown CS, Ling FW, Farmer RG, et al: Buspirone in the treatment of premenstrual syndrome. *Drug Ther Bull* 8

(suppl):112-116, 1990

Brown TA, Barlow DH: Comorbidity among anxiety disorders: implications for treatment and DSM-IV. *J Consult Clin Psychol* 60(6):835-844, 1992 1460147

Buydens-Branchey L, Branchey M, Reel-Brander C: Efficacy of buspirone in the treatment of opioid withdrawal. *J Clin Psychopharmacol* 25(3):230-236, 2005 15876901

Cantillon M, Brunswick R, Molina D, Bahro M: Buspirone vs haloperidol: a double-blind trial for agitation in a nursing home population with Alzheimer's disease. *Am J Geriatr Psychiatry* 4(3):236-267, 1996

Chugani DC, Chugani HT, Wisnitzer M, et al: Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: a randomized trial. *J Pediatr* 170:45.e4-53.e4, 2016 26746121

Cinciripini PM, Lapitsky L, Seay S, et al: A placebo-controlled evaluation of the effects of buspirone on smoking cessation: differences between high- and low-anxiety smokers. *J Clin Psychopharmacol* 15(3):182-191, 1995 7635995

Cowen PJ, Anderson IM, Grahame-Smith DG: Neuroendocrine effects of azapirones. *J Clin Psychopharmacol* 10 (3 suppl):21S-25S, 1990 1973937

Davari-Ashtiani R, Shahrababaki ME, Razjouyan K, et al: Buspirone versus methylphenidate in the treatment of attention deficit hyperactivity disorder: a double-blind and randomized trial. *Child Psychiatry Hum Dev* 41(6):641-648, 2010 20517641

Delle Chiaie R, Pancheri P, Casacchia M, et al: Assessment of the efficacy of buspirone in patients affected by generalized anxiety disorder, shifting to buspirone from prior treatment with lorazepam: a placebo-controlled, double-blind study. *J Clin Psychopharmacol* 15(1):12-19, 1995 7714222

- DeMartinis N, Rynn M, Rickels K, et al: Prior benzodiazepine use and buspirone response in the treatment of generalized anxiety disorder. *J Clin Psychiatry* 61(2): 91-94, 2000 10732655
- De Vivo M, Maayani S: Characterization of the 5-hydroxytryptamine<sub>1A</sub> receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in guinea pig and rat hippocampal membranes. *J Pharmacol Exp Ther* 238(1):248-253, 1986 2941565
- Dimitriou EC, Dimitriou CE: Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol* 18(6):465-469, 1998 9864079
- Dockens RC, Salazar DE, Fulmor IE, et al: Pharmacokinetics of a newly identified active metabolite of buspirone after administration of buspirone over its therapeutic dose range. *J Clin Pharmacol* 46(11):1308-1312, 2006 17050795
- Drevets WC, Thase ME, Moses-Kolko EL, et al: Serotonin-1A receptor imaging in recurrent depression: replication and literature review. *Nucl Med Biol* 34(7):865-877, 2007 17921037
- Eison AS, Eison MS: Serotonergic mechanisms in anxiety. *Prog Neuropsychopharmacol Biol Psychiatry* 18(1):47-62, 1994 8115673
- Eison AS, Temple DL Jr: Buspirone: review of its pharmacology and current perspectives on its mechanism of action. *Am J Med* 80(3B):1-9, 1986 2870639
- Eison AS, Yocca FD, Taylor DP: Mechanism of action of buspirone: current perspectives, in *Buspirone: Mechanisms and Clinical Aspects*. Edited by Tunnicliff G, Eison AS, Taylor DP. New York, Academic Press, 1991, pp 3-17
- Enkelmann R: Alprazolam versus buspirone in the treatment of outpatients with generalized anxiety

disorder. *Psychopharmacology (Berl)* 105(3):428-432, 1991 1798836

Fava M, Targum SD, Nierenberg AA, et al: An exploratory study of combination buspirone and melatonin SR in major depressive disorder (MDD): a possible role for neurogenesis in drug discovery. *J Psychiatr Res* 46(12):1553-1563, 2012 22998742

Feighner JP, Merideth CH, Hendrickson GA: A double-blind comparison of buspirone and diazepam in outpatients with generalized anxiety disorder. *J Clin Psychiatry* 43(12 Pt 2):103-108, 1982 6130066

Fletcher A, Forster EA, Bill DJ, et al: Electrophysiological, biochemical, neurohormonal and behavioural studies with WAY-100635, a potent, selective and silent 5-HT<sub>1A</sub> receptor antagonist. *Behav Brain Res* 73(1-2):337-353, 1996 8788530

Fontaine R, Chouinard G, Annable L: Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. *Am J Psychiatry* 141(7):848-852, 1984 6145363

Gammans RE, Johnston RE: Metabolism, pharmacokinetics, and toxicology of buspirone, in *Buspirone: Mechanisms and Clinical Aspects*. Edited by Tunnicliff G, Eison AS, Taylor DP. New York, Academic Press, 1991, pp 233-260

Gammans RE, Westrick ML, Shea JP, et al: Pharmacokinetics of buspirone in elderly subjects. *J Clin Pharmacol* 29(1):72-78, 1989 2708551

Ghaleiha A, Noorbala AA, Farnaghi F, et al: A double-blind, randomized, and placebo-controlled trial of buspirone added to risperidone in patients with chronic schizophrenia. *J Clin Psychopharmacol* 30(6):678-682, 2010 21105281

Ghanizadeh A, Ayoobzadehshirazi A: A randomized double-blind placebo-controlled clinical trial of adjuvant buspirone for irritability in autism. *Pediatr Neurol* 52(1):77-81, 2015 25451017



- Gilbert F, Dourish CT, Brazell C, et al: Relationship of increased food intake and plasma ACTH levels to 5-HT<sub>1A</sub> receptor activation in rats. *Psychoneuroendocrinology* 13(6):471-478, 1988 2907164
- Glaser T, Traber J: Buspirone: action on serotonin receptors in calf hippocampus. *Eur J Pharmacol* 88(1):137-138, 1983 6133764
- Gobert A, Rivet JM, Cistarelli L, et al: Buspirone modulates basal and fluoxetine-stimulated dialysate levels of dopamine, noradrenaline and serotonin in the frontal cortex of freely moving rats: activation of serotonin<sub>1A</sub> receptors and blockade of alpha<sub>2</sub>-adrenergic receptors underlie its actions. *Neuroscience* 93(4):1251-1262, 1999 10501449
- Goldberg HL, Finnerty RJ: The comparative efficacy of buspirone and diazepam in the treatment of anxiety. *Am J Psychiatry* 136(9):1184-1187, 1979 382878
- Goldberg HL, Finnerty R: Comparison of buspirone in two separate studies. *J Clin Psychiatry* 43(12 Pt 2):87-91, 1982 6759499
- Gonul AS, Oguz A, Yabanoglu I, et al: Buspirone and pindolol in augmentation therapy of treatment-resistant depression. *Eur J Neuropsychopharmacology* 9 (suppl 5): S215, 1999
- Greenblatt DJ, Harmatz JS, Gouthro TA, et al: Distinguishing a benzodiazepine agonist (triazolam) from a nonagonist anxiolytic (buspirone) by electroencephalography: kinetic-dynamic studies. *Clin Pharmacol Ther* 56(1):100-111, 1994 8033487
- Griffith JD, Jasinski DR, Casten GP, et al: Investigation of the abuse liability of buspirone in alcohol-dependent patients. *Am J Med* 80(3B):30-35, 1986 3963032
- Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 32(1):50-55, 1959 13638508
- Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56-62, 1960 14399272

- Hamon M, Bourgoin S, Gozlan H, et al: Biochemical evidence for the 5-HT agonist properties of PAT (8-hydroxy-2-(di-n-propylamino)tetralin) in the rat brain. *Eur J Pharmacol* 100(3-4):263-276, 1984 6203761
- Hilleman DE, Mohiuddin SM, Del Core MG, et al: Effect of buspirone on withdrawal symptoms associated with smoking cessation. *Arch Intern Med* 152(2):350-352, 1992 1739365
- Hirvonen J, Karlsson H, Kajander J, et al: Decreased brain serotonin 5-HT<sub>1A</sub> receptor availability in medication-naive patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-<sup>11</sup>C]WAY-100635. *Int J Neuropsychopharmacol* 11(4):465-476, 2008 17971260
- Howland RH: Drug therapies for tardive dyskinesia: part 2. *J Psychosoc Nurs Ment Health Serv* 49(7):17-20, 2011 21667885
- Hoyer D, Hannon JP, Martin GR: Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* 71(4):533-554, 2002 11888546
- Jacobsen FM: Possible augmentation of antidepressant response by buspirone. *J Clin Psychiatry* 52(5):217-220, 1991 2033029
- Kendler KS, Neale MC, Kessler RC, et al: Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Arch Gen Psychiatry* 49(9):716-722, 1992 1514877
- Laakmann G, Schüle C, Lorkowski G, et al: Buspirone and lorazepam in the treatment of generalized anxiety disorder in outpatients. *Psychopharmacology (Berl)* 136(4):357-366, 1998 9600581
- Lader M, Scotto JC: A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. *Psychopharmacology (Berl)* 139(4):402-406, 1998 9809861

- Landén M, Björling G, Agren H, et al: A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J Clin Psychiatry* 59(12):664–668, 1998 9921700
- Le Foll B, Boileau I: Repurposing buspirone for drug addiction treatment. *Int J Neuropsychopharmacol* 16(2):251–253, 2013 23174122
- Lee ST, Park JH, Kim M: Efficacy of the 5-HT<sub>1A</sub> agonist, buspirone hydrochloride, in migraineurs with anxiety: a randomized, prospective, parallel group, double-blind, placebo-controlled study. *Headache* 45(8):1004–1011, 2005 16109114
- Lesch KP: The ipsapirone/5-HT<sub>1A</sub> receptor challenge in anxiety disorders and depression, in *Serotonin 1A Receptors in Depression and Anxiety*. Edited by Stahl S, Gaspar M, Keppel Hesselink JM, et al. New York, Raven, 1992, pp 387–407
- Loane C, Politis M: Buspirone: what is it all about? *Brain Res* 1461:111–118, 2012 22608068
- Lucki I, Rickels K, Giesecke MA, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 23(2):207–211, 1987 2881573
- Mattila MJ, Aranko K, Seppala T: Acute effects of buspirone and alcohol on psychomotor skills. *J Clin Psychiatry* 43(12 Pt 2):56–61, 1982 6130074
- McRae-Clark AL, Carter RE, Killeen TK, et al: A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug Alcohol Depend* 105(1-2): 132–138, 2009 19699593
- McRae-Clark AL, Baker NL, Gray KM, et al: Buspirone treatment of cannabis dependence: A randomized, placebo-controlled trial. *Drug Alcohol Depend* 156:29–37, 2015 26386827

- Meller E, Goldstein M, Bohmaker K: Receptor reserve for 5-hydroxytryptamine<sub>1A</sub>-mediated inhibition of serotonin synthesis: possible relationship to anxiolytic properties of 5-hydroxytryptamine<sub>1A</sub> agonists. *Mol Pharmacol* 37(2):231-237, 1990 1968223
- Meltzer CC, Price JC, Mathis CA, et al: Serotonin <sub>1A</sub> receptor binding and treatment response in late-life depression. *Neuropsychopharmacology* 29(12):2258-2265, 2004 15483563
- Meltzer HY, Fleming R: Effect of buspirone on prolactin and growth hormone secretion in laboratory rodents and man. *J Clin Psychiatry* 43(12 Pt 2):76-79, 1982 6130077
- Meltzer HY, Gudelsky GA, Lowy MT, et al: Neuroendocrine effects of buspirone: mediation by dopaminergic and serotonergic mechanisms, in *Buspirone: Mechanisms and Clinical Aspects*. Edited by Tunnicliff G, Eison AS, Taylor DP. New York, Academic Press, 1991, pp 177-192
- Mennini T, Gobbi M, Ponzio F, et al: Neurochemical effects of buspirone in rat hippocampus: evidence for selective activation of 5HT neurons. *Arch Int Pharmacodyn Ther* 279(1):40-49, 1986 2421657
- Mennini T, Caccia S, Garattini S: Mechanism of action of anxiolytic drugs. *Prog Drug Res* 31:315-347, 1987 2894040
- Murphy SM, Owen R, Tyrer P: Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. *Br J Psychiatry* 154:529-534, 1989 2686797
- Newton RE, Marunycz JD, Alderdice MT, et al: Review of the side-effect profile of buspirone. *Am J Med* 80 (3B suppl):17-21, 1986 2870641
- Noyes R Jr, Garvey MJ, Cook BL, et al: Benzodiazepine withdrawal: a review of the evidence. *J Clin Psychiatry* 49(10):382-389, 1988 2902071
- Pan L, Gilbert F: Activation of 5-HT<sub>1A</sub> receptor subtype in the paraventricular nuclei of the hypothalamus induces

- CRH and ACTH release in the rat. *Neuroendocrinology* 56(6):797-802, 1992 1369587
- Parks CL, Robinson PS, Sibille E, et al: Increased anxiety of mice lacking the serotonin<sub>1A</sub> receptor. *Proc Natl Acad Sci U S A* 95(18):10734-10739, 1998 9724773
- Pattij T, Groenink L, Hijzen TH, et al: Autonomic changes associated with enhanced anxiety in 5-HT<sub>1A</sub> receptor knockout mice. *Neuropsychopharmacology* 27(3):380-390, 2002 12225695
- Pecknold JC, Matas M, Howarth BG, et al: Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo. *Can J Psychiatry* 34(8):766-771, 1989 2684380
- Pierce KL, Premont RT, Lefkowitz RJ: Seven-transmembrane receptors. *Nat Rev Mol Cell Biol* 3(9):639-650, 2002 12209124
- Pohl R, Balon R, Yeragani VK, et al: Serotonergic anxiolytics in the treatment of panic disorder: a controlled study with buspirone. *Psychopathology* 22 (suppl 1):60-67, 1989 2657839
- Rausch JL, Johnson ME, Kasik KE, et al: Temperature regulation in depression: functional 5HT<sub>1A</sub> receptor adaptation differentiates antidepressant response. *Neuropsychopharmacology* 31(10):2274-2280, 2006 16641936
- Riblet LA, Taylor DP, Eison MS, et al: Pharmacology and neurochemistry of buspirone. *J Clin Psychiatry* 43(12 Pt 2):11-18, 1982 6130068
- Rickels K: Buspirone in clinical practice. *J Clin Psychiatry* 51 (suppl):51-54, 1990 2211569
- Rickels K, Schweizer E: The clinical course and long-term management of generalized anxiety disorder. *J Clin Psychopharmacol* 10 (3 suppl):101S-110S, 1990 1973934
- Rickels K, Weisman K, Norstad N, et al: Buspirone and diazepam in anxiety: a controlled study. *J Clin Psychiatry*

43(12 Pt 2):81-86, 1982 6130078

Rickels K, Schweizer E, Csanalosi I, et al: Long-term treatment of anxiety and risk of withdrawal. Prospective comparison of clorazepate and buspirone. *Arch Gen Psychiatry* 45(5):444-450, 1988 2895993

Rickels K, Freeman E, Sondheim S: Buspirone in treatment of premenstrual syndrome. *Lancet* 1(8641):777, 1989 2564578

Rickels K, Amsterdam JD, Clary C, et al: Buspirone in major depression: a controlled study. *J Clin Psychiatry* 52(1):34-38, 1991 1988416

Rickels K, Downing R, Schweizer E, et al: Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 50(11):884-895, 1993 8215814

Rickels K, Khalid-Kahn S, Rynn M: Buspirone in the treatment of anxiety disorders, in *Anxiety Disorders*. Edited by Nutt DJ, Ballenger JC. Oxford, England, Blackwell Publishing, 2003, pp 381-397

Ritchie LD, Cox J: A multicenter study of buspirone in the treatment of anxiety disorders in the elderly. *Br J Clin Res* 4:131-139, 1993

Robinson DS: Buspirone in the treatment of anxiety, in *Buspirone: Mechanisms and Clinical Aspects*. Edited by Tunnicliff G, Eison AS, Taylor DP. New York, Academic Press, 1991, pp 3-17

Robinson D, Napoliello MJ, Schenk J: The safety and usefulness of buspirone as an anxiolytic drug in elderly versus young patients. *Clin Ther* 10(6):740-746, 1988 3219687

Robinson DS, Alms DR, Shrotriya RC, et al: Serotonergic anxiolytics and treatment of depression. *Psychopathology* 22 (suppl 1): 27-36, 1989a 2657837

Robinson DS, Shrotriya RC, Alms DR, et al: Treatment of panic disorder: nonbenzodiazepine anxiolytics, including

- buspirone. *Psychopharmacol Bull* 25(1):21-26, 1989b 2570437
- Robinson DS, Rickels K, Feighner J, et al: Clinical effects of the 5-HT<sub>1A</sub> partial agonists in depression: a composite analysis of buspirone in the treatment of depression. *J Clin Psychopharmacol* 10 (3 suppl):67S-76S, 1990 2198303
- Roy-Byrne PP: Comorbid MDD and GAD: revisiting the concept of "anxious depression." *Psychiatric Times* (Supplement 1: Perspectives in Psychiatry: A Clinical Update) August (1):25-30, 2008
- Sanghera MK, McMillen BA, German DC: Buspirone, a non-benzodiazepine anxiolytic, increases locus coeruleus noradrenergic neuronal activity. *Eur J Pharmacol* 86(1):107-110, 1982 6130954
- Sathananthan GL, Sanghvi I, Phillips N, Gershon S: MJ 9022: correlation between neuroleptic potential and stereotypy. *Curr Ther Res Clin Exp* 18(5):701-705, 1975 1208
- Savitz J, Lucki I, Drevets WC: 5-HT(1A) receptor function in major depressive disorder. *Prog Neurobiol* 88(1):17-31, 2009 19428959
- Scheibe G: Four-year follow-up in 40 outpatients with anxiety disorders: buspirone versus lorazepam. *Eur J Psychiatry* 10:25-34, 1996
- Schweizer E, Rickels K: Failure of buspirone to manage benzodiazepine withdrawal. *Am J Psychiatry* 143(12):1590-1592, 1986 2878622
- Schweizer E, Rickels K, Hassman H, et al: Buspirone and imipramine for the treatment of major depression in the elderly. *J Clin Psychiatry* 59(4):175-183, 1998 9590668
- Sharp T, Bramwell SR, Grahame-Smith DG: 5-HT<sub>1</sub> agonists reduce 5-hydroxytryptamine release in rat hippocampus in vivo as determined by brain microdialysis. *Br J Pharmacol* 96(2):283-290, 1989 2466516

- Sheehan DV, Raj AB, Sheehan KH, et al: Is buspirone effective for panic disorder? *J Clin Psychopharmacol* 10(1):3-11, 1990 2407755
- Sheikhmoonesi F, Zarghami M, Bahari Saravi SF, et al: A triple-blinded, randomized, placebo-controlled trial to examine the efficacy of buspirone added to typical antipsychotic drugs in patients with chronic schizophrenia. *J Res Med Sci* 20(2):140-145, 2015 25983765
- Skolnick P, Weissman BA, Youdim MBH: Monoaminergic involvement in the pharmacological actions of buspirone. *Br J Pharmacol* 86(3):637-644, 1985 2933109
- Smiley A: Effects of minor tranquilizers and antidepressants on psychomotor performance. *J Clin Psychiatry* 48 (suppl):22-28, 1987 2891686
- Smiley A, Moskowitz H: Effects of long-term administration of buspirone and diazepam on driver steering control. *Am J Med* 80(3B):22-29, 1986 3963031
- Stahl SM: Serotonin receptors and the mechanism of action of antidepressant drugs: postmortem, platelet, and neuroendocrine studies in depressed patients, in *Serotonin 1A Receptors in Depression and Anxiety*. Edited by Stahl S, Gaspar M, Hesselink JM, et al. New York, Raven, 1992, pp 135-162
- Stockmeier CA, Shapiro LA, Dilley GE, et al: Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression—postmortem evidence for decreased serotonin activity. *J Neurosci* 18(18):7394-7401, 1998 9736659
- Sumiyoshi T, Park S, Jayathilake K, et al: Effect of buspirone, a serotonin<sub>1A</sub> partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res* 95(1-3):158-168, 2007 17628435
- Sussman N, Chow JC: Current issues in benzodiazepine use of anxiety disorders. *Psychiatric Annals* 18(3):139-145,



1988

- Tompkins EC, Clemento AJ, Taylor DP, Perhach JL: Inhibition of aggressive behavior in rhesus monkeys by buspirone. *Research Communications in Psychology, Psychiatry and Behavior* 5(4):337-352, 1980
- Trivedi MH, Fava M, Wisniewski SR, et al; STAR\*D Study Team: Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 354(12):1243-1252, 2006 16554526
- Udelman HD, Udelman DL: Concurrent use of buspirone in anxious patients during withdrawal from alprazolam therapy. *J Clin Psychiatry* 51 (suppl):46-50, 1990 2211568
- Van de Kar LD, Karteszi M, Bethea CL, et al: Serotonergic stimulation of prolactin and corticosterone secretion is mediated by different pathways from the mediobasal hypothalamus. *Neuroendocrinology* 41(5):380-384, 1985 2997650
- Vicentic A, Li Q, Battaglia G, Van de Kar LD: WAY-100635 inhibits 8-OH-DPAT-stimulated oxytocin, ACTH and corticosterone, but not prolactin secretion. *Eur J Pharmacol* 346(2-3):261-266, 1998 9652368
- West R, Hajek P, McNeill A: Effect of buspirone on cigarette withdrawal symptoms and short-term abstinence rates in a smokers clinic. *Psychopharmacology (Berl)* 104(1):91-96, 1991 1882007
- Wieland S, Lucki I: Antidepressant-like activity of 5-HT<sub>1A</sub> agonists measured with the forced swim test. *Psychopharmacology (Berl)* 101(4):497-504, 1990 1975107
- Winhusen TM, Kropp F, Lindblad R, et al: Multisite, randomized, double-blind, placebo-controlled pilot clinical trial to evaluate the efficacy of buspirone as a relapse-prevention treatment for cocaine dependence. *J Clin Psychiatry* 75(7):757-764, 2014 24911028

- Wise CD, Berger BD, Stein L: Benzodiazepines: anxiety-reducing activity by reduction of serotonin turnover in the brain. *Science* 177(4044):180-183, 1972 5064914
- Wong H, Dockens RC, Pajor L, et al: 6-Hydroxybuspirone is a major active metabolite of buspirone: assessment of pharmacokinetics and 5-hydroxytryptamine<sub>1A</sub> receptor occupancy in rats. *Drug Metab Dispos* 35(8):1387-1392, 2007 17494642
- Wu YH, Smith KR, Rayburn JW, et al: Psychosedative agents. N-(4-phenyl-1-piperazinylalkyl)-substituted cyclic imides. *J Med Chem* 12(5):876-881, 1969 5822165
- Yocca FD: Neurochemistry and neurophysiology of buspirone and gepirone: interactions at presynaptic and postsynaptic 5-HT<sub>1A</sub> receptors. *J Clin Psychopharmacol* 10 (3 suppl):6S-12S, 1990 1973941
- Yocca FD, Altar CA: Partial agonism of dopamine, serotonin, and opiate receptors in psychiatry. *Drug Discovery Today: Therapeutic Strategies* 3(4):429-435, 2006
- Yocca FD, Iben L, Meller E: Lack of apparent receptor reserve at postsynaptic 5-hydroxytryptamine<sub>1A</sub> receptors negatively coupled to adenylyl cyclase activity in rat hippocampal membranes. *Mol Pharmacol* 41(6):1066-1072, 1992 1352034
- Zhu M, Zhao W, Jimenez H: Cytochrome P450 3A-mediated metabolism of buspirone in human liver microsomes. *Drug Metab Dispos* 33(4):500-507, 2005 15640381

# **Antipsychotics**

## CHAPTER 24

# Classic Antipsychotic Medications

Henry A. Nasrallah, M.D.

Rajiv Tandon, M.D.

---

### History and Discovery

---

Prior to the introduction of classic antipsychotic medications in the 1950s, treatment for psychotic disorders primarily consisted of institutional confinement and supportive care with minimal control of psychotic symptoms. The discovery of chlorpromazine, the first of the “classic” antipsychotics, was serendipitous and owes much to the observations of a French surgeon, Henri Laborit, who noted that chlorpromazine, when used as an adjunct to anesthesia, calmed patients significantly following surgery. Laborit recommended its use to two French psychiatrists, Jean Delay and Pierre Deniker, who used it successfully in psychotic patients. Heinz Lehmann was the first to use chlorpromazine in North America (in Montreal, Canada). In the early 1960s, the first large-scale placebo-controlled trials were conducted within the U.S. Veterans Administration system.

After the successes of chlorpromazine, numerous other phenothiazines were synthesized by modifying the side chains on the phenothiazine rings. Subsequently, several nonphenothiazine antipsychotics, such as haloperidol, were introduced. The last of these drugs approved by the U.S. Food and Drug Administration (FDA) was molindone, introduced in 1975. Of 51 classic antipsychotic drugs (representing eight different chemical classes) available in the world, 9 are currently available in the United States.

The ability of chlorpromazine and other conventional antipsychotics to suppress psychotic symptoms (delusions, hallucinations, and disorganization) had a profound impact on chronically hospitalized psychiatric populations worldwide. Massive numbers of psychiatric patients were discharged from state hospitals to the community. This period of deinstitutionalization led to a decrease in the number of patients in state and county mental hospitals in the United States from 559,000 in 1955 to 338,000 in 1970 to 107,000 in 1988, an 80% decrease over 30 years. Initially, this led to enthusiasm about the possibility that patients with schizophrenia and other psychoses would be able to function well in the community. However, it soon became apparent that improvement with antipsychotic treatment was incomplete. In addition, poor treatment adherence—with subsequent relapses—led to frequent rehospitalization (i.e., the “revolving door” phenomenon).

As psychiatrists began using chlorpromazine, they observed that treated patients frequently manifested signs and symptoms of parkinsonism. Along with other side effects such as dystonia and akathisia, these symptoms are collectively referred to as

*extrapyramidal side effects* (EPS). Because of the high prevalence of these movement disorders in patients receiving antipsychotic treatment, many psychiatrists believed EPS to be an unavoidable accompaniment of antipsychotic action; in fact, the onset of some EPS was considered to indicate the minimal effective antipsychotic dose (i.e., the “neuroleptic threshold”). The first report of persistent orobuccal movements (later labeled *tardive dyskinesia*) came from France in 1959. The pervasiveness of debilitating short-term and long-term motor side effects associated with classic antipsychotic drugs led to a search for agents that would be at least as efficacious but without the risk of EPS.

Clozapine, a dibenzodiazepine synthesized in 1959, was the first antipsychotic drug without EPS (i.e., atypical). It was initially marketed in Europe in 1972 but was withdrawn in some countries in 1975 after several reports of fatalities secondary to agranulocytosis. Clozapine was not introduced in the United States until 1989, after convincing studies demonstrated its efficacy in antipsychotic-refractory schizophrenia. Other atypical agents (also referred to as second-generation antipsychotics [SGAs]) have been launched in the past 15 years and are reported to be associated with lower levels of EPS and a broader spectrum of efficacy; of the 16 SGAs currently being marketed, 12 are available in the United States (see [Chapters 25–34](#) in this volume). Since the introduction of these newer agents, use of the classic antipsychotics (also referred to as traditional, conventional, or first-generation antipsychotics [FGAs]) has declined, especially in the United States—FGAs currently aggregate approximately 5% of all antipsychotic prescriptions in the country. Results of several government-sponsored effectiveness studies—for example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)—in the past decade have challenged the prevailing worldview of the greater effectiveness of SGAs over FGAs and have reinvigorated interest in the utility and clinical applicability of classic antipsychotics.

---

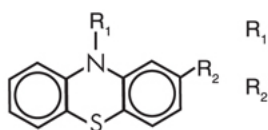
## Structure-Activity Relations

---

### Phenothiazines

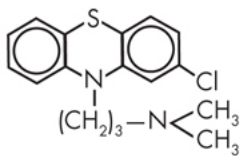
Members of the phenothiazine class of classic antipsychotics share the same basic phenothiazine ring but differ in substitutions at both their R1 and R2 positions ([Figure 24-1](#)). Based on the side chain attached to the nitrogen atom in the middle ring (R1), the phenothiazines are further subdivided into three subtypes: aliphatic, piperidine, and piperazine phenothiazines.

## Basic phenothiazine ring

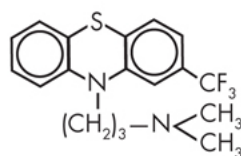


### A. Phenothiazines

#### 1. Aliphatic

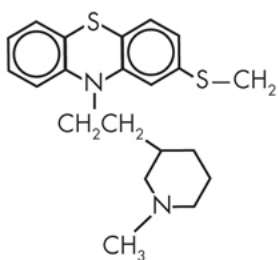


Chlorpromazine

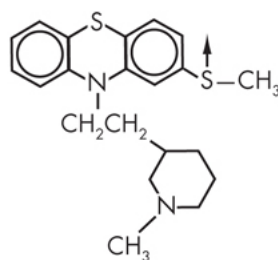


Triflupromazine

#### 2. Piperidine

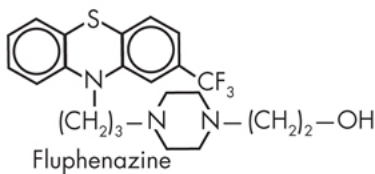


Thioridazine

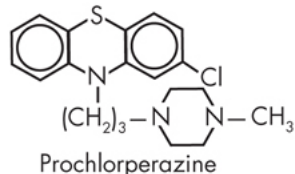


Mesoridazine\*

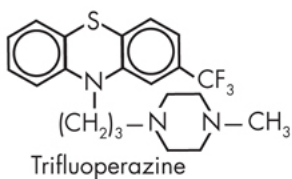
#### 3. Piperazine



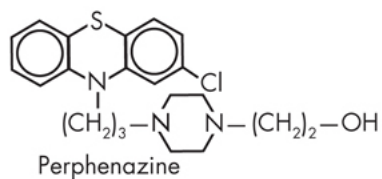
Fluphenazine



Prochlorperazine

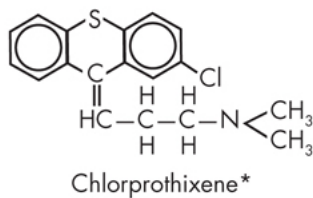


Trifluoperazine

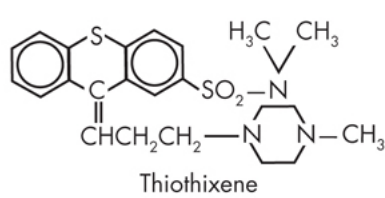


Perphenazine

### B. Thioxanthenes



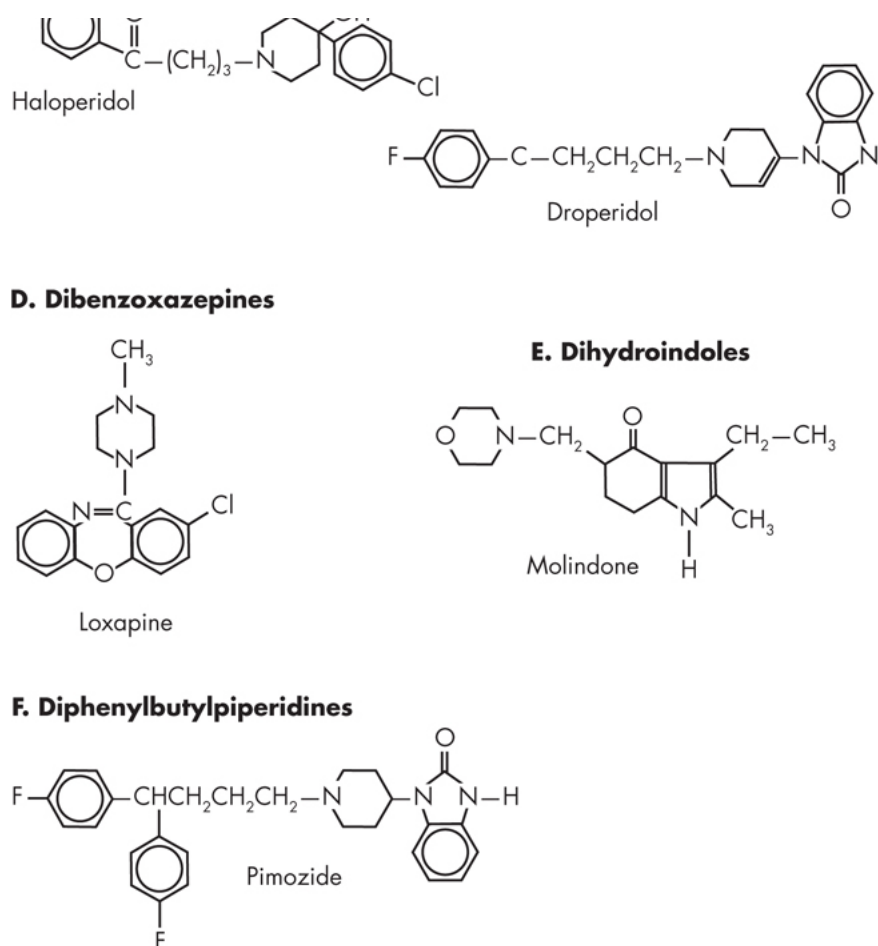
Chlorprothixene\*



Thiothixene

### C. Butyrophenones





**FIGURE 24-1.** Chemical structures of various classic antipsychotics.

\*No longer available in the United States.

### Aliphatic Phenothiazines

The aliphatic phenothiazines share a dimethylamide substitution at their tenth carbon. Chlorpromazine (Thorazine or Largactil) is the prototypical member of this class and remains the aliphatic phenothiazine most widely used throughout the world. With a chlorine atom attached to its second carbon, chlorpromazine is heavily sedating because of its high level of anticholinergic, anti- $\alpha$ -adrenergic, and antihistaminergic actions.

### Piperidine Phenothiazines

Piperidine phenothiazines—for example, thioridazine (Mellaril) and its metabolite, mesoridazine (Serentil)—are named for the presence of a piperidine ring at their tenth carbon. Although members of this group have similar efficacy and side effects compared with aliphatic phenothiazines, they are notable for having a less potent effect on nigrostriatal dopamine<sub>2</sub> ( $D_2$ ) receptors and a higher level of anticholinergic activity; consequently they are associated with a lower frequency of EPS. The use of these agents has been virtually extinguished by a black box warning about significant QTc prolongation that was added to their product label in 2000.

## Piperazine Phenothiazines

With a substitution of a piperazine group at the tenth carbon of a phenothiazine, the piperazines have greatly increased dopamine type 2 ( $D_2$ ) receptor blockade and a lower affinity for muscarinic,  $\alpha$ -adrenergic, and histaminergic receptors. Some of the most potent conventional antipsychotics available in the United States, including fluphenazine (Prolixin), perphenazine (Trilafon), and trifluoperazine (Stelazine), belong to this class. The well-known antiemetic prochlorperazine (Compazine) is also part of this class; although approved for the treatment of psychosis, it is rarely utilized as an antipsychotic.

## Thioxanthenes

Structurally and pharmacologically similar to the phenothiazines, the thioxanthenes also differ widely in their pharmacological profiles based on similar side-chain substitutions (see [Figure 24-1](#)). For instance, chlorprothixene shares the same dimethylamide and chloride substitution as chlorpromazine, with which it also shares its pharmacological profile. Thiothixene (Navane) has both a piperazine side chain and a strongly electrophilic substitution [ $SO_2N(CH_3)CH_3$ ], thus sharing the pharmacological profile of the piperazines.

## Butyrophenones

The butyrophenone class has a piperidine ring with a three-carbon chain ending in a carbonyl-substituted p-fluorobenzene ring. Haloperidol, arguably the best-known classic antipsychotic, is the most widely used member of this class. Haloperidol and other members of this class are strong dopamine receptor antagonists and show little antimuscarinic, antihistaminergic, and antiadrenergic activity.

## Dibenzoxazepines

Loxapine, the only FDA-approved agent within the dibenzoxazepine class, is composed of a tricyclic ring structure with a seven-member central ring. It has a piperazine side chain and chlorine at position R2 (see [Figure 24-1](#)). It exhibits an intermediate level of  $D_2$  blockade, as well as some serotonin<sub>2</sub> (5-HT<sub>2</sub>) antagonism. Its side-effect profile is characterized by intermediate sedation and autonomic effects. Loxapine has the distinction of being the most “atypical” of the classic antipsychotics because it is structurally similar to the dibenzodiazepine clozapine. Another notable feature of loxapine is that one of its metabolites, amoxapine, is marketed as an antidepressant.

## Dihydroindoles

Molindone is the only member of the dihydroindoles available in the United States. Sharing a similar structure with the indoleamines (see [Figure 24-1](#)), such as serotonin, molindone has the distinction of being the only classic antipsychotic not associated with any weight gain or a lowering of the seizure threshold.

## Diphenylbutylpiperidines



Pimozide, the only agent within the diphenyl-butyl-piperidine class available in the United States, is approved only for the treatment of Tourette syndrome and has the distinction of possessing the highest selectivity and potency for dopamine D<sub>2</sub> receptors among the conventional antipsychotics. It significantly prolongs the QTc interval, and this has limited its utilization. Derived from benperidol, pimozide shares many characteristics of the butyrophenones (see [Figure 24-1](#)).

## Benzamides and Iminodibenzyl Agents

Sulpiride, the prototypical substituted benzamide, is a relatively selective dopamine D<sub>2</sub> antagonist and lacks significant activity on cholinergic, histaminergic, or noradrenergic receptors. Because of this relative selectivity and a lower propensity to cause EPS, sulpiride is one of the more common classic antipsychotics utilized in Europe. No classic antipsychotic agent from either the benzamide or the iminodibenzyl class is available in the United States.

---

## Pharmacological Profile

---

The classic conventional antipsychotic drugs have a multitude of effects on various physiological variables through their actions on different neurotransmitter systems. The antipsychotic effects of these agents are believed to occur primarily through antagonism of D<sub>2</sub>-type dopaminergic receptors. Therapeutic and adverse effects of D<sub>2</sub> antagonism have been conceptualized in the context of the major dopaminergic tracts present in the brain, which include the mesocortical, mesolimbic (A10), tuberoinfundibular (A12), and nigrostriatal (A8 and A9) tracts.

The effect of D<sub>2</sub> receptor blockade on the mesolimbic dopaminergic systems is believed to represent the putative mechanism of action of conventional antipsychotics, but D<sub>2</sub> blockade in other tracts is believed to result in a number of adverse cognitive and behavioral side effects. Such side effects are frequently observed in both animals and human subjects. D<sub>2</sub> receptor antagonism in the mesocortical dopaminergic pathway leads to a blunting of cognition (bradyphrenia) and avolition-apathy (sometimes referred to as the *neuroleptic-induced deficit syndrome*), which can be difficult to differentiate from the primary negative symptoms of schizophrenic illness itself.

Blockade of the tuberoinfundibular tract projecting to the hypothalamus and pituitary gland results in multiple neuroendocrine side effects processed through the pituitary gland. Although dopamine is involved in enhancing the release of most pituitary hormones, it is actually responsible for the tonic inhibition of prolactin release. With significant dopaminergic blockade of the tuberoinfundibular tract, prolactin release is no longer prevented, and the release of other pituitary hormones is no longer enhanced. High levels of prolactin combined with decreased levels of follicle-stimulating hormone and luteinizing hormone often result in amenorrhea, galactorrhea, gynecomastia, decreased bone density, impaired libido, and erectile dysfunction.

High levels (exceeding 78%) of D<sub>2</sub> dopaminergic blockade within the nigrostriatal system, which projects to the basal ganglia and caudate, produce some of the most undesirable side effects of conventional antipsychotics. Movement disorders or EPS such as akathisia, rigidity, and hypokinesia were once believed to be necessary “evidence” of a therapeutic antipsychotic dosage. However, the advent of the new-generation

antipsychotics that are associated with minimal EPS conclusively dispensed with this misconception. At higher levels of D<sub>2</sub> blockade, one may also observe dystonia, catalepsy, and a rigid, immobile catatonic state.

Classic antipsychotic agents have varying degrees of activity at serotonergic, cholinergic, noradrenergic, histaminergic, and other nondopaminergic receptors. Although it is unclear whether any of these activities contribute to or interfere with their effectiveness in the treatment of psychotic symptoms, they clearly result in a variety of adverse effects. Because of differences in the pharmacological activity of different classic antipsychotic agents at these receptors, there are predictable differences in their side-effect profiles.

## Pharmacokinetics

Generally, the pharmacokinetic profiles of the conventional antipsychotics remain poorly understood. Even for some of the more extensively studied agents, many hundreds of potential metabolites remain undiscovered, and the physiological activity of several metabolites has yet to be adequately defined. Nonetheless, certain general statements can be made concerning the classic antipsychotics as a group.

## Administration and Absorption

Many of the conventional antipsychotics are available in both oral and intramuscular formulations. Although relatively common in the past, intravenous usage of parenteral formulations of antipsychotics is not FDA-approved. Peak plasma levels with oral preparations are generally reached in 1–4 hours, with these levels being reached slightly more rapidly with liquid concentrates. Oral preparations are extensively metabolized in the liver during their first pass through portal circulation by undergoing a range of transformations, including glucuronidation, oxidation, reduction, and methylation. Steady-state levels are reached in a period of four to five times the half-life of the drug in question.

Intramuscular administration results in faster, more predictable absorption, with peak plasma levels in 30–60 minutes and clinical efficacy as rapidly as 15 minutes. With intramuscular or intravenous administration, plasma levels may be as much as four times the levels of the oral route because of circumvention of the hepatic first-pass metabolism.

Although 10 classic antipsychotics are available in a long-acting (depot) formulation around the world, haloperidol and fluphenazine are the only classic antipsychotics currently available in such a formulation in the United States. The currently available decanoate forms of both haloperidol and fluphenazine are administered through injection into a major muscle, and the drug is slowly released to the bloodstream over time. As the esterified version of the drug diffuses into other tissues, the ester chain is hydrolyzed, resulting in the smooth release of the drug in question. Fluphenazine decanoate can be given every 2–3 weeks on the basis of its half-life of 7–10 days, whereas haloperidol decanoate may be given every 4 weeks because of its longer half-life. The bioavailability of intramuscular relative to oral administration is twofold greater.

## Distribution

Most of the conventional antipsychotics are highly protein bound (85%–90%). This feature is of importance when other highly protein-bound medications are used concomitantly

because of the risk of increasing levels of free or unbound drugs into the toxic range. The antipsychotic drugs are highly lipophilic, which allows unbound portions of the drug to readily cross the blood-brain barrier, with concentrations twofold higher in the brain than in the peripheral circulation. The drugs also readily cross the placenta to the fetus in pregnancy.

## Metabolism

The conventional antipsychotics are metabolized in the liver by hydroxylation and demethylation to forms that are more soluble and readily excreted by the kidneys and in the feces. Many of these compounds undergo further glucuronidation and remain active as dopamine receptor antagonists. Because of the many active metabolites of the antipsychotic agents, it has not been possible to obtain meaningful correlations between plasma levels and clinical response. Variables such as age, genetic variability among individuals, and coadministration of other drugs cause plasma levels to vary 10- to 20-fold across individuals. The majority of conventional antipsychotics are metabolized by the cytochrome P450 (CYP) enzyme subfamilies. Since CYP2D6 is important for the metabolism of many of these antipsychotics, genetic variation in the rate of 2D6 metabolism should be considered. CYP1A2 and 3A4 subfamily enzymes are also involved in the metabolism of some classic antipsychotics, and this may be relevant to understanding drug-drug interactions of those agents.

## Excretion

The major routes of excretion of the classic antipsychotics are through urine and feces by way of bile. These drugs are also excreted in sweat, saliva, tears, and breast milk. Elimination half-life varies from 18 to 40 hours for these drugs. Lower doses of antipsychotics are generally needed in elderly patients because of decreased renal clearance. Because of the long elimination half-lives of the classic antipsychotics, once-a-day dosing is possible for each of these agents following stabilization.

---

## Mechanism of Action

---

Dopamine has been at the center of neurobiological theories of psychosis for the past half-century, and even today, all agents approved as antipsychotics share the single common attribute of dopamine D<sub>2</sub> receptor antagonism. Amphetamine intoxication served as a drug-induced model of the positive symptoms of schizophrenia. Drugs that blocked dopaminergic receptors, specifically the D<sub>2</sub> receptor, were noted to have greater efficacy and potency as antipsychotics. Since dopaminergic agonists exacerbate psychosis and dopaminergic blockade treats it, dopamine has held central importance in our conceptualization of the neuropharmacology of schizophrenia.

---

## Indications and Efficacy

---

# Schizophrenia and Schizoaffective Disorder

Classic antipsychotics are best known for the acute and maintenance treatment of the psychotic (also known as positive) symptoms of schizophrenia and schizoaffective disorder. The major putative mechanism of action is through D<sub>2</sub> blockade of the mesolimbic tract. In many individuals, this blockade results in a measurable decrease in the positive symptoms of schizophrenia, including hallucinations, delusions, and disorganization ([Tandon et al. 2010, 2013](#)). However, negative and cognitive symptoms of schizophrenia respond less robustly. In fact, they may be worsened by blockade of mesocortical tracts that play roles in cognition and hedonic reinforcement.

The failure to improve the negative symptoms of schizophrenia is one of the major drawbacks of the classic antipsychotics. In fact, the EPS induced by the FGAs can worsen negative and cognitive symptoms by inducing bradykinesia and bradyphrenia. Another major limitation is the lack of improvement of positive symptoms (i.e., refractoriness) in about 25% of schizophrenia patients and partial response (i.e., treatment resistance) in another 25%.

## Substance-Induced Psychosis

As noted previously, conventional agents can reverse the psychosis associated with acute and chronic amphetamine intoxication as well as that associated with cocaine use. However, the risk of acute dystonia must be considered in these populations, as dopamine receptor downregulation is common, resulting in greater sensitivity to rapid D<sub>2</sub> blockade. Results in treatment of psychosis secondary to drugs acting in non-dopaminergic mechanisms (such as hallucinogens) are less satisfactory, although there may be some role for the classic antipsychotics in treating phencyclidine (PCP) psychosis.

## Personality Disorders

Although any personality disorder can be associated with transient psychotic features emerging under stressful conditions, Cluster B disorders are most often associated with this phenomenon. Treatment for transient psychotic episodes has included short-term use of low doses of a high-potency antipsychotic. Although some symptoms of personality disorders may be amenable to such pharmacological treatment, long-term conventional antipsychotic treatment is not recommended.

## Mood Disorders

The utility of antipsychotic agents in the treatment of mood disorders with psychotic features is well known. However, their utility in the treatment of nonpsychotic depression and bipolar disorder is described as well. Several conventional antipsychotics (such as thioridazine) are FDA approved for the treatment of depression and anxiety without overt psychosis. However, they are no longer used for this purpose because of the availability of other, more effective and better-tolerated agents. The utility of conventional agents as adjuncts to mood stabilizers in the treatment of patients with bipolar and related disorders has been well described, both in the acute management of mania and in the maintenance treatment of bipolar disorder with severe mood disturbance and/or psychotic features.

However, the newer atypical antipsychotics have largely replaced conventional antipsychotics in the management of bipolar disorder.

## Tourette Syndrome

The tics present within Tourette syndrome are believed to be due to a hyper-dopaminergic state that is amenable to treatment by dopamine receptor antagonists. Pimozide is the only conventional antipsychotic with this indication, which is its only FDA-approved indication.

## Huntington’s Disease

Although there is no cure for Huntington’s disease, the psychosis and choreiform movements associated with this disease may be ameliorated by dopamine receptor antagonism. Several conventional antipsychotics carry FDA indications for treatment of this disease.

## Nausea, Emesis, and Hiccups

The lower-potency antipsychotics exert a potent antiemetic effect through histamine<sub>1</sub> (H<sub>1</sub>) receptor antagonism. This effect is closely related to their original role in reducing perioperative stress and emesis. Many well-known antiemetics, such as promethazine (Phenergan), are phenothiazines with a short-chain substitution. In addition, chlorpromazine is approved for oral or intramuscular therapy of intractable hiccups.

## Side Effects and Toxicology

As noted earlier, side-effect profile—rather than efficacy in treating psychosis—is used to differentiate the conventional antipsychotics (Dodd et al. 2015). These agents serve as antagonists at four major neurotransmitter receptor systems in the central nervous system (CNS): the dopamine type 2 receptor family (D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>), muscarinic cholinergic receptors (M<sub>1</sub>), α-adrenergic receptors (α<sub>1</sub> and α<sub>2</sub>), and histamine receptors (H<sub>1</sub>) (Table 24-1).

**TABLE 24-1. Relative affinities of classic antipsychotics to various neurotransmit**

	Chlorpromazine	Thioridazine	Perphenazine	Trifluoperazine	Fluphenazine	Th
D <sub>1</sub>	High	—	High	High	High	M
D <sub>2</sub>	High	Very high	Very high	Very high	Very high	Ve
D <sub>3</sub>	High	Very high	Unknown	Unknown	Very high	Ur
D <sub>4</sub>	High	Very high	Unknown	High	Very high	Ur
H <sub>1</sub>	High	High	Moderate	Moderate	High	M

*Note.* Receptor families: dopamine (D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>), histamine (H<sub>1</sub>), muscarinic cholinergic HT<sub>1</sub>, 5-HT<sub>2</sub>).

	Chlorpromazine	Thioridazine	Perphenazine	Trifluoperazine	Fluphenazine	Th
M <sub>1</sub>	High	High	Low	Low	Low	Lo
α <sub>1</sub>	Very high	Very high	High	High	High	M
α <sub>2</sub>	Moderate	Very high	Moderate	Low	Low	M
5-HT <sub>1</sub>	Low	Low	Low	Low	Low	Lo
5-HT <sub>2</sub>	High	High	Moderate	Moderate	Moderate	M

*Note.* Receptor families: dopamine (D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>), histamine (H<sub>1</sub>), muscarinic cholinergic HT<sub>1</sub>, 5-HT<sub>2</sub>).

The therapeutic action of classic antipsychotics in ameliorating the positive symptoms of schizophrenia is believed to be due to D<sub>2</sub> blockade in the mesolimbic dopamine tract. Blockade of D<sub>2</sub> receptors in the mesocortical, nigrostriatal, and tuberoinfundibular systems leads to the tract-related side effects described earlier in this chapter (see section “Pharmacological Profile”). Lower-potency agents have greater antihistaminergic, anticholinergic, and antiadrenergic actions. However, they have fewer D<sub>2</sub>-related side effects because of their lower affinity to D<sub>2</sub> receptors and relatively high anticholinergic activity. Higher-potency agents, such as haloperidol, produce more D<sub>2</sub>-related movement disorders and prolactin elevation but otherwise have a cleaner side-effect profile, having fewer anticholinergic, antiadrenergic, and antihistaminergic side effects. Anticholinergic action often leads to dry mouth (xerostomia), blurred vision (mydriasis), constipation, urinary retention, sinus tachycardia, confusion, impaired cognition, paralytic ileus, exacerbation of open-angle glaucoma, and drowsiness. Antagonism of α<sub>1</sub>-adrenergic receptors is associated with orthostatic hypotension, QTc prolongation, reflex tachycardia, dizziness, incontinence, and sedation. Antagonism of α<sub>2</sub> receptors can be associated with retrograde ejaculation and priapism. Antagonism of H<sub>1</sub> receptors leads to sedation, drowsiness, and weight gain.

The frequencies of adverse reactions to classic antipsychotic agents are summarized in [Table 24-2](#).

**TABLE 24-2. Incidence of adverse reactions to classic antipsychotics at therapeutic doses**

	Phenothiazines			
	Chlorpromazine	Mesoridazine	Thioridazine	Fluphenazine
<b>Cognitive effects</b>				
Drowsiness, sedation	High	High	High	Low
Insomnia, agitation	Low	Low	Low	Low
<b>Extrapyramidal effects</b>				
Parkinsonism	Low to Moderate	Low to Moderate	Low	High
Akathisia	Low	Moderate	Low	High
Dystonic reactions	Low	Low	Low	High

	Phenothiazines			
	Chlorpromazine	Mesoridazine	Thioridazine	Fluphenazine
<b>Cardiovascular effects</b>				
Orthostatic hypotension	High	High	High	Low
Tachycardia	Moderate	Moderate	High	Low
ECG abnormalities	Moderate	Low	Moderate	Low
Cardiac arrhythmias	Low	Moderate	Moderate	Low
<b>Anticholinergic effects</b>				
	High	High	High	Low
<b>Endocrine effects</b>				
Sexual dysfunction	Moderate	Moderate	High	Moderate
Galactorrhea	Moderate	Moderate	Moderate	High
Weight gain	High	High	High	Moderate
<b>Skin reactions</b>				
Photosensitivity	Moderate	Low	Moderate	Low
Rashes	Moderate	Low	Moderate	Low
Pigmentation	High	Low	Low	Low
<b>Ocular effects</b>				
Lenticular pigmentation	Low	Low	Low	Low
Pigmentary retinopathy	Low	Low	Moderate	Low
<b>Other effects</b>				
Blood dyscrasias	Low to Moderate	Low	Low	Low
Hepatic disorder	Low	Low	Low	Low
Seizures	Moderate	Moderate	Moderate	Low

## Cognitive Side Effects

CNS side effects of classic antipsychotics can be subclassified into cognitive and neuromuscular side effects. Cognitive effects include sedation, confusion, disturbed concentration, memory impairment, and delirium ([Himelhoch et al. 1996](#)). Antihistaminergic and anticholinergic actions lead to sedation and slowed mentation. These effects, which are most pronounced with lower-potency agents (e.g., chlorpromazine), are most severe earlier in treatment, with some tolerance developing over time. Anticholinergic delirium is the most common cause of medication-induced delirium. Because delirium results in high rates of morbidity and mortality (over 20%

mortality), this potential side effect is important, especially in populations of individuals who are more sensitive to anticholinergic medications, such as the elderly. In addition, every antipsychotic—especially the low-potency agents—can potentially lower the seizure threshold.

## Extrapyramidal Side Effects

Neuromuscular CNS side effects are due to antagonism of D<sub>2</sub> receptors in the nigrostriatal dopaminergic pathway. Generally, antipsychotics manifest EPS when dopaminergic blockade exceeds 75%–80% of D<sub>2</sub> receptors. EPS are most frequent with the high-potency agents such as haloperidol. A greater risk of EPS differentiates the classic from the atypical antipsychotics—in fact, the term *atypical* was originally coined to highlight this ability to produce an antipsychotic effect equivalent to that of the typical high-potency agents with lower EPS.

### Acute-Onset EPS

Acute-onset EPS include medication-induced parkinsonism, acute dystonia, and akathisia. *Antipsychotic-induced parkinsonism* occurs in 15% of patients after several weeks of treatment. It is more common in patients older than 40 years, although it can occur at any age. Symptoms are identical to those of Parkinson's disease and include muscle stiffness ("lead-pipe" rigidity), cogwheel rigidity, shuffling gait, stooped posture, drooling, bradykinesia, resting tremor, masked facies, and akinesia. Slowed, restricted movements of the body and face (*akinesia*) may be mistakenly diagnosed as being due to depression or the negative symptoms of schizophrenia.

It is estimated that up to 10% of patients may experience an acute dystonic episode, which usually occurs within the first few hours or days of treatment. It is more common in youth, in recent cocaine users, and with intramuscular doses of high-potency antipsychotics. *Dystonia* is an acute, sustained, painful muscular contraction. Potential areas of involvement include the tongue (protrusions, twisting), jaw, neck (spasmodic retrocollis or torticollis), and back (opisthotonos). If the dystonia involves the eyes, it results in a symmetrical or unilateral upward lateral movement called an *oculogyric crisis*. Laryngeal dystonia can result in sudden death secondary to a patient's inability to breathe. Dystonia can be extremely uncomfortable and frightening for patients and can lead to noncompliance with medication for fear of recurrence. Treatment of dystonia requires rapid diagnosis and intravenous administration of antihistaminergic or anticholinergic agents. Anticholinergic agents are often initiated with high-potency antipsychotics in an effort to avoid this side effect.

*Akathisia* is a subjective feeling of motor restlessness in which patients feel an irresistible urge to move continuously. It is described as an unpleasant sensation and may result in dysphoria. Akathisia can occur at any time during treatment and is the most prevalent of the EPS. It frequently leads to noncompliance with medications and is believed to increase suicide risk in some patients.

### Late-Onset EPS

*Tardive dyskinesia* is characterized by a persistent syndrome of involuntary choreoathetoid movements of the head, limbs, and trunk. It generally takes at least 3–6 months of exposure to antipsychotics before the disorder develops. Perioral movements involving buccolingual masticatory musculature are the most common early manifestation



of tardive dyskinesia. Tardive dyskinesia has an estimated yearly incidence of 5% among adults and as high as 25% in the elderly who receive continuous conventional antipsychotic therapy and has been a major source of litigation in past psychiatric practice. The risk of developing tardive dyskinesia is reported to increase with age and to be higher in certain ethnic groups; female gender, presence of mood disorders, and early onset of EPS have also been associated with increased risk of tardive dyskinesia.

Tardive dyskinesia may be masked by continuing dopamine blockade and has a variable course following development. Over time, spontaneous resolution or improvement has been described in some individuals. There is no single effective treatment, although treatment with clozapine has been reported to improve symptoms. Cases of tardive dyskinesia have been described with every antipsychotic, although classic antipsychotics are associated with a much greater risk of tardive dyskinesia than second-generation or atypical agents ([Correll et al. 2004](#)). Other tardive syndromes include tardive dystonia, tardive akathisia, and tardive pain.

## Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a poorly understood syndrome that usually appears within hours or days of initiation of antipsychotic treatment. This syndrome is characterized by muscular rigidity, hyperpyrexia, autonomic instability (hypo- or hypertension, tachycardia, diaphoresis, pallor), and altered consciousness. NMS has an estimated incidence of 0.02%–2% and carries a mortality rate of 20%–30%. Death most often occurs secondary to dysrhythmias, renal failure secondary to rhabdomyolysis, aspiration pneumonia, or respiratory failure. Laboratory findings include elevated creatine phosphokinase, elevated white blood cell count, elevated liver enzymes, myoglobinemia, and myoglobinuria. The syndrome can last up to 10–14 days.

Treatment requires immediate discontinuation of the offending antipsychotic and supportive care with aggressive intravenous hydration. In the past, mild cases of NMS were treated with intravenous bromocriptine, while more severe cases were treated with intravenous dantrolene. However, randomized controlled clinical trials of NMS treatment have never been performed because of its infrequent occurrence.

## Cardiac Effects

$\alpha$ -Adrenergic antagonism is associated with orthostatic hypotension with reflex tachycardia, with tolerance possibly developing later in the treatment course. Orthostasis is important because of an increase in falls and related injuries.

Recent studies involving several antipsychotics have drawn attention to the risk of cardiac dysrhythmias, which is especially prominent with use of lower-potency conventional antipsychotics. High dosage, rapid titration, intramuscular administration, and especially intravenous administration may be associated with a lengthening of the QTc interval, with resulting risk of serious dysrhythmias such as torsades de pointes and ventricular fibrillation. Studies with thioridazine have raised concerns about piperidine antipsychotics, leading to a decrease in the use of this class. In reality, *torsades de pointes* is rarely encountered during treatment with conventional antipsychotics, although some have speculated that a syndrome of unexplained sudden death described with all conventional antipsychotics may be related to sudden dysrhythmias.

## Gastrointestinal Side Effects

The anticholinergic actions of conventional agents include dry mouth, nausea, vomiting, and constipation that can progress to paralytic ileus. Antihistaminergic action is associated with medication-related weight gain, which greatly increases the patient's risk of developing diabetes.

Cholestatic jaundice is a hypersensitivity reaction described with the aliphatic phenothiazines, especially chlorpromazine (incidence of 0.1%). This reaction typically manifests during the first 1-2 months of treatment and presents with nausea, malaise, fever, pruritus, abdominal pain, and jaundice, with resulting elevations in levels of bilirubin and alkaline phosphatase. This condition rarely lasts more than 2-4 weeks after discontinuation.

## Weight Gain, Diabetes Mellitus, and Dyslipidemia

With the introduction of atypical antipsychotics, several of which cause significant weight gain, there is renewed awareness of the metabolic side effects associated with antipsychotic therapy such as obesity, elevated cholesterol and triglyceride levels, and an increased risk of diabetes mellitus. These metabolic changes increase the risk of ischemic heart disease and contribute to the increased mortality observed in schizophrenia. Antihistaminergic action is associated with medication-related weight gain, which greatly increases the patient's risk of developing diabetes. Diabetes is currently described as a worldwide epidemic. Serotonin 5-HT<sub>2C</sub> receptor blockade also significantly contributes to weight gain ([Tandon and Halbreich 2003](#)). There are significant differences among classic antipsychotics with reference to their propensity to cause these metabolic adverse effects. Molindone is the least likely to cause weight gain, whereas thioridazine and chlorpromazine are among the most likely to do so. In general, high-potency agents cause less weight gain than do low-potency agents.

## Genitourinary Side Effects

Renal effects secondary to blockade of M<sub>1</sub> receptors include urinary hesitancy or retention, which can lead to a comparable increase in urinary tract infections in both genders. As mentioned previously, antagonism of tuberoinfundibular dopaminergic tracts increases prolactin secretion. Clinical manifestations of hyperprolactinemia include gynecomastia, galactorrhea, diminished libido, erectile dysfunction, amenorrhea, decreased bone density, menstrual irregularities, infertility, delayed ovulation, and possibly increased risk of breast cancer. Other sexual side effects, such as erectile disorder, retrograde ejaculation (due to blockade of  $\alpha_2$ -adrenergic receptors), anorgasmia, and occasionally priapism, can also occur with conventional antipsychotics.

## Hematological Side Effects

Hematological effects of conventional antipsychotics include transient leukopenia (white blood cell [WBC] count  $<3,500/\text{mm}^3$ ), which is common but not usually problematic, and agranulocytosis (WBC count  $<500/\text{mm}^3$ ), a life-threatening problem. Agranulocytosis occurs most often during the first 3 months of treatment, with an incidence of 1 in

500,000. Aliphatic and piperidine phenothiazines are the most common causal agents among the conventional antipsychotics. Rarely, thrombocytopenic or nonthrombocytopenic purpura, hemolytic anemia, and pancytopenia may occur.

## Ocular Side Effects

In addition to direct anticholinergic ocular effects such as blurred vision (mydriasis and cycloplegia) and exacerbation of open-angle glaucoma, direct optic toxicity has been described. The conventional antipsychotics are associated with several kinds of optical pathology involving the lens, cornea, and retina. Lenticular opacities have been reported with some phenothiazines, including perphenazine, chlorpromazine, and thioridazine. An irreversible increase in retinal pigmentation has been described with thioridazine when high dosages (>800 mg/day) are used. This retinal pigmentation, which can progress even after drug discontinuation, can lead to reduced visual acuity and even blindness. Early symptoms include poor night vision and secondary nocturnal confusion.

## Dermatological Side Effects

Cutaneous side effects of conventional antipsychotics involve hypersensitivity rashes—most commonly maculopapular erythematous rashes of the trunk, face, neck, and extremities—and photosensitivity reactions that can lead to severe sunburn. Care must be taken with injectable versions of many antipsychotics because of direct dermatological toxicity if the skin or subcutaneous layers are exposed. Prolonged use of chlorpromazine can lead to blue-gray discoloration in body areas exposed to sunlight.

---

## Drug-Drug Interactions

---

Careful consideration of a patient's existing drug regimen should be given prior to the initiation of antipsychotic therapy.

## Protein Binding

Because conventional antipsychotics are tightly protein bound, care must be taken when these medications are administered with other highly protein-bound medications. Mutual displacement of medications such as phenytoin, digoxin, warfarin, and valproate could lead to a short-term increase in serum levels of these drugs and of the conventional antipsychotic. However, protein binding has not been of serious clinical significance.

## Cytochrome P450 Inhibition

As mentioned previously, conventional antipsychotics are primarily hepatically metabolized through the CYP2D6 and 3A4 enzymes. In addition, each inhibits the 2D6 enzyme to some degree. Care must be taken when conventional agents are co-administered with potent CYP2D6 inhibitors such as fluoxetine, paroxetine, cimetidine, erythromycin, and certain class IC antiarrhythmics (e.g., quinidine). Similarly, potent CYP3A4 inhibitors such as nefazodone, fluvoxamine, and ketoconazole should be used with care. Inhibitors of

CYP2D6 and 3A4, as well as competitive substrates, should be used carefully with conventional antipsychotics because of their potential to increase plasma levels. CYP1A2, induced by nicotine and inhibited by estrogen, plays a role in metabolizing some antipsychotics.

---

## Conclusion

---

The classic antipsychotics revolutionized the practice of psychiatry and the treatment of the severely mentally ill throughout the world. Second-generation “atypical” antipsychotics have commercially eclipsed these first-generation agents to a large extent, in that more than 90% of patients with schizophrenia and related psychoses in the United States are currently receiving one of the atypical oral agents. In regard to long-acting (depot) agents, second-generation injectable agents are gradually displacing classic antipsychotic injectables such as haloperidol decanoate and fluphenazine decanoate. The landmark National Institute of Mental Health-funded CATIE study, which compared four SGA oral agents (olanzapine, quetiapine, risperidone, and ziprasidone) against one FGA oral agent (perphenazine), showed that there was no difference between the two generations in clinical effectiveness (defined as all-cause discontinuation) ([Lieberman et al. 2005](#)). However, the CATIE study excluded subjects with tardive dyskinesia from random assignment to perphenazine and instead assigned them to one of the atypical agents. This methodological stipulation may have confounded the findings, because the 231 subjects with tardive dyskinesia were later found to have a higher severity of psychopathology and a much greater likelihood of substance use ([Nasrallah 2006](#)). Additionally, the subjects’ low propensity to develop EPS led to a “ceiling effect” finding of no EPS differences between perphenazine and the SGAs. Nonetheless, both classic antipsychotics and atypical antipsychotics can cause serious side effects, with neurological adverse events being much more likely with the FGAs and metabolic complications being more common with the SGAs.

Conventional antipsychotics will always be remembered for their critical role as the foundation of antipsychotic pharmacotherapy and as the main impetus for the remarkable neuropharmacological progress in psychiatric neuroscience over the second half of the twentieth century. They retain an important, if limited, role in the antipsychotic armamentarium of the twenty-first century.

---

## Suggested Readings

---

- Glazer WM: Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. *J Clin Psychiatry* 61 (suppl 4):15-20, 2000 10739326
- Janicak PA, Marder SR, Tandon R, Goldman M: *Schizophrenia—Recent Advances in Diagnosis and Treatment*. Springer, Berlin, 2014
- Meyer JM, Nasrallah HA (eds): *Medical Illness and Schizophrenia*, 2nd Edition. Washington, DC, American Psychiatric Publishing, 2010
- Nasrallah HA, Smeltzer D: *Contemporary Diagnosis and Management of Schizophrenia*, 2nd Edition. Newtown, PA, Handbooks in Health Care, 2011
- Sachdev PS: Neuroleptic-induced movement disorders: an overview. *Psychiatr Clin North Am* 28(1):255-274, x, 2005 15733622
- Smith D, Pantelis C, McGrath J, et al: Ocular abnormalities in chronic schizophrenia: clinical implications. *Aust N Z J Psychiatry* 31(2):252-256, 1997 9140633

Tandon R, Belmaker RH, Gattaz WF, et al; Section of Pharmacopsychiatry, World Psychiatric Association: World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res* 100(1-3):20-38, 2008 18243663

---

## References

---

- Correll CU, Leucht S, Kane JM: Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 161(3):414-425, 2004 14992963
- Dodd M, Samara MT, Tardy M, et al: Haloperidol versus first-generation antipsychotics for the treatment of schizophrenia and other psychotic disorders. *Cochrane Database Syst Rev* 1:CD009831, 2015 25592299
- Himelhoch S, Taylor SF, Goldman RS, et al: Frontal lobe tasks, antipsychotic medication, and schizophrenia syndromes. *Biol Psychiatry* 39(3):227-229, 1996 8837987
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353(12):1209-1223, 2005 16172203
- Nasrallah HA: CATIE's surprises: In antipsychotics' square-off, were there winners or losers? *Curr Psychiatr* 5(2):49-65, 2006
- Tandon R, Halbreich U: The second-generation 'atypical' antipsychotics: similar improved efficacy but different neuroendocrine side effects. *Psychoneuroendocrinology* 28 (suppl 1):1-7, 2003 12504068
- Tandon R, Nasrallah HA, Keshavan MS: Schizophrenia, "just the facts" 5. Treatment and prevention. Past, present, and future. *Schizophr Res* 122(1-3):1-23, 2010 20655178
- Tandon R, Gaebel W, Barch DM, et al: Definition and description of schizophrenia in the DSM-5. *Schizophr Res* 150(1):3-10, 2013 23800613

# CHAPTER 25

## Clozapine

Stephen R. Marder, M.D.

Yvonne S. Yang, M.D., Ph.D.

---

### History and Discovery

---

Clozapine has played a critical role in the history of therapeutics for psychosis. When clozapine was initially developed in the 1960s (following its synthesis in 1958 in Switzerland), there was skepticism as to whether an agent that barely caused catalepsy in rodents could be an effective antipsychotic. According to [Hippius \(1999\)](#), there was limited enthusiasm for this drug because its profile was inconsistent with the “neuroleptic dogma” that extrapyramidal side effects (EPS) were an essential feature of an antipsychotic agent. Nevertheless, Hippius and others challenged this dogma and supported clozapine’s development in Germany. As a result, clozapine was eventually marketed in a number of countries in Europe.

Enthusiasm about clozapine's unique profile turned to despair when it was reported that 13 patients in Finland developed agranulocytosis during treatment with clozapine and that 8 of these patients died ([Griffith and Saameli 1975](#)). This news led to a near halt in research on clozapine, and in the United States, clozapine's investigational new drug application came to a standstill. However, attempts to switch patients to other antipsychotic agents resulted in substantial deterioration in some individuals ([Hippius 1999](#)). Some of these patients were switched back to clozapine and carefully monitored with regular white blood cell (WBC) counts. Thus, it was found that if clozapine was discontinued, the agranulocytosis was reversible and the drug could be readministered safely ([Honigfeld et al. 1998](#)). Moreover, studies revealed that clozapine was particularly effective for patients who were severely ill and for patients who had not responded to treatment with conventional antipsychotics ([Kane et al. 1988](#); [Kronig et al. 1995](#)). After a series of stops and starts, clozapine was finally demonstrated to have superiority over chlorpromazine for treatment-resistant schizophrenia, and it was approved by the U.S. Food and Drug Administration (FDA) in 1990 ([Crilly 2007](#); [Iqbal et al. 2003](#)).

The discovery that clozapine, the earliest second-generation antipsychotic (SGA), was an effective antipsychotic that caused minimal EPS led to a reassessment of the reigning models of the antipsychotic effect. The exact mechanism of clozapine's antipsychotic action was and remains unknown; however, its efficacy, which is greater than first-generation antipsychotics (FGAs), led to the development of the SGAs. At this point in time, attempts to comprehend clozapine's mechanism of action have produced more questions than answers in our

understanding of the physiology and pharmacology of schizophrenia; however, it remains the most effective antipsychotic.

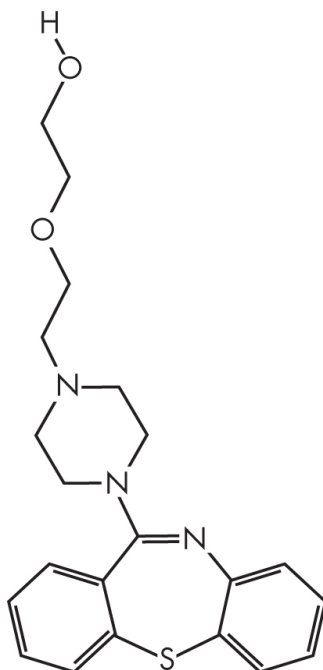
---

## Structure-Activity Relations

---

Clozapine, or 3-chloro-6-(4-methylpiperazin-1-yl)-5H-benzo[b][1,4]benzodiazepine ([PubChem Compound Database 2016a](#)), belongs to the group of tricyclic antipsychotics known as the dibenzepines. This group is characterized by a seven-member dibenzazepine central ring substituted with oxygen, nitrogen, sulfur, or carbon ([Iskra and Decker 2012](#)). The antipsychotic dibenzepines include a loxapine-like group of compounds (the dibenzoxazepines) and a clozapine-like group (the dibenzodiazepines). The structures of clozapine and its derivatives olanzapine and quetiapine can be seen in [Figure 25-1](#). Interestingly, the structure of the FGA antipsychotic loxapine ([PubChem Compound Database 2016b](#)) is quite similar to that of clozapine, with only two substitutions distinguishing them.





---

**FIGURE 25-1.** Chemical structures of clozapine, olanzapine, quetiapine, and loxapine.

Structures of olanzapine and quetiapine are based on clozapine's chemical structure, and their similarities can be seen clearly here. It is also striking how similar the structure of loxapine, a typical antipsychotic, is to that of clozapine, the prototypical atypical antipsychotic.

*Source.* Structures from PubChem Compound Database, National Center for Biotechnology Information. Available at: <http://www.ncbi.nlm.nih.gov/pccompound>.

Clozapine is also known to be a fast-off dopamine type 2 ( $D_2$ ) receptor antagonist, with a rapid disassociation time of less than 1 minute for 50% binding of  $D_2$  receptors (Seeman 2014). Tresadern et al. (2011) examined more than 1,800 compounds and found that “increased hydrophilicity, increased number of nitrogen atoms, lower molecular weight, fewer rings, less chiral centers, and

increased partial positive charge all contribute to a faster dissociation from the D<sub>2</sub> receptor” (p. 27).

---

## Pharmacological Profile

---

To quote [Wenthur and Lindsley \(2013\)](#), “clozapine is a broad spectrum ligand,” because it binds to more receptors than perhaps any molecule in psychopharmacology ([Stahl 2013](#)). Clozapine and the other SGAs are often identified through their equal or greater antagonism of the 5-hydroxytryptamine (serotonin) type 2A (5-HT<sub>2</sub>) receptor compared with the D<sub>2</sub> receptor. However, clozapine in fact binds to more than 20 receptors more strongly than to the D<sub>2</sub> receptor and binds to at least four receptors either just as strongly or more strongly than to 5-HT<sub>2A</sub> ([Stahl 2013](#); [Wenthur and Lindsley 2013](#)). Of all the antipsychotics, quetiapine, whose structure was based on that of clozapine, is most similar in pharmacological profile to clozapine.

## Dopamine Receptors

Clozapine is a D<sub>2</sub> antagonist that binds to D<sub>2</sub> receptors approximately 50–100 times less strongly than haloperidol and 10 times less strongly than chlorpromazine ([Ashby and Wang 1996](#)). At therapeutic concentrations, clozapine occupies only 40%–60% of D<sub>2</sub> receptors, in contrast to most FGAs, which occupy more than 80% of D<sub>2</sub> receptors ([Wenthur and Lindsley 2013](#)). Clozapine binds less strongly to D<sub>2</sub> receptors than to dopamine itself and may be displaced by endogenous dopamine ([Seeman 2014](#)). It also

has equivalent occupancy of dopamine  $D_1$  and  $D_2$  receptors at therapeutic dosages ([Tauscher et al. 2004](#)). In order, clozapine binds most strongly to  $D_4 > D_1 > D_5 > D_2 > D_3$  receptors ([Wenthur and Lindsley 2013](#)).

## Serotonin Receptors

Clozapine binds to 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub> receptors 15–30 times more strongly than to  $D_2$  receptors ([Stahl 2013](#); [Wenthur and Lindsley 2013](#)). Clozapine also has high affinity for 5-HT<sub>5</sub> receptors and acts as a partial agonist at 5-HT<sub>1A</sub> receptors.

## Muscarinic Receptors

Clozapine binds strongly to muscarinic  $M_1$  receptors, and to other muscarinic receptors in the following order:  $M_1 > M_3 > M_4 > M_2$ . Clozapine's high affinity for muscarinic receptors likely causes many of clozapine's well-known side effects of sedation, constipation, and the dangerous complication of ileus.

## Adrenergic Receptors

Clozapine binds strongly to  $\alpha_1$ -adrenergic receptors in the central nervous system, based on positron emission tomography studies of <sup>3</sup>H-prazosin binding displacement in animal studies ([Ashby and Wang 1996](#)). Clozapine's antagonism of  $\alpha_1$ -adrenergic receptors likely contributes to

its sedative properties as well as some of its cardiac side effects including orthostatic hypotension and tachycardia.

## Histamine Receptors

Clozapine binds very strongly to histamine type 1 ( $H_1$ ) receptors, which likely contributes to clozapine's associated sedation, increase in appetite, weight gain, and therefore possibly diabetes and metabolic syndrome. Preliminary research has been done on histamine agonists to counteract the metabolic effects of SGAs; however, no well-powered placebo-controlled, randomized trials have been performed ([Poyurovsky et al. 2005](#)).

## Glutamate Receptors

Although clozapine does not bind directly to glutamate receptors, it has been shown to inhibit the reuptake of glycine at the synapse in rats, resulting in increased glycine at the synapse, and thus increasing *N*-methyl-D-aspartate (NMDA) receptor signaling ([Javitt et al. 2005](#)). Moreover, clozapine's main metabolite, *N*-desmethylozapine (NDMC), or norclozapine, is an  $M_1$  agonist known to increase NMDA receptor activity ([Wenthur and Lindsley 2013](#)).

## GABA Receptors

Clozapine has a low affinity for  $\gamma$ -aminobutyric acid (GABA) receptors.

## Animal Studies

Animal behavioral models have been of limited use in schizophrenia, due to a lack of well-accepted animal models of psychopathology in schizophrenia. The reasons for this are numerous. First of all, no single model has been identified that can represent the genetic complexity and breadth and variability of symptom domains of schizophrenia. Second, the subjective quality of many psychotic experiences, such as paranoia, hallucinations, and delusions, makes these symptoms and experiences difficult to measure in animals. Third, unlike the heart or the pancreas, the human brain is many times more complex than even that of a monkey, not to mention a rodent brain, for instance as evidenced by the large number of folds in the human brain and the complete absence of folds in the rodent brain. Last, *schizophrenia* and *psychosis* continue to function as “umbrella terms” for what are likely numerous diseases presenting with overlapping symptoms and syndromes, making differentiation of one illness from another difficult in humans, not to mention animal models.

Despite these limitations, a number of constructs, including prepulse inhibition and the conditioned avoidance response, are being studied from a more reductionist standpoint. These models are being looked to less as complete representations of the disease than as models of specific neurophysiological aspects of psychosis that can inform us about particular characteristics of the illness ([Wong and Josselyn 2016](#)). The use of animal models in this manner has suggested unique properties of clozapine. For instance, as reviewed by [Geyer et al. \(2001\)](#), among four techniques to induce prepulse inhibition, a sensory gating phenomenon that is thought to relate to the relative

difficulty patients with schizophrenia have separating salient from nonsalient environmental information, deficits in prepulse inhibition induced by NMDA receptor antagonists were most likely to respond to clozapine-like SGAs, and not to FGAs.

The conditioned avoidance response is another well-established construct used to predict efficacy of a potential antipsychotic agent. Conditioned avoidance response refers to learned behavior to avoid a conditioned stimulus once it has been associated with a negative unconditioned stimulus. Early on in the development of antipsychotic drugs, it was found that effective agents specifically disrupted this response, and thus exhibited dopaminergic blockade ([Wadenberg 2010](#)). Although clozapine did not meet the commonly accepted criteria of capability to cause catalepsy at higher dosages and to antagonize amphetamine-induced stereotypies in animals, it does block the conditioned avoidance response, suggesting that it has antipsychotic efficacy.

---

## Pharmacokinetics and Disposition

---

Clozapine is readily absorbed orally. However, because of extensive first-pass metabolism, its absolute oral bioavailability is only moderate. Peak plasma levels of clozapine are reached approximately 2 hours after oral administration. The elimination half-life is about 12 hours, and patients will usually reach steady-state plasma concentrations within 7 days. The coadministration of highly protein-bound drugs may lead to increased free

clozapine levels, although the total (free plus bound) levels may be unchanged. Clozapine's volume of distribution is lower than that of other antipsychotic drugs but is nonetheless large, with a mean of 2.0–5.1 L/kg (range: 1.0–10.2 L/kg). Clozapine crosses the blood–brain barrier easily.

As mentioned, clozapine undergoes extensive first-pass metabolism in the liver and gut. Although clozapine is predominately metabolized by cytochrome P450 (CYP) 1A2, CYP2D6 and CYP3A3/4 also contribute ([Buur-Rasmussen and Brøsen 1999](#); [Wenthur and Lindsley 2013](#)).

Plasma concentrations of clozapine average about 10–80 ng/mL per mg of drug given per kg of weight. Thus, a typical daily dose of 300–400 mg (about 5 mg/kg) is associated with plasma levels ranging between 200 ng/mL and 400 ng/mL. However, there is considerable variability among individuals treated with clozapine. A number of studies have focused on the clinical implications of this variation in plasma concentrations. These studies, when taken together, indicate that patients are more likely to do well when their plasma levels are greater than 350 ng/mL ([Bell et al. 1998](#); [Kronig et al. 1995](#); [Miller 1996](#); [Miller et al. 1994](#); [Potkin et al. 1994](#)). If patients have not responded after 6 weeks with a plasma level of 250 ng/mL, the clinician should increase the level to approximately 350 ng/mL. High levels, such as 600 ng/mL, are not associated with a greater likelihood of improvement than are moderate levels, and they may be associated with a higher incidence of side effects. Therefore, patients with high levels and side effects may benefit from having the dosage reduced. In interpreting plasma concentrations of clozapine, it is important for clinicians to consider whether the laboratory is reporting just the parent drug or

clozapine plus norclozapine. If it is the combination, levels will be higher.

---

## Pharmacogenetic Profile

---

In recent years, a number of studies have been done linking genetic polymorphisms to either response to clozapine or likelihood of side effects such as weight gain and agranulocytosis in patients. Specific genetic polymorphisms include the D<sub>3</sub> receptor gene *rs6280*, where substitution of glycine for serine in a coding region of the genes is associated with higher response rates to clozapine and risperidone ([Moore et al. 2014](#)). Polymorphisms of the HLAQB1 gene, an allele at the major histocompatibility complex, are associated with greater likelihood of developing agranulocytosis, especially during rechallenge with clozapine after a prior episode of agranulocytosis. CYP genetic variants have been associated with decreased response to clozapine, and polymorphisms in the gene for brain-derived neurotrophic factor (BDNF) have been found to be associated with improved response ([Srirenakumar et al. 2015](#)). The Pro12Ala polymorphism of the PPAR- $\gamma$ 2 gene appears to predispose patients on clozapine to metabolic syndrome: patients with the Pro-Ala substitution had a 53.8% likelihood of having metabolic syndrome, whereas Pro-Pro polymorphism patients had only a 16.3% likelihood ([Fernández et al. 2012](#)). Although not yet integrated into clinical practice, the pharmacogenetics of clozapine may soon help to inform clinicians about the likelihood of a patient to either respond to clozapine treatment or to develop a concerning side effect.



---

# Mechanism of Action

---

The effectiveness of antipsychotics was previously thought to be associated with dopamine D<sub>2</sub> receptor blockade, and induction of EPS was thought to be necessary for antipsychotic action. Clozapine's low rates of EPS but superior efficacy as an antipsychotic undermined and eventually overturned these ideas. Currently, the exact mechanism of clozapine's antipsychotic effect remains unknown, but several theories have been proposed. In this section, we will discuss the possible mechanisms of both clozapine's low rate of EPS as well as its highly effective antipsychotic effect.

## Mechanisms of Clozapine's Low Propensity to Cause EPS

### Dual 5-HT<sub>2A</sub>-D<sub>2</sub> Antagonism

It has been thought that the low level of EPS from clozapine treatment (and many other SGAs) was due to its greater activity at the 5-HT<sub>2A</sub> receptor than at the D<sub>2</sub> receptor ([Meltzer and Massey 2011](#); [Meltzer et al. 1989, 2003](#)). This model, as laid out by [Stahl \(2013\)](#), is as follows: D<sub>2</sub> receptor antagonism in the mesolimbic pathway (projecting from the midbrain ventral tegmental area to the nucleus accumbens) reduces excessive dopamine signaling in the nucleus accumbens and reduces positive symptoms. However, D<sub>2</sub> receptor antagonism of the nigrostriatal pathway, which projects from the substantia nigra to the striatum of the basal ganglia, causes Parkinson-like involuntary

movements, dystonias, and other EPS. Clozapine's antagonism of the 5-HT<sub>2A</sub> receptor in the striatum results in increased local release of D<sub>2</sub>, which results in relief from the EPS caused by D<sub>2</sub> antagonism. Similarly, in the tuberoinfundibular tract, which projects from the hypothalamus to the anterior pituitary gland, D<sub>2</sub> antagonism causes increased prolactin secretion, resulting in gynecomastia, galactorrhea, amenorrhea, and decreased libido. Local 5-HT<sub>2A</sub> antagonism at the pituitary gland from SGAs increases local D<sub>2</sub> signaling and thus reverses the increase in prolactin secretion.

Although this characteristic of the SGAs may be associated with their relatively lower rates of EPS compared with FGAs, there is evidence that calls this into question. For instance, risperidone has high affinity for 5-HT<sub>2A</sub> receptors yet also has high rates of gynecomastia and galactorrhea. Also, quetiapine produces very few EPS but has no specificity for 5-HT<sub>2A</sub> receptors.

### **Low Percentage of D<sub>2</sub> Receptor Occupancy**

Clozapine and some other SGAs have been shown to occupy less than 60% of D<sub>2</sub> receptors at therapeutic doses, in contrast to the greater than 80% D<sub>2</sub> receptor binding of agents in the FGA class. This may explain the low rate of EPS with most SGAs.

### **Fast-Off D<sub>2</sub> Receptor Dissociation**

It has been proposed by [Kapur and Seeman \(2001\)](#) and others that it is the rapid dissociation of clozapine from the D<sub>2</sub> receptor that could give rise to its low occurrence of EPS and efficacy for psychosis. This fast dissociation, or

“loose binding,” characteristic allows clozapine to be displaced by endogenous dopamine, thus allowing more physiological signaling than during treatment with most other antipsychotics. In their 2001 review, Kapur and Seeman noted that if D<sub>2</sub> receptor occupancy was high, EPS occurred even in the presence of strong 5-HT<sub>2A</sub> antagonism, whereas rapid dissociation from the D<sub>2</sub> receptor in in vitro studies had the closest correlation with atypicality.

## Mechanisms of Clozapine's Exceptional Antipsychotic Efficacy

To date, clozapine remains the most effective antipsychotic in the clinician's arsenal. What could explain clozapine's superior efficacy? Let us examine two very similar antipsychotics, clozapine and its derivative quetiapine. Clozapine and quetiapine have very similar pharmacological profiles, have the highest dissociation constants from the D<sub>2</sub> receptor, have fast-off dynamics at the D<sub>2</sub> receptor, and have high binding affinity to the 5-HT<sub>2A</sub> receptor. However, the antipsychotic efficacy of quetiapine cannot match that of clozapine ([McEvoy et al. 2006](#)). What can explain clozapine's superior efficacy over all other antipsychotics? This remains one of the ongoing mysteries in the treatment of schizophrenia. A few theories are discussed in the next four subsections.

### **D<sub>1</sub>:D<sub>2</sub> Equivalent Occupancy**

The differences in efficacy between clozapine and quetiapine despite their similarities could be explained by

the differential D<sub>1</sub>:D<sub>2</sub> occupancy ratio between clozapine and the other members of the SGA class. In a positron emission tomography study using <sup>11</sup>C-SCH23390 and <sup>11</sup>C-raclopride to determine D<sub>1</sub> and D<sub>2</sub> receptor occupancy in patients with schizophrenia, clozapine was found to have the highest D<sub>1</sub>:D<sub>2</sub> receptor occupancy ratio (0.88), compared with olanzapine (0.54), quetiapine (0.41), and risperidone (0.31) ([Tauscher et al. 2004](#)).

### **D<sub>4</sub> Receptor Binding**

Clozapine also has a very high affinity for the dopamine 4 (D<sub>4</sub>) receptor. The D<sub>4</sub> receptor is widely distributed in the cortex and less so in striatal areas. Because of clozapine's specific high binding to D<sub>4</sub> receptors, it was thought this D<sub>4</sub> binding could be the unique characteristic giving clozapine its superior efficacy against psychosis. However, other agents with high D<sub>4</sub> receptor activity have failed to demonstrate antipsychotic activity.

### **Combination of Activity at Multiple Specific Receptor Types**

Of the theories just discussed, none individually can explain the unique efficacy of clozapine for psychosis. Another possibility is that the unique signature of clozapine's receptor binding profile among the dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors explains its unique efficacy. It is also possible that clozapine has unknown activity at other receptors such as glutamate, GABA, and neuropeptides receptors.

### **Metabolites**

It has been thought that clozapine's primary metabolite, NDMC, or norclozapine, may have a role in its antipsychotic effect, because it represents 10%–90% of circulating active drug in patient serum ([Wenthur and Lindsley 2013](#)). However, trials of norclozapine have not demonstrated antipsychotic efficacy.

---

## Indications and Efficacy

---

### Acute Schizophrenia and Schizoaffective Disorder

Because of its side-effect profile, clozapine should not be administered as a first-line agent for schizophrenia or schizoaffective disorder. However, it should be considered a second- or third-line agent. In a recent meta-analysis of 15 antipsychotics that included 43,049 patients and considered often-used antipsychotics including olanzapine, risperidone, haloperidol, quetiapine, and aripiprazole, clozapine was found to be the most effective antipsychotic based on change in symptoms ([Leucht et al. 2013](#)).

### Treatment-Refractory Schizophrenia

Early studies suggested that clozapine was particularly effective in patients with more severe treatment-refractory forms of schizophrenia. This was important when it was discovered that clozapine was associated with a risk of agranulocytosis. Given that clozapine was viewed as an agent that might be helpful for patients who had not

responded to other antipsychotics, a study was designed to test whether there was a role for clozapine in this population. The result was the design of a multicenter study comparing clozapine with chlorpromazine in severely ill patients with treatment-refractory schizophrenia ([Kane et al. 1988](#)). Treatment-refractory illness was characterized on the basis of a history of drug nonresponsiveness and a lack of improvement during a 6-week trial of up to 60 mg of haloperidol. Treatment with clozapine resulted in greater improvement in nearly every dimension of psychopathology. Thirty percent of the clozapine-treated patients met stringent improvement criteria, compared with only 4% of those treated with chlorpromazine.

Other studies suggest that the proportion of patients improving with clozapine treatment will be higher if clozapine is continued for a longer time. For example, a 16-week trial by [Pickar et al. \(1992\)](#) found a 38% improvement rate. A more recent report ([Kane et al. 2001](#)) found that 60% of patients with treatment-refractory illness improved after a 29-week trial of clozapine.

Two large trials compared clozapine with SGAs in patients with treatment-resistant illness. In the United States, the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) compared clozapine with risperidone, olanzapine, or quetiapine in patients with schizophrenia who had not shown a positive response in an earlier phase of the study because of a lack of efficacy ([Stroup et al. 2006](#)). Clozapine was administered open-label, whereas the other antipsychotics were administered double-blind. Patients assigned to clozapine had the lowest discontinuation rates, with 56% of patients taking clozapine discontinuing treatment, compared with 71% of those taking olanzapine,

86% of those taking risperidone, and 93% of those taking quetiapine. Clozapine-treated patients also showed greater symptom improvement than those receiving the other agents. Another trial in the United Kingdom, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study—band 2 (CUtLASS-2) ([Lewis et al. 2006](#)), randomly assigned 136 patients who had responded poorly to two prior antipsychotics to either clozapine or an SGA selected prior to the randomization. Patients who received clozapine demonstrated greater improvement than those taking the comparison drugs.

A large body of evidence indicates that clozapine has an important role in the treatment of patients who have not responded to either FGAs or other SGAs. Clozapine's advantages are clearest in patients who have not responded to FGAs, but they are still apparent in those who have had an inadequate response to other SGAs. Because clozapine is associated with a risk of agranulocytosis and other side effects (summarized in this chapter in the section "Side Effects and Toxicology"), patients should probably receive a trial of one or two other SGAs before receiving a trial of clozapine. Clinical guidelines ([Lehman et al. 2004a, 2004b](#); [Marder et al. 2002](#); [Miller et al. 2004](#)) differ to a minor degree on the number of trials that should precede a trial with clozapine, but most recommend at least two agents, one of which is an SGA. There is a consensus that patients should not be considered to have treatment-refractory illness until they have received an adequate treatment trial with clozapine.

# Hostile and Aggressive Behavior in Schizophrenia

Clozapine may have other advantages for patients with schizophrenia. A number of studies suggest that clozapine may decrease hostility and aggression, compared with other agents. In a study of 157 inpatients ([Citrome et al. 2001](#)), clozapine resulted in greater reductions in the hostility item from the Positive and Negative Syndrome Scale (PANSS) than did the FGAs and other SGAs. A study by [Chengappa et al. \(2003\)](#) found significant reductions in the rates of seclusion and restraint among patients with schizophrenia who received clozapine during the first 3 years after its introduction. Other randomized studies have consistently found that patients treated with clozapine exhibit less hostility and less aggressive behavior than patients taking comparators ([Essock et al. 2000](#); [Kane et al. 1988](#)). In an observational prospective study of outpatients, the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study, however, clozapine was not found to be superior to olanzapine, quetiapine, or risperidone monotherapy for reduction of hostile and aggressive behavior ([Bitter et al. 2005](#)). These findings suggest that clozapine may be of particular benefit to patients with treatment-refractory illness who demonstrate hostile and aggressive behavior, especially while on inpatient units.

## Schizophrenia Patients With High Suicide Risk



Clozapine may also be a preferred agent for patients with schizophrenia who are at a higher risk for suicide. Large epidemiological studies have found that mortality from suicide is reduced among individuals taking clozapine ([Reid et al. 1998](#); [Walker et al. 1997](#)). [Meltzer and Okayli \(1995\)](#) followed patients who were switched to clozapine and found a reduction in the number of serious suicide attempts as well as in expressed depression and hopelessness. One convincing study was a comparison of clozapine and olanzapine in 980 patients with schizophrenia who were considered at risk for suicide. In that study, clozapine was more effective in reducing the risk of suicide ([Meltzer 2002](#)). In a more recent Finnish study, SGAs were associated with decreased mortality in first-episode patients, whereas FGAs were associated with increased mortality. When clozapine, olanzapine, quetiapine, and risperidone were compared, only clozapine was found to have a strong antisuicide effect ([Kiviniemi et al. 2013](#)).

## Schizophrenia With Comorbid Substance Abuse

Although the effectiveness of clozapine in patients with comorbid substance abuse has not been demonstrated in randomized controlled trials, there is some supporting evidence from naturalistic studies. One retrospective study ([Green et al. 2003](#)) found that patients treated with clozapine were more likely than those treated with risperidone to abstain from alcohol and cannabis use. A prospective study ([Green et al. 2007](#)) found that patients treated with clozapine were often able to reduce their substance abuse. This finding was supported by other

prospective studies ([Brunette et al. 2006](#); [Drake et al. 2000](#)), indicating that clozapine is effective for reducing substance abuse.

## Mania in Bipolar Disorder

Given that all available antipsychotics are effective in reducing manic symptoms, it is not surprising that clozapine is effective for bipolar mania. However, accumulating evidence suggests that clozapine is particularly effective for manic symptoms that are not responsive to other agents. [McElroy et al. \(1991\)](#) were among the first to observe clozapine's unique effects in patients with bipolar disorder. Subsequent studies have confirmed clozapine's effectiveness as monotherapy and as a supplementation medication for mania in bipolar disorder. In an open-label randomized trial in acutely manic patients ([Barbini et al. 1997](#)), clozapine was as effective as chlorpromazine and had a more rapid onset of action. [Suppes et al. \(1999\)](#) randomly assigned patients with treatment-resistant schizoaffective or bipolar illness to either supplemental clozapine or treatment as usual during a 1-year open-label trial. Among both groups of patients, those treated with clozapine demonstrated greater improvement.

## Treatment-Resistant and Rapid-Cycling Bipolar Disorder

In addition to efficacy for mania, treatment-resistant schizophrenia, and treatment-resistant schizoaffective

disorder, there is evidence that clozapine is effective for treatment-resistant bipolar disorder as well. Interest was initially sparked when several case series demonstrated that clozapine reduced the number of inpatient hospitalizations, polypharmacy, and frequency of cycling in both psychotic and nonpsychotic treatment-resistant bipolar disorder, as well as rapid-cycling bipolar disorder ([Calabrese et al. 1991](#); [Frye et al. 1996](#); [Suppes et al. 1994](#)). Several open-label studies went on to demonstrate similar results: clozapine was effective and well tolerated in patients with treatment-resistant bipolar disorder ([Calabrese et al. 1996](#); [Ciapparelli et al. 2000](#); [Green et al. 2000](#)), although [Suppes et al. \(2004\)](#) later showed that patients with rapid-cycling treatment-resistant bipolar disorder were less responsive to clozapine than non-rapid-cycling patients. Psychotic bipolar disorder was not found to be more predictive of response than nonpsychotic bipolar disorder ([Gitlin 2006](#)). More recently, a 2-year retrospective study of 21,473 patients, of whom 326 were taking clozapine, found a decreased number of inpatient days and total psychotropic medication burden for those treated with clozapine ([Nielsen et al. 2012](#)). The only randomized, treatment-as-usual controlled study ([Suppes et al. 1999](#)) showed fewer hospitalizations and decreased polypharmacy for patients randomly assigned to receive clozapine compared with treatment as usual. The striking dearth of large-scale, randomized, double-blind studies for use of clozapine in bipolar disorder can be explained by clozapine's risk of dangerous effects including cardiomyopathy, seizures, and agranulocytosis; its compliance burden due to side-effect profile and regular blood draws; and absence of patent protection ([Gitlin 2006](#)).

# Depression With Psychotic Features

Limited evidence suggests that clozapine is effective as monotherapy and as an adjunctive treatment for patients with major depression with psychotic features. This evidence is currently confined to case reports with relatively small numbers of cases ([Ranjan and Meltzer 1996](#); [Rothschild 1996](#)).

# Psychosis in Parkinson's Disease

Psychosis with delusions and hallucinations occurs in approximately 25% of patients with Parkinson's disease ([Wolters and Berendse 2001](#)). These symptoms frequently appear in patients who are receiving dopaminomimetic drugs, but they may also occur as a result of a cholinergic deficit. Three double-blind studies ([The French Clozapine Parkinson Study Group 1999](#); [Jones and Stoukides 1992](#); [The Parkinson Study Group 1999](#); [Pollak et al. 2004](#)) found that clozapine at doses as low as 25–50 mg was effective in reducing psychotic symptoms. Moreover, these doses were not associated with an increase in tremor and rigidity. A report from the American Academy of Neurology ([Miyasaki et al. 2006](#)) recommended clozapine as a preferred agent for psychosis in Parkinson's disease.

# Schizophrenia in Children and Adolescents

Two randomized controlled trials from the National Institute of Mental Health have evaluated the effectiveness

of clozapine in childhood-onset schizophrenia. The first ([Kumra et al. 1996](#)) compared clozapine and haloperidol in individuals with a mean age of about 14 years who had done poorly on FGAs. Clozapine was superior for both positive and negative symptoms. A more recent double-blind study ([Shaw et al. 2006](#)) compared clozapine and olanzapine in subjects with a mean age of about 12 years. The results from this study were less clear. Although there were substantial differences favoring clozapine, the differences were statistically significant only for negative symptoms. The small sample ( $n=12$  for clozapine and  $n=13$  for olanzapine) was a limiting factor for obtaining statistical significance. Both studies found that this younger population appeared to be particularly vulnerable to clozapine's side effects. Nevertheless, these studies suggest an important role for clozapine in younger patients with schizophrenia with refractory symptoms.

## Augmentation Strategies in Partial Responders to Clozapine

A number of studies have evaluated augmentation strategies for individuals who are partial responders to clozapine. A recent meta-analysis ([Sommer et al. 2012](#)) reviewed 29 double-blind randomized trials of agents used to augment the effects of clozapine. The most-studied antipsychotics added to clozapine were risperidone and aripiprazole, and the most-studied mood stabilizer was lamotrigine. Although some of the studies reported positive findings, none of the strategies was viewed as having adequate empirical support. Augmentation with electroconvulsive therapy has been shown to be more

promising, with a recent prospective, randomized study demonstrating a 50% response rate in patients treated with clozapine who received electroconvulsive therapy compared with those who received only clozapine ([Petrides et al. 2015](#)).

## Maintenance Therapy in Schizophrenia

Clozapine use has largely been confined to patients with treatment-refractory schizophrenia. As a result, clozapine has not been studied in traditional relapse prevention designs in which patients who are stable are randomly assigned to either clozapine or a comparator. Nevertheless, there are substantial data supporting clozapine's long-term effectiveness. [Breier et al. \(2000\)](#) evaluated the outcomes of 30 patients with schizophrenia who received clozapine for 1 year. Patients taking clozapine experienced fewer relapses and rehospitalizations than they did in the year prior to being changed to clozapine. A study in the state hospitals in Connecticut compared patients who were assigned to clozapine with patients who were maintained on their usual antipsychotics ([Essock et al. 2000](#)). Although clozapine did not result in a greater likelihood of hospital discharge, patients who were treated with clozapine had a higher likelihood of remaining in the community following discharge. This finding supports the observation that clozapine is associated with a reduced risk of relapse compared with conventional antipsychotics.

A study from the U.S. Department of Veterans Affairs Cooperative Studies Program compared haloperidol and clozapine in patients with treatment-refractory

schizophrenia ([Rosenheck et al. 1997](#)). This study was not designed as a relapse prevention trial but rather as a comparison of the two agents in individuals who were poor responders to conventional therapy. However, the 1-year study is somewhat informative about the usefulness of the two drugs in patients living in the community. Fifty-seven percent of the patients taking clozapine completed the study, compared with only 28% of the patients taking haloperidol ( $P<0.001$ ). Using 20% improvement on the PANSS as the criterion for response, the investigators found that 42% of patients treated with clozapine and 31% of patients treated with haloperidol were responders ( $P=0.09$ ). In addition, clozapine-treated patients had fewer mean days of hospitalization (143.8 days) compared with haloperidol-treated patients (168.1 days;  $P=0.03$ ).

## Other Indications

Clozapine may also help patients with polydipsia-hyponatremia syndrome ([Canuso and Goldman 1999](#)). Patients with this syndrome tend to intoxicate themselves through excessive water drinking, and the resultant hyponatremia may result in seizures.

Clozapine has historically been used to treat tardive dyskinesia (TD), although it has not been formally studied extensively for this purpose. In a 1991 review, Lieberman et al. reviewed eight small studies and conducted their own study of 30 patients with TD and found that in 50% of patients with TD, clozapine reduced their TD symptoms by approximately 43% ([Lieberman et al. 1991](#)). Other studies found equivocal results; however, in no study did clozapine cause TD to worsen. [Kimiagar et al. \(2012\)](#) found TD

symptoms were reversed with a combination of clozapine, clonazepam, and tetrabenazine. Clozapine's mechanism of action in reducing TD remains unknown.

---

## Side Effects and Toxicology

---

### Hematological Effects

The side effects of clozapine make it one of the most challenging medications for psychiatrists to prescribe. The main factor that limits its use is the potential serious side effect of agranulocytosis. Agranulocytosis is defined as a drop in absolute neutrophil count (ANC) to levels below 500/mm<sup>3</sup>. In 1975, there were 17 cases of agranulocytosis in Finland, and widespread use of the medication for the treatment of schizophrenia was temporarily halted ([Amsler et al. 1977](#); [de la Chapelle et al. 1977](#)).

Agranulocytosis is a potentially lethal side effect that occurs in less than 1% of patients treated in the United States ([Alvir et al. 1993](#)). In the United States, all patients who are taking clozapine are entered into a national registry known as the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program ([www.clozapinerems.com](http://www.clozapinerems.com)). Through this national registry, patients are prescribed the medication only if their ANC count shows no signs of clinically meaningful suppression ([Honigfeld 1996](#)). In a review of the morbidity and mortality of clozapine-treated patients ([Honigfeld et al. 1998](#)) over a 5-year period, 99,502 patients were registered through the previous Clozaril National Registry. Of these, 2,931 (2.95%) patients developed leukopenia (WBC count=3,500/mm<sup>3</sup>),



and 382 (0.38%) patients developed agranulocytosis (ANC  $<500/\text{mm}^3$ ). Twelve of the cases of agranulocytosis (0.012%) were fatal.

When clozapine treatment is discontinued upon identification of marked leukopenia, patients usually recover within 14-24 days and without any long-term consequences. However, rechallenging patients who have experienced agranulocytosis almost always leads to recurrence of the problem. The onset of the second episode is more aggressive than that of the first. In nine patients who were known to be rechallenged, the average time to onset of the second episode was 10 weeks shorter (14 weeks) than for the first episode (24 weeks) ([Safferman et al. 1992](#)). Agranulocytosis has been successfully treated by discontinuing the medication, providing supportive measures, and administering granulocyte colony-stimulating factor, a medication that is commonly prescribed to patients with medical illnesses that precipitate WBC count suppression ([Raison et al. 1994](#); [Weide et al. 1992](#); [Wickramanayake et al. 1995](#)).

In January 2006, Novartis and the FDA issued a notification to clinicians regarding modifications to the recommended monitoring schedule for patients receiving clozapine. In October 2015, these guidelines were updated under a unifying national registry, the Clozapine REMS Program. In order to prescribe clozapine, the prescribing physician, the dispensing pharmacy, and the patient must be registered with the REMS Program. Under the new monitoring guidelines, a patient beginning clozapine treatment must have a baseline ANC count of no less than  $1,500/\text{mm}^3$ , or  $1,000/\text{mm}^3$  if the patient has benign ethnic neutropenia. If during clozapine treatment a patient's ANC drops below  $1,000/\text{mm}^3$ , clozapine must be stopped; for

patients with benign ethnic neutropenia, treatment must be stopped if the ANC drops below 500/mm<sup>3</sup>. Weekly ANC levels must be obtained for 6 months, at which time the frequency can be reduced to every 2 weeks, provided that treatment and monitoring have not been interrupted and WBC counts and ANCs have remained within acceptable ranges. After 1 year, monitoring can be reduced to monthly blood tests.

## Cardiac Effects

Well-known side effects of clozapine on the cardiovascular system include tachycardia, bradycardia, syncope, and orthostatic hypotension. Tachycardia is thought to be attributable to the anticholinergic activity of the medication at the M<sub>2</sub> receptor, leading to vagal nerve inhibition, hypotension is due to  $\alpha$ -adrenergic blockade, and bradycardia is thought to be neurally mediated reflex bradycardia, also known as the vasovagal response. The forms of cardiovascular toxicity that are of greatest concern, however, are clozapine-associated myocarditis and cardiomyopathy. In January 2002, Novartis reported that there had been 213 cases of myocarditis, 85% of which occurred at recommended dosages of clozapine within the first 2 months of therapy ([Novartis 2002](#)). The presence of eosinophilia in many of the reported cases indicates that an immunoglobulin E (IgE)-mediated hypersensitivity reaction may be involved ([Kilian et al. 1999](#)). [Novartis \(2002\)](#) also reported 178 cases of clozapine-associated cardiomyopathy, 80% of which were in patients younger than 50 years. Almost 20% of the incidents resulted in death, an alarming figure that may reflect delay in diagnosis and treatment. A

later review spanning the years 1970 through 2004, however, indicated that overall the rate of potentially fatal cardiomyopathy or myocarditis was between 0.015% and 0.188%, low enough to justify continued treatment with clozapine ([Merrill et al. 2005](#)).

The detection of cardiac toxicity is challenging, because its manifestations (tachycardia, fatigue, and orthostatic hypotension) are frequently observed in clozapine-treated patients, particularly when alterations in dosage are made ([Lieberman and Safferman 1992](#)). [Alawami et al. \(2014\)](#) found in a 2014 review that cardiac toxicity in the form of cardiomyopathy occurred, on average, 14.4 months after initiation of treatment, indicating this potentially life-threatening condition could occur long after the greatest threat of other side effects such as agranulocytosis has passed. The poor specificity of signs for cardiac toxicity demands that patients with any personal or family history of heart disease be identified, and the threshold for medical evaluation of patients developing respiratory and cardiovascular symptoms must be low ([Wooltorton 2002](#)). Therefore, we recommend monitoring of erythrocyte sedimentation rate and/or C-reactive protein, eosinophil count, and troponins on a weekly basis for the first 4 weeks of therapy ([Freudenreich and McEvoy 2016](#)). The etiology of the myocarditis and cardiomyopathy remains unclear at this time.

For hypotension caused by clozapine, we also recommend a slow upward titration of the medication and monitoring of orthostatic vital signs during the first weeks of therapy. Patients should be educated about the risk of orthostatic hypotension and should be taught to rise slowly from supine positions. Concomitant treatment with  $\beta$ -blocking agents may be necessary for persistent tachycardia. However, the

use of  $\beta$ -blockers may exacerbate the hypotensive effects of clozapine and should be used cautiously.

## Metabolic Effects

### Weight Gain

Weight gain has been observed in both premarketing and postmarketing trials of clozapine ([Henderson 2001](#); [Simpson and Varga 1974](#); [Wirshing et al. 1998, 1999](#)). [Allison et al. \(1999\)](#) performed a meta-analysis of the weight-gain data in short-term trials of medications. The average weight gain observed with clozapine was 4.45 kg, which exceeded the weight gain observed with all of the other medications in the study, including the conventional agent thioridazine (3.19 kg), a medication known for its weight-gain liability. The weight gain observed with clozapine seems to occur for a prolonged period of time—up to 40 weeks. In one naturalistic study, [Henderson \(2001\)](#) observed patients in a clozapine clinic for 5 years and noted weight gain occurring for up to 46 months in some patients.

Phase II of CATIE provided an opportunity to compare weight gain among patients assigned to clozapine, olanzapine, risperidone, and quetiapine ([McEvoy et al. 2006](#)). The numbers of patients assessed in the analyses were small, with only 45 patients in the clozapine group, 17 in the olanzapine group, 14 in the quetiapine group, and 14 in the risperidone group. Although the differences in weight gain among these agents were not statistically significant, they were interesting, with patients taking clozapine gaining a mean of 0.5 lb per month, compared with 1.0 lb with olanzapine, 0.4 lb with quetiapine, and 0.5 lb with risperidone.

## Diabetes

The weight gain observed with clozapine can place patients at risk for significant health problems. Diabetes is naturally the most concerning potential sequela of this weight gain. Numerous case reports have linked clozapine with new-onset diabetes ([Wirshing et al. 1998](#)). In [Henderson's \(2001\)](#) naturalistic study of 81 patients observed over a 5-year period, 36.6% of the patients developed diabetes.

Patients treated with clozapine should be routinely screened for diabetes and other metabolic abnormalities, including raised lipid levels. Patients with risk factors for diabetes should be monitored more closely. Reports and clinical experience suggest that in a case of antipsychotic-associated diabetes or diabetic ketoacidosis, discontinuation of the antipsychotic agent may result in reversal of the hyperglycemia and diabetes. During clozapine therapy, we recommend monitoring fasting glucose, cholesterol, and lipids at baseline and every 6 months thereafter.

Prevention of weight gain with clozapine, through nutrition and diet counseling, is recommended. Caloric restriction and exercise for 30 minutes per day should be recommended. Screening questions by physicians that we find useful include the following: "Have you noticed if your belt or pants size has changed?" "Have you noticed an increase in thirst or urinary frequency?"

## Dyslipidemias

Clozapine treatment is associated with dyslipidemias, including elevations in triglycerides and cholesterol, particularly low-density lipoprotein cholesterol ([McEvoy et al. 2006](#); [Wirshing et al. 2002a](#)).

In 2004, in response to growing concern that the majority of antipsychotic medications may be associated with weight gain and other metabolic changes, the American Diabetes Association and other groups published a set of guidelines for monitoring weight, glucose, and lipids ([American Diabetes Association et al. 2004](#)). Also in 2004, a very comprehensive literature review was conducted by [Marder et al. \(2004\)](#) to provide guidance to clinicians regarding monitoring of weight, glucose, lipids, and other parameters of physical health in patients with schizophrenia. Labeling changes were made for all antipsychotic medications, including clozapine, regarding these metabolic risk factors.

## Seizures

A well-known side effect of clozapine treatment is the risk for seizures, which are thought to occur in 5%-10% of patients treated with this medication ([Welch et al. 1994](#)). The cause of seizures is unclear, but it is generally thought that rapid escalations in dosage and possibly high plasma levels of clozapine may account for the development of seizures ([Klimke and Klieser 1995](#)). Clozapine-associated seizures occur most often at dosages greater than 600 mg/day. The relationship between clozapine plasma levels and seizures is somewhat inconsistent in the literature ([Simpson and Cooper 1978](#); [Vailleau et al. 1996](#)).

The anticonvulsant agents sodium valproate, gabapentin, and topiramate have been used successfully to treat clozapine-induced seizures ([Navarro et al. 2001](#); [Toth and Frankenburg 1994](#); [Usiskin et al. 2000](#)). Topiramate has an advantage over sodium valproate in that it is associated with very little weight gain. In cases in our clinic where

patients have developed seizures while taking clozapine, we institute rapid loading with anticonvulsant medication and temporarily discontinue the clozapine treatment. We then slowly reintroduce and retitrate the clozapine once the patient is taking an adequate dose of anticonvulsant medication.

## Anticholinergic Effects

Anticholinergic side effects resulting from clozapine's muscarinic receptor antagonism include sedation, weight gain, dry mouth, constipation, and, in some cases, ileus and/or bowel obstruction. Constipation can be a difficult but important side effect to manage in severely mentally ill individuals, who may not complain about the problem until a medical emergency, such as acute bowel obstruction, occurs. In institutional settings and in prisons, where patients may have little access to exercise and where monitoring of patients' fluid intake is not performed, constipation from clozapine can be serious or even fatal ([Drew and Herdson 1997](#); [Hayes and Gibler 1995](#); [Levin et al. 2002](#)). Typically, constipation can be avoided by proactive modifications in patients' diets and education about adequate fluid intake and exercise. The medical treatment that we favor is prophylactic therapy with sorbitol. We are less inclined to recommend treatments involving bulking agents, particularly in the setting of poor fluid intake. High-fiber diets can also be beneficial.

## Other Side Effects

Sedation is one of the most common and difficult side effects of clozapine to manage. Patients with sedation often do not want their dosages increased and will complain of sedation as one of the most annoying consequences of clozapine treatment ([Angermeyer et al. 2001](#)). In our experience, sedation is usually the limiting factor controlling both the rate at which the dose of clozapine can be increased and the maximum dosage the patient can tolerate. However, no rigorous studies have been published.

There have been several reports of respiratory arrest or depression during the early stages of treatment with clozapine ([Novartis 2002](#)). Two of the patients who experienced respiratory arrest were concomitantly taking benzodiazepines.

Sialorrhea is a commonly reported side effect of clozapine (occurring in over 50% of patients) that can be problematic for patients. The etiology of sialorrhea is unclear, but the condition does not seem to be caused by the dopamine blockade. It may be mediated through  $\alpha$ -adrenergic receptor blockade. Case series and small pilot studies indicate that treating sialorrhea with antiadrenergic agents, such as the clonidine patch, or anticholinergic agents, such as benztropine and intranasal ipratropium bromide, or atropine ophthalmic drops administered sublingually, may be successful ([Calderon et al. 2000](#)). We generally recommend that patients sleep with a towel on their pillow, as this side effect seems to be most bothersome during the night. Unfortunately, the use of concomitant antiadrenergic or anticholinergic agents adds to the potential side-effect burdens of hypotension and constipation, respectively.

Neuroleptic malignant syndrome, a syndrome of unknown etiology that includes hyperthermia, autonomic instability,



and severe rigidity, has been reported in several patients treated with clozapine ([Anderson and Powers 1991](#)). The etiology of neuroleptic malignant syndrome that occurs in the context of clozapine use, as well as that occurring with use of conventional antipsychotics, remains unclear.

Hepatotoxicity has been reported with clozapine, especially in the setting of polypharmacy ([Macfarlane et al. 1997](#); [Wirshing et al. 1997](#)). Asymptomatic elevation of transaminase levels was observed most commonly, affecting between 30% and 50% of patients treated with clozapine. Icteric hepatitis was uncommonly seen in [Macfarlane et al.'s \(1997\)](#) review of clozapine-related hepatotoxicity and was noted in 84 of 136,000 patients (0.06%). Fatal acute fulminant hepatitis has been documented in 2 patients (0.001%). Although serious toxicity is rare, prescribers of clozapine should be aware of its hepatotoxic potential.

Sexual side effects, including priapism and impotence, have been reported with clozapine. Urinary retention and bladder dysfunction can also result from treatment with clozapine. In a study surveying patients' sexual side effects, we found that clozapine-treated patients actually had fewer sexual complaints than patients on other antipsychotic medications (e.g., fluphenazine, risperidone) ([Wirshing et al. 2002b](#)).

Clozapine has been shown to induce de novo obsessive-compulsive symptoms (OCS). In a naturalistic study following 543 patients, 38.9% of patients taking clozapine reported OCS, compared with 20.1% taking olanzapine and 23.2% taking risperidone ([Scheltema Beduin et al. 2012](#)). A report of two case studies of patients with bipolar disorder taking clozapine demonstrated clearly a temporal relationship between initiation of clozapine and OCS ([Lemke and Bustillo 2013](#)). [Schirmbeck and Zink \(2012\)](#)

recommend reduction of clozapine dose after augmentation with a mood stabilizer and possibly crossover to or addition of a non-OCD-inducing antipsychotic; however, there is no evidence as yet to support these approaches.

Although this daunting array of side effects—along with the management of the risk of agranulocytosis—makes the treatment of patients with clozapine complex, it is common for patients to report a sense of relief from the dysphoric moods they experienced while taking conventional antipsychotics. Additionally, the freedom from EPS may account for the enhanced sense of well-being in patients treated with clozapine.

## Discontinuation and Reinitiation (Rechallenge)

As summarized in their 2013 review, Nielsen et al. posit that clozapine should be discontinued in all cases of agranulocytosis ( $\text{ANC} < 500/\text{mm}^3$ ), myocarditis, and cardiomyopathy and not discontinued for known benign side effects such as eosinophilia, benign neutrophilia or leukocytosis, idiopathic sinus tachycardia, or benign hyperthermia (Nielsen et al. 2013). Seizures should not be an absolute contraindication to clozapine treatment, because they may be managed by initiation of an anticonvulsant either prophylactically prior to initiation of clozapine or by stabilization of seizures prior to initiation of clozapine.

Historically, if a patient's WBC count decreased below  $2,000/\text{mm}^3$  or their ANC decreased below  $1,000/\text{mm}^3$ , clozapine was discontinued and the patient was regarded as nonrechallengeable; that is, reinitiation of clozapine

should not be attempted. With new FDA regulations implemented in October 2015, clinicians were given the freedom to evaluate each patient on a case-by-case basis and to weigh the relative risk of psychosis with risk of agranulocytosis. If and when a clinician opts to restart clozapine in any patient, regardless of the circumstance, they must begin at 12.5 mg orally once or twice daily and titrate upward gradually. If the patient has not experienced adverse effects from clozapine in the past, the reinitiation dose may be titrated upward more rapidly than their initial titration.

---

## Drug-Drug Interactions

---

As mentioned in the section “Pharmacokinetics and Disposition,” clozapine is predominately metabolized by CYP1A2, although CYP2D6 and CYP3A3/4 also contribute to its metabolism (Buur-Rasmussen and Brøsen 1999). Smoking, which induces CYP1A2, lowers clozapine plasma levels, and up to two times normal doses of clozapine may be required to maintain a therapeutic serum level. Fluvoxamine and ciprofloxacin, potent inhibitors of CYP1A2, dramatically increase plasma levels of clozapine (Heeringa et al. 1999; see also the FDA table “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers” at [www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)), and on occasion, adverse effects are seen (Koponen et al. 1996). Other reports suggest that inhibitors of CYP2D6, including paroxetine and fluoxetine, can elevate clozapine

levels ([Joos et al. 1997](#); [Spina et al. 1998](#)). In general, if the patient initiates a strong CYP1A2 inhibitor, use one-third of their normal dose. For moderate or weak CYP1A2 inhibitors, or CYP2D6 or CYP3A3/4 inhibitors, consider decreasing their dose. If they initiate strong CYP3A3/4 inducers, or moderate or weak CYP1A2 inducers, monitor for decreased effectiveness and consider increasing their clozapine dose if necessary. Cytochrome-related problems can be avoided by monitoring clozapine plasma levels while gradually increasing clozapine from a low starting dose.

---

## Conclusion

---

Clozapine maintains an important place in the treatment of severe psychosis. Side effects, including agranulocytosis, cardiomyopathy, seizures, sedation, and weight gain, make it the most difficult antipsychotic to prescribe. For this reason, clozapine should be reserved for patients who have not responded to one or more other antipsychotics. On the whole, however, this very effective treatment is underutilized in most communities. This is unfortunate, because patients' conditions should never be labeled treatment refractory or patients deemed partial responders until they have received an adequate trial of clozapine.

---

## References

---

Alawami M, Wasywich C, Cicovic A, Kenedi C: A systematic review of clozapine induced cardiomyopathy. *Int J Cardiol* 176(2):315-320, 2014 25131906

- Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156(11):1686-1696, 1999 10553730
- Alvir JM, Lieberman JA, Safferman AZ, et al: Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* 329(3):162-167, 1993 8515788
- American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity: Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 27(2):596-601, 2004 14747245
- Amsler HA, Teerenhovi L, Barth E, et al: Agranulocytosis in patients treated with clozapine. A study of the Finnish epidemic. *Acta Psychiatr Scand* 56(4):241-248, 1977 920225
- Anderson ES, Powers PS: Neuroleptic malignant syndrome associated with clozapine use. *J Clin Psychiatry* 52(3):102-104, 1991 2005071
- Angermeyer MC, Löffler W, Müller P, et al: Patients' and relatives' assessment of clozapine treatment. *Psychol Med* 31(3):509-517, 2001 11305859
- Ashby CRJ Jr, Wang RY: Pharmacological actions of the atypical antipsychotic drug clozapine: a review. *Synapse* 24(4):349-394, 1996 10638826
- Barbini B, Scherillo P, Benedetti F, et al: Response to clozapine in acute mania is more rapid than that of chlorpromazine. *Int Clin Psychopharmacol* 12(2):109-112, 1997 9219046
- Bell R, McLaren A, Galanos J, et al: The clinical use of plasma clozapine levels. *Aust N Z J Psychiatry* 32(4):567-574, 1998 9711372
- Bitter I, Czobor P, Dossenbach M, et al: Effectiveness of clozapine, olanzapine, quetiapine, risperidone, and haloperidol monotherapy in reducing hostile and

aggressive behavior in outpatients treated for schizophrenia: a prospective naturalistic study (IC-SOHO). *Eur Psychiatry* 20(5-6):403-408, 2005 16084068

Breier A, Buchanan RW, Irish D, et al: Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. 1993. *Psychiatr Serv* 51(10):1249-1253, 2000 11013322

Brunette MF, Drake RE, Xie H, et al: Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 32(4):637-643, 2006 16782758

Buur-Rasmussen B, Brøsen K: Cytochrome P450 and therapeutic drug monitoring with respect to clozapine. *Eur Neuropsychopharmacol* 9(6):453-459, 1999 10625111

Calabrese JR, Meltzer HY, Markovitz PJ: Clozapine prophylaxis in rapid cycling bipolar disorder. *J Clin Psychopharmacol* 11(6):396-397, 1991 1770164

Calabrese JR, Kimmel SE, Woyshville MJ, et al: Clozapine for treatment-refractory mania. *Am J Psychiatry* 153(6):759-764, 1996 8633686

Calderon J, Rubin E, Sobota WL: Potential use of ipatropium bromide for the treatment of clozapine-induced hypersalivation: a preliminary report. *Int Clin Psychopharmacol* 15(1):49-52, 2000 10836287

Canuso CM, Goldman MB: Clozapine restores water balance in schizophrenic patients with polydipsia-hyponatremia syndrome. *J Neuropsychiatry Clin Neurosci* 11(1):86-90, 1999 9990561

Chengappa KN, Goldstein JM, Greenwood M, et al: A post hoc analysis of the impact on hostility and agitation of quetiapine and haloperidol among patients with schizophrenia. *Clin Ther* 25(2):530-541, 2003 12749512

Ciapparelli A, Dell'Osso L, Pini S, et al: Clozapine for treatment-refractory schizophrenia, schizoaffective

- disorder, and psychotic bipolar disorder: a 24-month naturalistic study. *J Clin Psychiatry* 61(5): 329–334, 2000 10847306
- Citrome L, Volavka J, Czobor P, et al: Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. *Psychiatr Serv* 52(11):1510–1514, 2001 11684748
- Crilly J: The history of clozapine and its emergence in the US market: a review and analysis. *Hist Psychiatry* 18(1):39–60, 2007 17580753
- de la Chapelle A, Kari C, Nurminen M, et al: Clozapine-induced agranulocytosis. A genetic and epidemiologic study. *Hum Genet* 37(2):183–194, 1977 885538
- Drake RE, Xie H, McHugo GJ, et al: The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophr Bull* 26(2):441–449, 2000 10885642
- Drew L, Herdson P: Clozapine and constipation: a serious issue. *Aust N Z J Psychiatry* 31(1):149–150, 1997 9088503
- Essock SM, Frisman LK, Covell NH, et al: Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals. *Arch Gen Psychiatry* 57(10):987–994, 2000 11015817
- Fernández E, Carrizo E, Connell L, et al: Pro12Ala polymorphism of the PPAR-gamma2 gene, metabolic syndrome and response to metformin in clozapine-treated patients. *Schizophr Res* 137(1–3):262–263, 2012 22377103
- The French Clozapine Parkinson Study Group: Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* 353(9169):2041–2042, 1999 10376627
- Freudenreich O, McEvoy J: Guidelines for prescribing clozapine in schizophrenia. UptoDate. Edited by Post TW. March 2016. Available at: <http://www.uptodate.com/contents/guidelines-for->

[prescribing-clozapine-in-schizophrenia](#). Accessed March 31, 2016.

Frye MA, Altshuler LL, Bitran JA: Clozapine in rapid cycling bipolar disorder. *J Clin Psychopharmacol* 16(1):87-90, 1996 8834431

Geyer MA, Krebs-Thomson K, Braff DL, et al: Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology (Berl)* 156(2-3):117-154, 2001 11549216

Gitlin M: Treatment-resistant bipolar disorder. *Mol Psychiatry* 11(3):227-240, 2006 DOI: 10.1038/sj.mp.4001793 16432528

Green AI, Tohen M, Patel JK, et al: Clozapine in the treatment of refractory psychotic mania. *Am J Psychiatry* 157(6):982-986, 2000 10831480

Green AI, Burgess ES, Dawson R, et al: Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. *Schizophr Res* 60(1):81-85, 2003 12505141

Green AI, Drake RE, Brunette MF, et al: Schizophrenia and co-occurring substance use disorder. *Am J Psychiatry* 164(3):402-408, 2007 17329463

Griffith RW, Saameli K: Letter: Clozapine and agranulocytosis. *Lancet* 2(7936):657, 1975 52022

Hayes G, Gibler B: Clozapine-induced constipation. *Am J Psychiatry* 152(2):298, 1995 7840373

Heeringa M, Beurskens R, Schouten W, et al: Elevated plasma levels of clozapine after concomitant use of fluvoxamine. *Pharm World Sci* 21(5):243-244, 1999 10550852

Henderson DC: Clozapine: diabetes mellitus, weight gain, and lipid abnormalities. *J Clin Psychiatry* 62 (suppl 23):39-44, 2001 11603884

Hippius H: A historical perspective of clozapine. *J Clin Psychiatry* 60 (suppl 12):22-23, 1999 10372606



- Honigfeld G: Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis. *Psychiatr Serv* 47(1):52-56, 1996 8925346
- Honigfeld G, Arellano F, Sethi J, et al: Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 59 (suppl 3):3-7, 1998 9541331
- Iqbal MM, Rahman A, Husain Z, et al: Clozapine: a clinical review of adverse effects and management. *Ann Clin Psychiatry* 15(1):33-48, 2003
- Iskra J, Decker A: Halogenated Heterocycles: Synthesis, Application, and Environment. New York, Springer, 2012
- Javitt DC, Duncan L, Balla A, et al: Inhibition of system A-mediated glycine transport in cortical synaptosomes by therapeutic concentrations of clozapine: implications for mechanisms of action. *Mol Psychiatry* 10(3):275-287, 2005 15278098
- Jones KM, Stoukides CA: Clozapine in treatment of Parkinson's disease. *Ann Pharmacother* 26(11):1386-1387, 1992 1477443
- Joos AA, König F, Frank UG, et al: Dose-dependent pharmacokinetic interaction of clozapine and paroxetine in an extensive metabolizer. *Pharmacopsychiatry* 30(6): 266-270, 1997 9442550
- Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45(9): 789-796, 1988 3046553
- Kane JM, Marder SR, Schooler NR, et al: Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. *Arch Gen Psychiatry* 58(10):965-972, 2001 11576036
- Kapur S, Seeman P: Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? A new hypothesis. *Am J Psychiatry* 158(3): 360-369, 2001 11229973

- Kilian JG, Kerr K, Lawrence C, et al: Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 354(9193):1841–1845, 1999 10584719
- Kimiagar I, Dobronevsky E, Prokhorov T, et al: Rapid improvement of tardive dyskinesia with tetrabenazine, clonazepam and clozapine combined: a naturalistic long-term follow-up study. *J Neurol* 259(4):660–664, 2012 22068977
- Kiviniemi M, Suvisaari J, Koivumaa-Honkanen H, et al: Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. *Schizophr Res* 150(1):274–280, 2013 23953217
- Klimke A, Klieser E: [The atypical neuroleptic clozapine (Leponex)—current knowledge and recent clinical aspects]. *Fortschr Neurol Psychiatr* 63(5):173–193, 1995 7782019
- Koponen HJ, Leinonen E, Lepola U: Fluvoxamine increases the clozapine serum levels significantly. *Eur Neuropsychopharmacol* 6(1):69–71, 1996 8866941
- Kronig MH, Munne RA, Szymanski S, et al: Plasma clozapine levels and clinical response for treatment-refractory schizophrenic patients. *Am J Psychiatry* 152(2): 179–182, 1995 7840349
- Kumra S, Frazier JA, Jacobsen LK, et al: Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry* 53(12):1090–1097, 1996 8956674
- Lehman AF, Kreyenbuhl J, Buchanan RW, et al: The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. *Schizophr Bull* 30(2):193–217, 2004a 15279040
- Lehman AF, Lieberman JA, Dixon LB, et al: Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 161(2 suppl):1–56, 2004b 15000267

- Lemke NT, Bustillo JR: Clozapine-induced obsessive-compulsive symptoms in bipolar disorder. *Am J Psychiatry* 170(8):930, 2013 23903341
- Leucht S, Cipriani A, Spineli L, et al: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382(9896):951-962, 2013 23810019
- Levin TT, Barrett J, Mendelowitz A: Death from clozapine-induced constipation: case report and literature review. *Psychosomatics* 43(1):71-73, 2002 11927763
- Lewis SW, Barnes TR, Davies L, et al: Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull* 32(4):715-723, 2006 16540702
- Lieberman JA, Safferman AZ: Clinical profile of clozapine: adverse reactions and agranulocytosis. *Psychiatr Q* 63(1):51-70, 1992 1438605
- Lieberman JA, Saltz BL, Johns CA, et al: The effects of clozapine on tardive dyskinesia. *Br J Psychiatry* 158:503-510, 1991 1675900
- Macfarlane B, Davies S, Mannan K, et al: Fatal acute fulminant liver failure due to clozapine: a case report and review of clozapine-induced hepatotoxicity. *Gastroenterology* 112(5):1707-1709, 1997 9136851
- Marder SR, Essock SM, Miller AL, et al: The Mount Sinai conference on the pharmacotherapy of schizophrenia. *Schizophr Bull* 28(1):5-16, 2002 12047022
- Marder SR, Essock SM, Miller AL, et al: Physical health monitoring of patients with schizophrenia. *Am J Psychiatry* 161(8): 1334-1349, 2004 15285957
- McElroy SL, Dessain EC, Pope HG Jr, et al: Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* 52(10):411-414, 1991 1938976

- McEvoy JP, Lieberman JA, Stroup TS, et al; CATIE Investigators: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 163(4):600-610, 2006 16585434
- Meltzer HY: Suicidality in schizophrenia: a review of the evidence for risk factors and treatment options. *Curr Psychiatry Rep* 4(4):279-283, 2002 12126596
- Meltzer HY, Massey BW: The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr Opin Pharmacol* 11(1):59-67, 2011 21420906
- Meltzer HY, Okayli G: Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry* 152(2):183-190, 1995 7840350
- Meltzer HY, Shigehiro M, Lee J-C: Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2, and serotonin<sub>2</sub> pKi values. *J Pharmacol Exp Ther* 251:238-246, 1989 2571717
- Meltzer HY, Li Z, Kaneda Y, et al: Serotonin receptors: their key role in drugs to treat schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 27(7):1159-1172, 2003 14642974
- Merrill DB, Dec GW, Goff DC: Adverse cardiac effects associated with clozapine. *J Clin Psychopharmacol* 25(1):32-41, 2005 15643098
- Miller A, Hall CS, Buchanan RW, et al: The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. *J Clin Psychiatry* 65(4):500-508, 2004 15119912
- Miller DD: The clinical use of clozapine plasma concentrations in the management of treatment-refractory schizophrenia. *Ann Clin Psychiatry* 8(2):99-109, 1996 8807035

- Miller DD, Fleming F, Holman TL, et al: Plasma clozapine concentrations as a predictor of clinical response: a follow-up study. *J Clin Psychiatry* 55 (suppl B):117-121, 1994 7961554
- Miyasaki JM, Shannon K, Voon V, et al; Quality Standards Subcommittee of the American Academy of Neurology: Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 66(7):996-1002, 2006 16606910
- Moore TR, Hill AM, Panguluri SK: Pharmacogenomics in psychiatry: implications for practice. *Recent Pat Biotechnol* 8(2):152-159, 2014 25185985
- Navarro V, Pons A, Romero A, et al: Topiramate for clozapine-induced seizures. *Am J Psychiatry* 158(6):968-969, 2001 11384919
- Nielsen J, Kane JM, Correll CU: Real-world effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. *Bipolar Disord* 14(8):863-869, 2012 23107278
- Nielsen J, Correll CU, Manu P, et al: Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? *J Clin Psychiatry* 74(6):603-613, quiz 613, 2013 23842012
- Novartis: Clozaril (Clozapine) Tablets: Prescribing Information. Hanover, NJ, Novartis Pharmaceuticals, 2002
- The Parkinson Study Group: Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 340(10):757-763, 1999 10072410
- Petrides G, Malur C, Braga RJ, et al: Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry* 172(1):52-58, 2015 25157964

- Pickar D, Owen RR, Litman RE, et al: Clinical and biologic response to clozapine in patients with schizophrenia. Crossover comparison with fluphenazine. Arch Gen Psychiatry 49(5):345-353, 1992 1375019
- Pollak P, Tison F, Rascol O, et al: Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry 75(5):689-695, 2004 15090561
- Potkin SG, Bera R, Gulasekaram B, et al: Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. J Clin Psychiatry 55 (9 suppl B):133-136, 1994 7961557
- Poyurovsky M, Pashinian A, Levi A, et al: The effect of betahistine, a histamine H1 receptor agonist/H3 antagonist, on olanzapine-induced weight gain in first-episode schizophrenia patients. Int Clin Psychopharmacol 20(2):101-103, 2005 15729086
- PubChem Compound Database, National Center for Biotechnology Information: Clozapine. March 2016a. Available at: <https://pubchem.ncbi.nlm.nih.gov/compound/2818>. Accessed March 31, 2016.
- PubChem Compound Database, National Center for Biotechnology Information: Loxapine. March 2016b. Available at: <https://pubchem.ncbi.nlm.nih.gov/compound/3964>. Accessed March 31, 2016.
- Raison CL, Guze BH, Kissell RL: Successful treatment of clozapine-induced agranulocytosis with granulocyte colony-stimulating factor. J Clin Psychopharmacol 14(4):285-286, 1994 7525662
- Ranjan R, Meltzer HY: Acute and long-term effectiveness of clozapine in treatment-resistant psychotic depression. Biol Psychiatry 40(4):253-258, 1996 8871771
- Reid WH, Mason M, Hogan T: Suicide prevention effects associated with clozapine therapy in schizophrenia and

- schizoaffective disorder. *Psychiatr Serv* 49(8):1029-1033, 1998 9712207
- Rosenheck R, Cramer J, Xu W, et al; Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia: A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. *N Engl J Med* 337(12):809-815, 1997 9295240
- Rothschild AJ: Management of psychotic, treatment-resistant depression. *Psychiatr Clin North Am* 19(2):237-252, 1996 8827188
- Safferman AZ, Lieberman JA, Alvir JM, et al: Rechallenge in clozapine-induced agranulocytosis (letter). *Lancet* 339(8804):1296-1297, 1992 1349691
- Scheltema Beduin AA, Swets M, Machielsen M, et al; Genetic Risk and Outcome of Psychosis Investigators: Obsessive-compulsive symptoms in patients with schizophrenia: a naturalistic cross-sectional study comparing treatment with clozapine, olanzapine, risperidone, and no antipsychotics in 543 patients. *J Clin Psychiatry* 73(11):1395-1402, 2012 23218156
- Schirmbeck F, Zink M: Clozapine-induced obsessive-compulsive symptoms in schizophrenia: a critical review. *Curr Neuropharmacol* 10(1):88-95, 2012 22942882
- Seeman P: Clozapine, a fast-off-D2 antipsychotic. *ACS Chem Neurosci* 5(1):24-29, 2014 24219174
- Shaw P, Sporn A, Gogtay N, et al: Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry* 63(7):721-730, 2006 16818861
- Simpson GM, Cooper TA: Clozapine plasma levels and convulsions. *Am J Psychiatry* 135(1):99-100, 1978 412427
- Simpson GM, Varga E: Clozapine—a new antipsychotic agent. *Curr Ther Res Clin Exp* 16(7):679-686, 1974 4210457

- Sommer IE, Begemann MJ, Temmerman A, et al: Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: a quantitative literature review. *Schizophr Bull* 38(5):1003–1011, 2012 21422107
- Spina E, Avenoso A, Facciola G, et al: Effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia. *Int Clin Psychopharmacol* 13(3):141–145, 1998 9690983
- Sriretnakumar V, Huang E, Müller DJ: Pharmacogenetics of clozapine treatment response and side-effects in schizophrenia: an update. *Expert Opin Drug Metab Toxicol* 11(11):1709–1731, 2015 26364648
- Stahl SM: *Stahl's Essential Psychopharmacology*, 4 Edition. New York, Cambridge University Press, 2013
- Stroup TS, Lieberman JA, McEvoy JP, et al; CATIE Investigators: Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 163(4):611–622, 2006 16585435
- Suppes T, Phillips KA, Judd CR: Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: a report of three cases. *Biol Psychiatry* 36(5):338–340, 1994 7993960
- Suppes T, Webb A, Paul B, et al: Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. *Am J Psychiatry* 156(8):1164–1169, 1999 10450255
- Suppes T, Ozcan ME, Carmody T: Response to clozapine of rapid cycling versus non-cycling patients with a history of mania. *Bipolar Disord* 6(4):329–332, 2004 15225152
- Tauscher J, Hussain T, Agid O, et al: Equivalent occupancy of dopamine D1 and D2 receptors with clozapine:



- differentiation from other atypical antipsychotics. *Am J Psychiatry* 161(9):1620-1625, 2004 15337652
- Toth P, Frankenburg FR: Clozapine and seizures: a review. *Can J Psychiatry* 39(4): 236-238, 1994 8044732
- Tresadern G, Bartolome JM, Macdonald GJ, et al: Bioorganic and Medicinal Chemistry. *Bioorg Med Chem* 19(7):2231-2241, 2011 21421319
- Usiskin SI, Nicolson R, Lenane M, et al: Gabapentin prophylaxis of clozapine-induced seizures. *Am J Psychiatry* 157(3):482-483, 2000 10698845
- Vaillau JL, Jeanny B, Chomard P, et al: [Importance of determining clozapine plasma level in follow-up of schizophrenic patients]. *Encephale* 22(2):103-109, 1996 8706619
- Wadenberg ML: Conditioned avoidance response in the development of new antipsychotics. *Curr Pharm Des* 16(3):358-370, 2010 20109144
- Walker AM, Lanza LL, Arellano F, et al: Mortality in current and former users of clozapine. *Epidemiology* 8(6):671-677, 1997 9345668
- Weide R, Köppler H, Heymanns J, et al: Successful treatment of clozapine induced agranulocytosis with granulocyte-colony stimulating factor (G-CSF). *Br J Haematol* 80(4):557-559, 1992 1374635
- Welch J, Manschreck T, Redmond D: Clozapine-induced seizures and EEG changes. *J Neuropsychiatry Clin Neurosci* 6(3): 250-256, 1994 7950347
- Wenthur CJ, Lindsley CW: Classics in chemical neuroscience: clozapine. *ACS Chem Neurosci* 4(7):1018-1025, 2013 24047509
- Wickramanayake PD, Scheid C, Josting A, et al: Use of granulocyte colony-stimulating factor (filgrastim) in the treatment of non-cytotoxic drug-induced agranulocytosis. *Eur J Med Res* 1(3):153-156, 1995 9445760

- Wirshing DA, Spellberg BJ, Erhart SM, et al: Novel antipsychotics and new onset diabetes. *Biol Psychiatry* 44(8):778-783, 1998 9798083
- Wirshing DA, Wirshing WC, Kysar L, et al: Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 60(6):358-363, 1999 10401912
- Wirshing DA, Boyd JA, Meng LR, et al: The effects of novel antipsychotics on glucose and lipid levels. *J Clin Psychiatry* 63(10):856-865, 2002a 12416594
- Wirshing DA, Pierre JM, Marder SR, et al: Sexual side effects of novel antipsychotic medications. *Schizophr Res* 56(1-2):25-30, 2002b 12084416
- Wirshing WC, Ames D, Bisheff S, et al: Hepatic encephalopathy associated with combined clozapine and divalproex sodium treatment. *J Clin Psychopharmacol* 17(2):120-121, 1997 10950478
- Wolters EC, Berendse HW: Management of psychosis in Parkinson's disease. *Curr Opin Neurol* 14(4):499-504, 2001 11470967
- Wong AH, Josselyn SA: Caution when diagnosing your mouse with schizophrenia: the use and misuse of model animals for understanding psychiatric disorders. *Biol Psychiatry* 79:32-38, 2016 26058706
- Wooltorton E: Antipsychotic clozapine (Clozaril): myocarditis and cardiovascular toxicity. *CMAJ* 166(9):1185-1186, 2002 12000254

# CHAPTER 26

## Olanzapine

Amy L. Silberschmidt, M.D.

Jacob S. Ballon, M.D., M.P.H.

S. Charles Schulz, M.D.

---

### History and Discovery

---

The story of specific antipsychotic medications for patients with schizophrenia and other severe psychiatric illnesses began in the early 1950s, when chlorpromazine was first given to psychotic patients in France ([Delay and Bernitzer 1952](#)). The antipsychotic qualities of this compound, as well as its “tranquilizing” effect, were dramatic and substantial. Studies performed around the world during the 1950s showed the usefulness of this new compound and of the others that followed. As is well known, multicenter trials of antipsychotic medications found that the approved medications were substantially and significantly better than placebo ([Guttmacher et al. 1964](#)). Furthermore, despite the range of chemical structures, the clinical effects were

similar. In addition, the need to investigate the new medications for psychiatric illness led to improved clinical trial methodology for the field. During the 1960s, randomized and placebo-controlled trials became the standard for assessing the new medications for schizophrenia. These trials led to adoption of antipsychotic medications as the standard somatic treatment for schizophrenia.

However, over time, the adverse effects of these medications began to be recognized as more troublesome (Table 26-1). For example, many patients complained of medication-induced parkinsonism, dystonias, slowed thinking, blunted affect, akathisia, and tardive dyskinesia. These side effects were uncomfortable for patients taking the medications and, in many cases, led to poor treatment adherence.

---

**TABLE 26-1.    Shortcomings of traditional antipsychotic medications**

---

Significant response in only 60%–70% of patients
Movement disorder side effects
Dystonia
Parkinsonism
Tardive dyskinesia
Akathisia
Slowed thinking (“cognitive parkinsonism”)
Secondary negative symptoms

---

Looking for ways to achieve the same treatment benefit with fewer side effects, investigators at Eli Lilly began to screen numerous compounds for potentially useful

psychotropic properties. In 1990, the company applied for and received a patent for the compound olanzapine. It is interesting to note that the new compound had many structural similarities to clozapine, which in 1989 had been approved for use in treating refractory schizophrenia. Hailed as a novel second-generation antipsychotic drug, clozapine was thought to have potential for schizophrenia, mania, and anxiety. Clozapine was noted for its efficacy as well as its freedom from neurological side effects.

Olanzapine was first given to patients with schizophrenia in 1995 ([Baldwin and Montgomery 1995](#)). The patients in the study experienced a substantial decrease in their symptoms while receiving 5–30 mg/day of the compound. The study researchers noted a low degree of extrapyramidal side effects (EPS), although concern was raised regarding elevation of liver enzymes, as one patient had to discontinue the study for that reason.

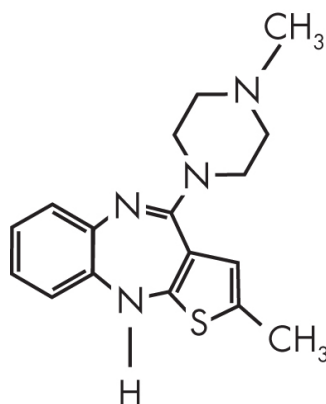
The initial testing of olanzapine had useful results and led to a program of three pivotal trials of the drug. These first three controlled studies compared olanzapine (at two fixed dosages: 1 mg/day and 10 mg/day) against placebo ([Beasley et al. 1996a](#)); olanzapine at three fixed dosages (low, medium, or high) against olanzapine at 1.0 mg/day or haloperidol at 15 mg/day or placebo ([Beasley et al. 1996b](#)); and olanzapine against haloperidol in a large international study ([Tollefson et al. 1997](#)). The positive results for olanzapine led to U.S. Food and Drug Administration (FDA) approval in 1997 and subsequent widespread use in the United States and around the world.

---

## Structure-Activity Relations

---

Olanzapine is a thienobenzodiazepine derivative that bears a close structural resemblance to clozapine. The formal chemical name of olanzapine is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. Structurally, olanzapine differs from clozapine by two additional methyl groups and the lack of a chloride moiety (Figure 26-1). The in vitro receptor binding profiles of olanzapine and clozapine are relatively similar. According to the package insert, olanzapine is known to have a high affinity for dopaminergic ( $D_{1-4}$ ), serotonergic (5-HT<sub>2A/2C</sub>, 5-HT<sub>6</sub>), histaminergic ( $H_1$ ), and  $\alpha$ -adrenergic ( $\alpha_1$ ) receptors, with moderate affinity for muscarinic ( $M_{1-5}$ ) receptors and weak activity at benzodiazepine,  $\gamma$ -amino-butyric acid type A (GABA<sub>A</sub>), and  $\beta$ -adrenergic receptors (Eli Lilly 2015).



**FIGURE 26-1.** Chemical structure of olanzapine.

---

## Pharmacological Profile

---

In vitro and preclinical behavioral studies of olanzapine predicted significant antipsychotic activity with a low propensity to induce EPS. Because clozapine is the

prototype for second-generation antipsychotic action, it serves as the yardstick for “atypicality” of comparator compounds. Despite widespread general use of the term *atypical* to refer to any antipsychotic developed after clozapine, the term was originally coined to connote medications with an EPS risk no greater than that of placebo. While it is true that olanzapine carries a lower risk of tardive dyskinesia than do many other antipsychotics, its risk is still appreciably greater than that of placebo, and therefore the term *atypical* does not apply ([Farah 2013](#)).

One property that may lower a compound’s risk of EPS is nonselective binding of dopamine receptors. Classical antipsychotics selectively block dopamine D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>) receptors over D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) receptors—for example, haloperidol has a D<sub>2</sub>-to-D<sub>1</sub> binding ratio of 25:1. Clozapine nonselectively binds all five dopamine receptor subtypes, with a D<sub>2</sub>-to-D<sub>1</sub> ratio of 0.7:1, whereas olanzapine is only partially selective for the D<sub>2</sub>-like group, with a D<sub>2</sub>-to-D<sub>1</sub> ratio of approximately 3:1, intermediate between those of haloperidol and clozapine.

In animal models predictive of antipsychotic efficacy, olanzapine produces effects indicating dopamine antagonism, with a low propensity to produce EPS. For example, in rats, olanzapine reduces climbing behavior induced by apomorphine and antagonizes stimulant-induced hyperactivity, both characteristic of antipsychotic effects. The ratio of the dose needed to produce catalepsy to the dose needed to inhibit conditioned avoidance, another model for atypical efficacy, is higher for olanzapine than for conventional agents ([Moore 1999](#)).

Another potential mechanism whereby dopamine antagonists may exert antipsychotic effects with minimal

EPS is through selective activity in the A10 dopaminergic tracts from the ventral tegmentum to mesolimbic areas compared with effects antagonizing the A9 nigrostriatal projections that mediate EPS. Olanzapine in chronic administration, like clozapine, selectively inhibits firing of A10 neurons without significant inhibition of A9 tracts ([Stockton and Rasmussen 1996a](#)). Olanzapine shows increased c-fos activity in the nucleus accumbens relative to the dorsolateral striatum, thus demonstrating selective blockade of the mesolimbic dopamine tract compared with the nigrostriatal tract ([Robertson and Fibiger 1996](#)).

A leading theory regarding atypicality relates to the fleeting effects of atypical antipsychotics at the D<sub>2</sub> receptor, coupled with regional selectivity of these compounds ([Seeman 2002](#)). Olanzapine's D<sub>2</sub> receptor occupancy saturation—which has been shown to be intermediate between that of clozapine and that of haloperidol—may be responsible for its decreased risk of EPS ([Tauscher et al. 1999](#)). However, because the current second-generation antipsychotic medications have substantially differing effects at many of the targets thought to play a role in atypicality, there is not yet consensus regarding the true rationale for atypicality in these agents compared with the first-generation antipsychotics ([Farah 2005](#)).

Amphetamine administration in rats is often used as a model for psychosis. The sympathomimetic activity and dopamine release provide a target for testing antipsychotic medications. Olanzapine disrupts the activity of amphetamines in rats ([Gosselin et al. 1996](#)). Olanzapine was shown in a rat model to decrease dopamine release in the A10 dopaminergic neurons of the ventral tegmentum greater than the A9 dopaminergic neurons of the striatum after chronic administration and after an amphetamine



challenge ([Stockton and Rasmussen 1996a, 1996b](#)). Olanzapine does not induce catalepsy in rats at doses needed for antipsychotic efficacy.

Another model of psychosis in rats is produced by administration of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP). Chronic PCP use in humans is associated with symptoms similar to those in schizophrenia, including negative symptoms, thus making it a putative model for schizophrenia ([Krystal et al. 1994](#)). Olanzapine has been shown to decrease the hyperactivity of NMDA receptors under chronic PCP administration, which may have a bearing on its effect on negative symptoms ([Ninan et al. 2003](#)). With chronic administration, glutamatergic activity continues to be affected by olanzapine ([Jardemark et al. 2000](#)). Despite these findings, olanzapine has no direct affinity for the NMDA receptor ([Stephenson and Pilowsky 1999](#)).

Receptor-binding studies show that olanzapine has a broad range of neurotransmitter effects ([Bymaster et al. 1996](#)). Although olanzapine has potent muscarinic  $M_{1-5}$  receptor affinity in vitro (another contributor to putative anti-EPS effects), in practice few olanzapine-treated patients have anticholinergic side effects that are clinically significant.  $\alpha_1$ -Adrenergic and  $H_1$  histaminergic antagonism contribute to olanzapine's adverse-effect profile of orthostatic hypotension ( $\alpha_1$ ), sedation ( $H_1$ ), and possibly weight gain ( $H_1$ ). Olanzapine, like other second-generation antipsychotics, has a higher affinity for 5-HT<sub>2</sub> receptors than for D<sub>2</sub> receptors ([Kapur et al. 1999](#)). There is also indirect evidence that olanzapine blocks 5-HT<sub>2C</sub> receptors ([Sharpley et al. 2000](#)). Olanzapine has little or no effect on

$\alpha_2$ - and  $\beta$ -adrenergic,  $H_2$ , nicotinic, GABA, opioid, sigma, or benzodiazepine receptors.

---

## Pharmacokinetics and Disposition

---

Olanzapine is well absorbed after oral administration, with peak concentrations typically occurring 4–6 hours after ingestion ([Kassahun et al. 1997](#)). Approximately 40% of a given dose undergoes first-pass metabolism and therefore does not reach the systemic circulation, and food has little effect on olanzapine's bioavailability ([Callaghan et al. 1999](#); [Eli Lilly 2015](#); [Kassahun et al. 1997](#)).

Two bioequivalent oral formulations of olanzapine are currently available: a standard oral tablet and an oral disintegrating tablet. The oral disintegrating tablets are intended for swallowing and absorption through the gut; however, sublingual administration has also been favored by some, as it allows the clinician to verify that the medication was taken. [Markowitz et al. \(2006\)](#) discovered that although the oral disintegrating preparation of olanzapine is absorbed more quickly than the standard oral tablet, this preparation's onset of effect is approximately the same regardless of whether it is taken sublingually or conventionally swallowed. In either case, the onset of action with the oral dissolving tablet is faster than that with the standard oral tablet. After a 12.5-mg oral dose of  $^{14}\text{C}$ -labeled olanzapine, approximately 57% of the radiocarbon is recovered in urine and 30% in feces. In vitro studies suggest that olanzapine is approximately 93% protein

bound, binding primarily to albumin and  $\alpha_1$ -acid glycoprotein ([Kassahun et al. 1997](#)).

Olanzapine is available as an intramuscular preparation, intended for treatment of the acute agitation typically seen in schizophrenia or in acute manic episodes of bipolar disorder. The peak plasma concentration is typically reached between 15 and 45 minutes after administration. The potency of intramuscular olanzapine is nearly five times greater than that of the orally administered drug, based on plasma levels. Clinical antipsychotic onset with intramuscular olanzapine is evident within 2 hours of administration, with benefits lasting for at least 24 hours ([Kapur et al. 2005](#)).

Olanzapine is also available in a long-acting injectable (LAI) preparation composed of a dihydrate form of olanzapine pamoate. As a dihydrate molecule, it is less soluble in water than a monohydrate and thus has the longer half-life required for a depot formulation. This formulation is designed to be dosed once every 4 weeks ([Mamo et al. 2008](#)).

Finally, olanzapine is available in a combined preparation with fluoxetine. The olanzapine-fluoxetine combination (OFC) tablet provides fixed doses of olanzapine and fluoxetine. Overall, few pharmacokinetic changes result from adding fluoxetine to olanzapine, and those that do occur are generally related to cytochrome P450 (CYP) 2D6 inhibition. There is no change in the overall half-life of olanzapine. Although minor yet statistically significant changes occur in the concentration of olanzapine when it is coadministered with fluoxetine, these changes are not *clinically* significant and do not alter the side-effect profile of olanzapine ([Gossen et al. 2002](#)).

Olanzapine is extensively metabolized to multiple metabolites, but primarily to 10-*N*-glucuronide and 4'-*N*-desmethylolanzapine ([Macias et al. 1998](#)). In vitro studies assessing the oxidative metabolism of olanzapine suggest that CYP1A2 is the enzyme primarily responsible for the formation of 4'-*N*-desmethylolanzapine, flavin-containing monooxygenase-3 (FMO3) is responsible for the formation of 4'-*N*-oxide olanzapine, and CYP2D6 is the primary enzyme responsible for the formation of 2-hydroxymethyl olanzapine ([Ring et al. 1996b](#)). Although CYP1A2 appears to be a major route of metabolism, olanzapine clearance in one study was not significantly correlated with salivary paraxanthine-to-caffeine ratio (thought to be a measure of CYP1A2 activity) ([Hägg et al. 2001](#)). Another analysis, however, found that the 4'-*N*-desmethylolanzapine-to-olanzapine plasma metabolic ratio significantly correlated with olanzapine clearance ([Callaghan et al. 1999](#)). Olanzapine pharmacokinetic parameters do not differ significantly between extensive and poor metabolizers of CYP2D6 (see [Hägg et al. 2001](#)).

Olanzapine shows linear pharmacokinetics within the recommended dosage range ([Aravagiri et al. 1997](#); [Bergstrom et al. 1995](#); [Callaghan et al. 1999](#)). Mean half-life is 36 hours, mean clearance is 29.4 L/hour, mean volume of distribution is 19.2 L/kg, and area under the concentration-time curve over 24 hours ( $AUC_{0-24}$ ) is 333 ng\*hour/mL. The half-lives of the two major metabolites (4'-*N*-desmethylolanzapine and 10-*N*-glucuronide) are 92.6 and 39.6 hours, respectively ([Macias et al. 1998](#)). Other analyses also have found the mean half-life of olanzapine to be approximately 30 hours and the mean apparent clearance to be approximately 25 L/hour ([Callaghan et al. 1999](#); [Eli Lilly 2015](#); [Kassahun et al. 1997](#)). Once-daily

administration of olanzapine produces steady-state concentrations in about a week that are approximately twofold higher than concentrations after a single dose ([Callaghan et al. 1999](#)).

Clearance of olanzapine is approximately 25%–30% lower in women than in men, based on results of population pharmacokinetic analyses ([Callaghan et al. 1999](#); [Patel et al. 1995, 1996](#)). A study of 20 male and 7 female patients with schizophrenia receiving olanzapine also found that women had higher trough concentrations after receiving 1 week of olanzapine 12.5 mg/day ([Kelly et al. 1999](#)). Despite the differences in clearance and plasma levels, there is no difference between sexes in the incidence of EPS or other movement disorders ([Aichhorn et al. 2006](#)).

Olanzapine's pharmacokinetics in the elderly and in children differ from those in adults. In the elderly, olanzapine clearance is approximately 30% lower than in younger individuals, and the half-life is approximately 50% longer ([Callaghan et al. 1999](#); [Patel et al. 1995](#)). A study of eight children and adolescents (ages 10–18 years) found pharmacokinetic parameters similar to those reported in nonsmoking adults, with an average  $T_{\max}$  (time required to reach the maximal plasma concentration) of 4.7 hours, an average apparent oral clearance of 9.6 L/hour, and an average half-life of 37.2 hours ([Grothe et al. 2000](#)). The highest concentrations were seen when smaller-sized patients received dosages greater than 10 mg/day; therefore, dosing should take into consideration the size of the child.

Impairment in either hepatic or renal function has not been associated with altered olanzapine disposition. In a study of four healthy individuals and eight patients with hepatic cirrhosis, no significant differences in olanzapine

pharmacokinetics were found, although urinary concentrations of olanzapine 10-*N*-glucuronide were increased in patients with cirrhosis ([Callaghan et al. 1999](#)). A study comparing olanzapine pharmacokinetics in six subjects with normal renal function, six subjects with renal failure who received an olanzapine dose 1 hour before hemodialysis, and six subjects with renal failure who received an olanzapine dose during their 48-hour interdialytic interval did not find any significant differences. These data suggest that olanzapine dosage does not need to be adjusted in patients with renal or hepatic disease ([Callaghan et al. 1999](#)).

---

## Mechanism of Action

---

In discussing olanzapine's mechanism of action in the treatment of schizophrenia, it should be noted that there is no established molecular mechanism that can unify the symptoms of schizophrenia. No precise animal or in vitro model for the illness exists, nor is there a consensus on its precise etiology or pathophysiology. Numerous neurochemical hypotheses have been proposed, including theories implicating abnormalities in dopaminergic, glutamatergic, serotonergic, and other systems, such as neurotensin ([Boules et al. 2007](#)) or neuregulin ([Benzel et al. 2007](#)). However, the discovery that multiple receptor types exist for each neurotransmitter has added many layers of complexity to the search for explanations regarding the root causes of schizophrenia. Thus, it is no longer possible to use broad terms such as "increased dopamine" when discussing ideas about the etiology of the disorder.

Despite the caveats mentioned above regarding our rudimentary knowledge of the nature of schizophrenia, it is important to note that all approved antipsychotic medications have a significant effect on the dopaminergic system, largely through the blockade of D<sub>2</sub> receptors ([Kapur and Remington 2001](#)). Even though there are substantial differences in D<sub>2</sub> receptor affinity among the traditional antipsychotics and the second-generation antipsychotics, they all are either full antagonists or partial agonists at the dopamine D<sub>2</sub> receptor. Of interest is evolving research indicating the importance of multiple-receptor blockade to the effectiveness of the second-generation antipsychotic class. As the various neurotransmitter systems have been investigated in the neuropsychopharmacology of schizophrenia, evidence is emerging that the second-generation antipsychotics, and olanzapine in particular, may improve different schizophrenia symptom domains by means of effects on 5-HT receptors, on multiple-receptor binding, on region-specific and more fleeting binding to dopamine receptors, on glutamate neurotransmission, and perhaps on neuropeptide neurotransmitters. In the following paragraphs, we discuss each of these specific ideas about olanzapine's mechanism of action in turn.

In clinical investigations with positron emission tomography (PET) imaging, [Kapur et al. \(1998\)](#) showed that olanzapine at a wide range of dosages blocks a high percentage (95% or greater) of 5-HT<sub>2A</sub> receptors and also blocks dopamine receptors in a dose-dependent fashion—crossing the putative antipsychotic blockade line at dosages commonly used to diminish psychotic symptoms of schizophrenia. This study indicated that olanzapine's

primary mechanism was related to the blockade of dopamine receptors and additionally noted that olanzapine showed stronger affinity for 5-HT<sub>2A</sub> receptors than for dopamine receptors at all dosage ranges.

A more compelling hypothesis regarding the mechanism of olanzapine's effects emerged from in vivo PET scanning work performed in a series of experiments at the University of Toronto and in Sweden. Results of the initial PET scanning studies of patients receiving clozapine indicated that atypical dopamine D<sub>2</sub> receptor binding was occurring ([Farde and Nordström 1992](#); [Farde et al. 1992](#); [Kapur et al. 2000](#)). The group subsequently found similar unusual D<sub>2</sub> receptor binding with quetiapine and, to some degree, olanzapine ([Kapur et al. 1998](#)). The authors proposed that the so-called atypical antipsychotic effect—successful treatment of psychotic symptoms without induction of movement disorder side effects—may be the result of a “fast off” property of some second-generation agents, wherein the drug blocks the dopamine D<sub>2</sub> receptor but leaves it quickly, a receptor occupancy pattern that effectively decreases psychosis yet causes minimal interference to the body's own dopamine receptor activity. Thus, for olanzapine, this mechanism might help explain how the drug can exert strong therapeutic effects on schizophrenia symptoms yet cause few EPS at standard dosages. From a clinical viewpoint, it is important to note that at higher olanzapine dosages (30 mg/day), greater dopamine receptor blockade is seen, and movement disorder side effects, such as akathisia, are more likely to occur.

Over the past 30 years, there has been substantial interest in the role of glutamate, an excitatory



neurotransmitter, in the pathophysiology of schizophrenia (see, e.g., [Coyle 2006](#); [Kim et al. 1980](#); [Krystal et al. 1994](#); [Moghaddam and Javitt 2012](#)). Glutamate's inclusion in theories about the development of schizophrenia is supported by the psychotomimetic properties of glutamate antagonists such as PCP and ketamine. These NMDA receptor antagonists induce a group of behaviors that often show closer parallels to schizophrenia than do those induced by dopamine sympathomimetic agents, in both mice and humans. Clinical trial evidence points to the potential usefulness of glutamatergic agonists (e.g., D-cycloserine) in treating schizophrenia ([Kantrowitz et al. 2010](#)). One way of examining the potential effectiveness of medication is to look at changes in deficits in *prepulse inhibition* (i.e., attenuation of the startle response), a measure of sensory motor gating that is diminished in patients with schizophrenia and can be similarly diminished pharmacologically through administration of PCP ([Dulawa and Geyer 1996](#)). In a study of rats with isolation-induced disruption of prepulse inhibition, both quetiapine and olanzapine successfully reversed the prepulse inhibition deficit ([Bakshi et al. 1998](#)).

Neurotensin receptors are collocated with and modulate mesolimbic dopaminergic neurons ([Boules et al. 2014](#)). Cerebrospinal fluid (CSF) concentrations of neurotensin are abnormal in some untreated patients with schizophrenia and have been found to normalize with antipsychotic administration. The degree of clinical improvement, particularly in negative symptoms, was found to correlate with the degree of increase in CSF neurotensin ([Sharma et al. 1997](#)). In rats, olanzapine administration was shown to increase extracellular neurotensin in the ventral striatum and medial prefrontal cortex acutely. Over time, chronic

olanzapine administration decreased the concentration of neurotensin in the medial prefrontal cortex but increased the concentration in the ventral striatum. Furthermore, chronic olanzapine administration abolished the stimulatory effects of amphetamine administration in these regions ([Gruber et al. 2011](#)). Olanzapine does not bind to the neurotensin 1 (NT<sub>1</sub>) receptor in humans ([Theisen et al. 2007](#)) but may influence neurotensin through its action on other subtypes of neurotensin receptor or its downstream effects.

Neuregulins are a family of growth factors that stimulate the ERbB receptor tyrosine kinases and have been shown to play a role in the assembly of neural circuitry, myelination, neurotransmission, and synaptic plasticity. The neuregulin-1 gene (*NRG1*) has been associated with schizophrenia in several large genomewide association studies and meta-analyses ([Mei and Nave 2014](#)). In rats, (*NRG1*) expression increases in the hippocampus after 1 week of olanzapine administration; however, after 12 weeks, its expression decreases in the prefrontal cortex and cingulate cortex ([Deng et al. 2015](#)). In a study using immortalized lymphocytes from schizophrenia patients and control subjects from unrelated families, expression of the *NRG1* glial growth factor isoform was found to be lower in schizophrenia patients than in control subjects, both before and after stimulation with olanzapine ([Chagnon et al. 2008](#)).

In summary, olanzapine works at least at the dopamine, 5-HT, and glutamate receptors. There is intriguing circumstantial evidence that olanzapine may modulate neurotensin and neuregulin. Current theories suggest that dopamine receptor-blocking capabilities are a necessary but not sufficient requirement for antipsychotic

effectiveness. The other studied mechanisms, when taken in total, may be the factors leading to olanzapine's broad efficacy and side-effect profile.

---

## Indications and Efficacy

---

Olanzapine initially received FDA approval for the treatment of psychosis. Currently, it has multiple indications, including treatment of schizophrenia; acute treatment of manic or mixed states in bipolar disorder; and maintenance treatment of bipolar disorder, both as monotherapy and as an adjunct to mood stabilizer therapy. The OFC preparation has an FDA indication for bipolar depression and treatment-resistant depression. Intramuscular olanzapine carries an indication for acute agitation in schizophrenia and bipolar mania. Olanzapine is approved for adults and for children ages 13–18 years.

In addition to the approved indications, olanzapine has been studied—and at times used with limited evidence—in several other illnesses. In this section, we present the evidence base supporting the use of olanzapine for its FDA-indicated uses as well as for off-label uses.

## Approved Indications

### Schizophrenia

As noted earlier, olanzapine was originally developed as a medication with potential for treating schizophrenia, mania, and anxiety. To gain FDA approval for the treatment of schizophrenia, olanzapine was tested in four pivotal studies

to assess the compound for efficacy, safety, and dosage range. The earliest testing of olanzapine was an assessment of olanzapine dosages of 5–30 mg/day following an initial starting dosage of 10 mg/day. Brief Psychiatric Rating Scale (BPRS) scores were reduced substantially, and EPS incidence was low ([Baldwin and Montgomery 1995](#)). These encouraging results led to further studies and pointed to a dosage range to be tested.

**Efficacy studies.** The first pivotal study compared two dosages of olanzapine (1 mg/day and 10 mg/day) with placebo in a large international sample. The 10 mg/day dosage was statistically significantly superior to placebo on objective rating scales ([Beasley et al. 1996a](#)). The second pivotal study was a dose-ranging comparison of olanzapine versus haloperidol and placebo, also in a large international sample. Three dosage ranges for olanzapine were included: 1) low ( $5 \pm 2.5$  mg/day), 2) medium ( $10 \pm 2.5$  mg/day), and 3) high ( $15 \pm 2.5$  mg/day). Haloperidol was dosed to  $15 \pm 2.5$  mg/day. Olanzapine at the medium and high dosage ranges and haloperidol were associated with significant improvements compared with placebo ([Beasley et al. 1996b](#)). [Beasley et al. \(1997\)](#), using the same sample, further demonstrated that acute EPS were reported less frequently in all olanzapine dosage groups than in the haloperidol group. [Tollefson and Sanger \(1997\)](#) re-analyzed data from the first two studies and found that olanzapine had a direct therapeutic effect on negative symptoms that was not mediated by its effects on positive symptoms, EPS, or mood.

Another large international multicenter trial used a flexible dosing strategy to show olanzapine's clinical superiority to haloperidol on positive symptoms, negative

symptoms, comorbid depression, EPS, and overall drug safety. In this study, patients were started on olanzapine or haloperidol at dosages ranging from 5 to 20 mg/day. Ultimately, patients received olanzapine 13.2 mg/day compared with haloperidol 11.8 mg/day ([Tollefson et al. 1997](#)).

The group of studies described above led to olanzapine's approval for psychosis (later changed to schizophrenia). Several other studies have confirmed olanzapine's efficacy in the treatment of schizophrenia. With its added benefit of low movement disorder side effects, olanzapine has become an important addition to the armamentarium of the psychiatrist treating schizophrenia. [Leucht et al. \(1999\)](#) reported that olanzapine was statistically more effective than placebo (moderate effect) and also more effective than haloperidol (small effect) on global schizophrenia symptomatology.

A large National Institute of Mental Health (NIMH)-funded investigation sought to compare the second-generation antipsychotics olanzapine, risperidone, quetiapine, and ziprasidone with perphenazine in order to understand the efficacy and side-effect profiles of the newer versus older antipsychotic medications ([Lieberman et al. 2005](#)). This project, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), was designed to provide a double-blind yet reasonably naturalistic setting for clinicians to treat patients, using time to discontinuation for any reason as the primary outcome variable. Although olanzapine had the longest time to all-cause discontinuation of any medication in the trial, it also had the highest rate of discontinuation due to metabolic complications such as weight gain, whereas perphenazine had the highest rate of discontinuation due to EPS. Overall, however, the

discontinuation rate was high for all medications, with nearly 75% of patients changing medications within the 18-month study duration. Much discussion and written commentary has ensued since the initial findings were published, including analyses of cost-effectiveness ([Rosenheck et al. 2006](#)), of the effects of antipsychotic medication on psychosocial functioning ([Swartz et al. 2007](#)), and of the impact of switching medications ([Essock et al. 2006](#)), as well as numerous editorials about the treatment implications of the study.

Schizophrenia is often not fully responsive to antipsychotic treatment. Assessment of olanzapine in patients with treatment-refractory illness did not support its usefulness in a stringent nonresponder protocol ([Conley et al. 1998](#)). However, in an Eli Lilly-sponsored double-blind noninferiority multicenter trial, olanzapine's effect in lowering Positive and Negative Syndrome Scale (PANSS) scores was comparable to that of clozapine ([Tollefson et al. 2001](#)). A second phase of the CATIE project examined the use of clozapine in patients with treatment-refractory illness and found, based on the time to discontinuation, that clozapine was a superior treatment for patients who had not responded to other second-generation medications ([McEvoy et al. 2006](#)).

Although early research noted olanzapine's beneficial effects on negative symptoms and cognitive symptoms of schizophrenia, these effects were not as strong as the drug's effects on positive symptoms. Olanzapine's efficacy in negative symptoms was first reported by [Tollefson et al. \(1997\)](#) following completion of a large double-blind trial of olanzapine and haloperidol. When all symptom improvements were taken into account, olanzapine-treated subjects showed greater improvement than haloperidol-

treated patients in negative symptoms (as measured by improvement in scores on both the Scale for the Assessment of Negative Symptoms [SANS] and the BPRS negative symptom subscale). In a flexible-dose comparison between risperidone and olanzapine in patients followed for 1 year, olanzapine-treated patients showed significantly greater improvement on SANS scores than did risperidone-treated patients ([Alvarez et al. 2006](#)). Interestingly, in a study by researchers from Eli Lilly that followed patients taking either quetiapine or olanzapine for 6 months, the two groups showed similar improvements on the SANS at study completion ([Kinon et al. 2006](#)). In a meta-analysis of 50 studies of second-generation antipsychotics ([Komossa et al. 2010](#)), no difference in short-, medium-, or long-term improvement of negative symptoms (as measured by PANSS negative, BPRS negative, and/or SANS total scores) was found between olanzapine and the other medications, which included amisulpride, clozapine (1 of 12 studies found clozapine to be superior as measured by SANS total scores), quetiapine, and ziprasidone (1 of 2 studies found olanzapine to be superior on PANSS negative scores, but overall no difference was found). The same study found olanzapine to outperform risperidone on improvement of negative symptoms (as measured by SANS total score) ([Komossa et al. 2010](#)).

Cognitive functioning is the most important indicator of schizophrenia prognosis ([Green 2006](#)). In a 1-year comparison of olanzapine with risperidone, both groups showed modest benefits on a cognitive function battery ([Gurpegui et al. 2007](#)). In a study conducted over a 1-year period by Eli Lilly researchers in Spain, olanzapine-treated patients showed greater benefit in social functioning than did risperidone-treated patients, as assessed by scores on

the Social Functioning Scale (SFS). The greatest difference was in occupation/employment, but improvements were also seen on measures of independence, social engagement, and recreation ([Ciudad et al. 2006](#)).

In an 8-week double-blind, placebo-controlled study, the LAI formulation of olanzapine showed a statistically significant separation from placebo (as measured by decreases in PANSS total scores) that was evident by day 7 ([Lauriello et al. 2008](#)). Another study of olanzapine LAI that involved a longer period of treatment—24 weeks—found that a high percentage of subjects remained free of psychotic exacerbation ([Kane et al. 2010](#)). The published report of this study also discussed the relationship between oral and LAI olanzapine dosing and noted that the potential for accidental intravascular injection—which can cause sedation and/or delirium—requires that patients be observed for 3 hours after injection.

Studies have investigated olanzapine's efficacy in the treatment of schizophrenia spectrum and other psychotic disorders in adolescents. In a systematic review of the literature in children, second-generation antipsychotics were shown to be beneficial overall in improving psychotic symptoms ([Jensen et al. 2007](#)). Olanzapine's safety profile in adolescents is similar to its profile in adults, although its adverse effects on weight and prolactin are more significant in young people ([Kryzhanovskaya et al. 2009a](#)). A double-blind, flexible-dose study demonstrated comparable efficacy for risperidone, olanzapine, and haloperidol in psychotic young people ([Sikich et al. 2004](#)). A similar trial of olanzapine, risperidone, and quetiapine in early psychosis found equivalent rates of discontinuation for the three drugs over a 52-week period, with olanzapine and risperidone showing slightly greater reductions on PANSS



positive scores compared with quetiapine ([McEvoy et al. 2007](#)). In late 2009, olanzapine received FDA approval for the treatment of schizophrenia in teenagers, but with the recommendation that clinicians first consider the use of other agents, given concerns about metabolic consequences (for further discussion, see section titled “Side Effects and Toxicology” later in this chapter).

Studies have shown that approximately 25% of individuals with early signs of schizophrenia will ultimately develop the disease, although in the past, rates of conversion were estimated as being much higher (40%–50%; see [Kaur and Cadenhead 2010](#) for a review). Olanzapine’s use in a population considered to be at high risk for schizophrenia but not meeting full symptom criteria was evaluated in a double-blind multicenter study ([McGlashan et al. 2006](#)). The olanzapine group did not show statistically significant reductions in the rate of conversion to psychosis compared with the placebo group. However, a number of factors, including high dropout rates in both groups, the lack of a systematic method for diagnosing clinical psychiatric disorders, and problems regarding selection and classification of patients, limited the generalizability and reliability of the findings ([McGlashan et al. 2006](#)). The number needed to treat (NNT), a measure of effect size, was 4.5 in this study; thus, whereas early treatment with olanzapine may benefit some individuals, the increased risk of metabolic side effects associated with use of antipsychotics in adolescents mandates that an abundance of caution be exercised before making the decision to administer these medications to young people who are not yet ill. Olanzapine treatment was not found to improve cognition in adolescents identified as being at risk of psychosis, and olanzapine treatment did not significantly

alter neuropsychological deficits either at baseline or after conversion to psychosis ([Hawkins et al. 2008](#)). Given the long-term side-effect consequences, antipsychotic medication is not indicated in people with subthreshold levels of psychosis.

At the other end of the age spectrum, olanzapine has been investigated in the treatment of psychotic disorders in the elderly. Olanzapine, like all antipsychotic medications, carries an FDA black box warning regarding an increased risk of stroke associated with its use in elderly individuals with dementia-related psychosis. (The use of olanzapine in dementia is discussed in greater detail in a separate subsection; see “Dementia-Related Agitation and Psychosis” later in this chapter.) A study of olanzapine versus haloperidol in a group of older patients with chronic schizophrenia found a statistical advantage for olanzapine ([Barak et al. 2002](#)). In a study of olanzapine in 94 acutely ill inpatients age 65 years or older, some with psychosis, [Hwang et al. \(2003\)](#) reported mean reductions from baseline of greater than 50% on BPRS scores, thus illustrating olanzapine’s usefulness in treating a broad range of psychotic symptoms in older patients. As with any treatment used in elderly persons, special care must be taken to avoid cardiovascular complications. With olanzapine, orthostatic hypotension, oversedation, and thus the risk of falls must be factored into the dosing decision ([Gareri et al. 2006](#)).

**Treatment approaches.** Early studies of olanzapine assessed dosages ranging from 5 to 30 mg/day. When olanzapine was initially released, it was recommended that the medication be started at a dosage of 10 mg/day, often given as a bedtime dose. Subsequently, clinicians have used

average dosages higher than 10 mg/day (e.g., approximately 13 mg/day). In the flexible-dosing segment of CATIE, in which the available dosages were 7.5, 15.0, 22.5, and 30.0 mg/day), the average dosage was 20.1 mg/day ([Lieberman et al. 2005](#)). For inpatient treatment, clinicians often will give patients 5 mg of olanzapine in the morning and 10 mg at bedtime ([Schulz 1999](#)). Because some patients appear to have an inadequate response to olanzapine at the recommended dosages, clinicians have assessed the usefulness of olanzapine at dosages above the recommended 20 mg/day. Many hospital clinicians employ a loading strategy with olanzapine, particularly in patients presenting with acute agitation, using dosages up to 40 mg/day for the first 2 days and gradually decreasing to a target dosage of 20–30 mg/day ([Baker et al. 2003](#); [Brooks et al. 2008](#)). Although sedation and hypotension must be watched for in any individual patient, increased rates of those side effects were not seen in a study comparing the loading-dose strategy with conventional 10-mg/day dosing ([Baker et al. 2003](#)).

Typically, agitated patients are best treated with the rapid-dissolving preparation of olanzapine. Given its faster onset of action and the decreased risk of “cheeking” of medication, the rapid-dissolving tablet formulation is preferable to the conventional pill in the acute setting, particularly when some sedation is also needed. When patients are severely agitated, use of injectable olanzapine is often necessary. The intramuscular preparation has a rapid onset of action, similar to that of dissolvable tablets, as well as a certainty of delivery that is imperative in an emergency. The injectable preparation has been shown to be superior to placebo at doses of 10 mg and as effective as haloperidol, with significantly fewer side effects ([Breier et](#)

al. 2002). However, case reports caution against use of olanzapine in conjunction with intramuscular lorazepam because of the risk of hypotension (Zacher and Roche-Desilets 2005).

For patients who require long-term treatment, olanzapine LAI can be used on a once-monthly administration schedule. Because of concerns regarding cases of delirium and even coma reported in early studies, patients receiving olanzapine LAI must be observed for 3 hours after the injection. This monitoring requirement has significantly limited the use of the LAI form.

## **Bipolar Disorder and Treatment-Resistant Depression**

Before the introduction of second-generation antipsychotic medications, it was well known that traditional antipsychotic medications were useful in the treatment of mania. Findings from a study assessing the effects of olanzapine versus haloperidol on symptoms of schizoaffective disorder provided a rationale for studying olanzapine in bipolar disorder. Compared with the schizoaffective disorder patients who received haloperidol in this study, the patients who received olanzapine showed superior outcomes on many, but not all, measures (Tran et al. 1999).

The first controlled study of olanzapine in bipolar disorder was a 21-day comparison of olanzapine with placebo (Tohen et al. 1999). Significantly greater improvement in manic symptoms (as assessed by mean change from baseline to endpoint on Young Mania Rating Scale [YMRS] total score) was observed for patients taking olanzapine compared with those taking placebo. No

difference was seen in the outcomes for depression. In this study, EPS were not more frequent in the olanzapine-treated patients than in the patients taking placebo (Tohen et al. 1999). These findings were confirmed in a second pivotal study that also showed an advantage for olanzapine over placebo (Tohen et al. 2000). An open-label follow-up (49 weeks) added valuable information, especially noting that decreases in YMRS scores continued. For the longer term, depression scores also improved. Importantly, for the patients who were exposed to olanzapine at a mean dosage of approximately 14 mg/day, no cases of tardive dyskinesia occurred (Sanger et al. 2001).

An important question of practical interest is how olanzapine compares with conventional mood stabilizers. In a double-blind trial conducted by Eli Lilly, olanzapine was compared with lithium in the maintenance treatment of bipolar disorder (Tohen et al. 2005). In the study, patients were stabilized on a combination of lithium and olanzapine and then randomly assigned to receive one or the other for 52 weeks. In the noninferiority analysis, olanzapine was shown to be as effective as lithium in preventing depression relapse, and in fact the olanzapine-treated patients had lower rates of mixed or manic symptom relapse than did the lithium-treated patients over the 52-week follow-up. Weight gain was higher in the olanzapine group (Tohen et al. 2005). Further studies confirmed the equivalent efficacy of olanzapine and the most widely used anticonvulsant mood stabilizer, divalproex (Tohen et al. 2002).

This line of research led to FDA approval of olanzapine for the treatment of manic symptoms. The mean dosage used in olanzapine monotherapy for mania is similar to that used in schizophrenia: 13 mg/day. For acute mania in agitated

bipolar patients, intramuscular olanzapine has been shown to be effective ([Meehan et al. 2001](#)).

The treatment of bipolar depression is often complex. Monotherapy with antidepressants is associated with an increased risk of switching into mania. Olanzapine has been shown to be efficacious in both manic and—in combination with fluoxetine (OFC)—depressive phases of bipolar illness (see [Schulz and Cornelius 2010](#) for a review). In an 8-week double-blind trial conducted by Eli Lilly, OFC was compared against olanzapine monotherapy and placebo in patients with bipolar I disorder in a depressed phase. Although both treatments were more effective than placebo, OFC was significantly more effective than olanzapine in treating depressive symptoms. OFC-treated patients showed greater improvement in mood compared with olanzapine-treated patients by the fourth week of the study ([Tohen et al. 2003](#)). Subjects' health-related quality of life improved as well ([Shi et al. 2004](#)). [Brown et al. \(2006\)](#) also compared OFC with lamotrigine in a 7-week study. Although OFC demonstrated a statistical separation from lamotrigine by the first week, it is difficult to make a full comparison in such a short study. Lamotrigine requires slow titration to minimize the risk of serious rash; thus, it was received at the target dosage (200 mg/day) only for the last 2 weeks of the study, whereas the OFC dosage could be titrated to therapeutic levels much more quickly. Although the rapid titration of OFC is helpful when a more urgent approach is required, further study is needed to determine whether OFC's greater benefits versus olanzapine monotherapy persist once lamotrigine has had an opportunity to remain at a therapeutic dose for a longer period of time. Rates of treatment-emergent mania with OFC were low and did not significantly differ from

rates with placebo or olanzapine monotherapy ([Amsterdam and Shults 2005](#); [Tohen et al. 2003](#)).

In bipolar I adolescents, [Tohen et al. \(2007\)](#) reported significantly greater improvement in mania ratings with olanzapine than with placebo. Scientists at Eli Lilly demonstrated that OFC was superior to placebo in bipolar adolescents in a double-blind randomized controlled trial ([Detke et al. 2015](#)). Side effects were similar to those in adults, although the magnitude of changes in lipids was somewhat higher and that of changes in glucose somewhat lower. Both olanzapine and OFC have been FDA approved for bipolar depression in adolescents.

OFC has been studied in treatment-refractory major depressive disorder. [Thase et al. \(2007\)](#) conducted a study comparing OFC with olanzapine or fluoxetine monotherapy in patients who had not shown adequate response to at least two prior trials of antidepressants. In the pooled analysis ([Thase et al. 2007](#)), OFC produced greater improvement versus olanzapine monotherapy or fluoxetine monotherapy (as assessed by scores on the Montgomery-Åsberg Depression Rating Scale [(MADRS])). In a double-blind trial sponsored by Eli Lilly, olanzapine, fluoxetine, OFC, and venlafaxine showed similar rates of efficacy ([Corya et al. 2006](#)).

The second-generation antipsychotic medications have found a role in treating not only mania but also depression in bipolar disorder. Olanzapine monotherapy has demonstrated efficacy in both acute and maintenance phases of bipolar disorder, and when combined with fluoxetine in the OFC formulation, it has shown benefit in treating depression in bipolar I disorder. Particularly in cases of mania in which psychosis is prominent, olanzapine is a reasonable first-line agent, although consideration must



be given to the potential for metabolic consequences. In depression, olanzapine has been studied primarily in—and is FDA approved only for—treatment-refractory illness. Given the drug’s metabolic side-effect profile, it is appropriate to restrict its use to cases of resistant depression.

## Off-Label Uses

### **Dementia-Related Agitation and Psychosis**

Olanzapine does not have an FDA-approved indication for the treatment of dementia. Because elderly people are generally more sensitive to the EPS and tardive dyskinesia associated with first-generation antipsychotic medications, the second-generation medications are often preferred when antipsychotics are needed.

A large placebo-controlled trial of olanzapine in Alzheimer’s patients showed that the lower dosages of olanzapine (5–10 mg/day) were significantly better than placebo in treating target symptoms of agitation, hallucinations, and delusions ([Street et al. 2000, 2001](#)). The FDA placed a black box warning on the prescribing information of antipsychotic medications calling attention to the increased risk of death, primarily from cardiovascular and infectious complications. According to the warning, second-generation antipsychotic use over a 10-week period carries a 1.6- to 1.7-fold increased risk of mortality based on data from 17 placebo-controlled trials of second-generation antipsychotics in dementia-related psychosis. Ultimately, clinical judgment and thorough documentation are important, as in certain situations the hazards of



untreated psychotic agitation may outweigh the potential risks of treatment.

Several studies have examined olanzapine in the treatment of dementia without agitation ([Brooks and Hoblyn 2007](#)). A placebo-controlled multicenter trial conducted by researchers at Eli Lilly evaluated olanzapine at low fixed dosages (1.0, 2.5, 5.0, and 7.5 mg/day) in the treatment of dementia-related psychosis ([De Deyn et al. 2004](#)). Although olanzapine did not separate from placebo on the primary outcome measure, Hallucinations and Delusions items of the Neuropsychiatric Inventory—Nursing Home edition (NPI/NH), improvements were seen in each of the dosage groups studied. All patients who received dosages of 2.5 mg/day or greater were initially started on 2.5 mg/day, with the dosage titrated upward by 2.5 mg/week (as indicated based on their assigned study group), and there was an overall difference from placebo in the acute phase of the study, suggesting that a 2.5-mg dose was an effective starting dose in the more acute setting. On some secondary outcome measures, the greatest improvement was seen with the highest olanzapine dosage (7.5 mg/day), suggesting that for some patients, an increase to 7.5 mg/day is beneficial. Because no higher dosages were used in the study, it is unclear whether continuing to increase the dosage would lead to greater efficacy ([De Deyn et al. 2004](#)).

Acetylcholine has been the focus of treatments aimed at slowing the rate of cognitive deterioration among individuals with dementia. Cholinesterase inhibitors have been used on that basis. Olanzapine may have beneficial effects on prefrontal cortex cholinergic and serotonergic neurons that may facilitate acetylcholine release to that region. However, in a double-blind study conducted by

researchers at Eli Lilly, olanzapine was shown to worsen cognitive functioning, as assessed on the Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog), and there was no statistical difference between the olanzapine and placebo groups in scores on the Clinician's Interview-Based Impression of Change (CIBIC) scale ([Kennedy et al. 2005](#)). Patients in the olanzapine group also showed cognitive worsening on the Mini-Mental State Examination (MMSE). Previous studies found little or no benefit on cognition from olanzapine treatment in nonagitated patients with dementia ([De Deyn et al. 2004](#); [Street et al. 2000](#)).

The CATIE study also had an Alzheimer's disease component in which olanzapine, risperidone, and quetiapine were compared with placebo in the treatment of psychosis and agitation in outpatients ([Schneider et al. 2006b](#)). Patients were included if they had psychotic symptoms and resided either in an assisted living facility or at home, but they were excluded if they had skilled nursing needs or primary psychotic disorders. Patients who were to receive cholinesterase inhibitors or antidepressants were also excluded from the study. As in the schizophrenia portion of CATIE, the primary outcome variable was time to discontinuation. No difference was found among the groups in time to discontinuation, and no benefit was seen on the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change (ADCS-CGIC). The average time to discontinuation ranged from 5 to 8 weeks among the treatments. Discontinuation due to lack of efficacy occurred sooner for patients receiving placebo or quetiapine than for those receiving risperidone or olanzapine. Side effects such as parkinsonism, sedation, and increased body mass index

occurred more frequently with the study medications than with placebo ([Schneider et al. 2006b](#)).

Overall, there are limited data to support the effectiveness of second-generation antipsychotics in the treatment of dementia, and the available evidence does not support olanzapine as the first choice in this medication class. Risks for worsened cognitive function and metabolic concerns must be considered when use of antipsychotic medications is contemplated. Nonetheless, there are times when behavioral consequences and patient safety require more aggressive treatment, and antipsychotic medication may be warranted. Olanzapine is considered an intermediate-risk antipsychotic in this population ([Kales et al. 2014](#)). Ultimately, a painstaking evaluation of the risk-benefit ratio of antipsychotic medication use must precede any decision to prescribe these agents, in both the acute and the long-term time frames. Further study is needed, however, regarding the use of second-generation antipsychotic medications in this population ([Schneider et al. 2006a](#)).

## **Borderline Personality Disorder**

Borderline personality disorder is a severe psychiatric illness that afflicts nearly 1% of the population ([Torgersen et al. 2001](#)). Based on earlier studies indicating that low dosages of traditional antipsychotic medications might be useful for psychosis spectrum and overall symptoms in borderline personality disorder ([Goldberg et al. 1986](#); [Soloff et al. 1986](#)), [Schulz et al. \(1999\)](#) conducted an open-label study and found that olanzapine led to substantial improvement in psychoticism, depression, interpersonal sensitivity, and anger (as measured by Hopkins Symptom Checklist-90 ratings), as well as improvement on objective

measures of impulsivity and aggression. Of the 11 women enrolled, 9 (82%) completed the study. The design of the trial allowed for early flexible dosing, and the subjects ended the 8-week trial taking olanzapine at an average dosage of approximately 7.5 mg/day, usually at bedtime. In an extension of this open-label trial, Zanarini and Frankenburg (2001) showed olanzapine's superiority to placebo over a longer (26-week) study period. This interesting study indicated that lower dosages (5 mg/day) of olanzapine can be useful in this patient population.

In a study comparing olanzapine, fluoxetine, and OFC in women with borderline personality disorder, olanzapine monotherapy was found to be more effective (as assessed on the MADRS) than either fluoxetine or OFC in treating the depressive symptoms of the disorder. Additionally, olanzapine was superior to fluoxetine in treating symptoms of impulsivity and aggression, as measured by the Overt Aggression Scale (OAS). Weight gain was seen in a greater percentage of olanzapine-treated patients than of fluoxetine-treated patients (Zanarini et al. 2004).

Two large placebo-controlled studies evaluating olanzapine in borderline personality disorder yielded mixed results. Schulz et al. (2008) reported no significant advantage for olanzapine compared with placebo in a flexible dosing design, whereas Zanarini et al. (2011) noted a statistical advantage for higher-dosage olanzapine in a fixed-dose trial comparing low-dosage olanzapine, higher-dosage olanzapine, and placebo for 12 weeks. In an open-label 12-week extension phase of the same study, Zanarini et al. (2012) found that patients who had been treated with olanzapine in the initial study maintained and continued the modest improvements in their symptoms, while patients who were treated with placebo in the initial 12 weeks and

started on olanzapine in the extension phase achieved a level of symptom relief similar to that of those who had started with olanzapine. These mixed results have led to controversy in the field about the potential use of antipsychotic medications in borderline personality disorder.

Dialectical behavioral therapy (DBT) is a mainstay of current treatment for borderline personality disorder. In a double-blind, placebo-controlled trial, olanzapine was studied as an adjunctive agent in patients receiving DBT. Impulsive and aggressive behaviors were found to be lower in the group that received olanzapine than in the placebo group. The average olanzapine dosage in the trial was 8.8 mg/day. Statistically significant increases in weight gain and dyslipidemia were observed in the olanzapine group compared with the placebo group ([Soler et al. 2005](#)). Therefore, with consideration for side effects, olanzapine may be helpful for a broader range of illnesses, particularly when used in conjunction with psychotherapy.

## **Anorexia Nervosa**

Anorexia nervosa is a common and severe psychiatric illness that may well have the highest mortality rate of any mental disorder. Severe restriction of food intake, leading to low weight, is a primary feature of the illness; however, patients also have psychotic-like disturbances in self-perceived body size or shape, as well as unusual ideas about food and metabolism. Some investigators have begun to explore the possibility that olanzapine may help with this patient group. Initial reports were largely from pilot studies, including case series, but data are now emerging from small controlled trials.

In an open-label trial, 17 patients hospitalized for anorexia nervosa were given olanzapine in conjunction with concurrent cognitive-behavioral therapy (CBT) and DBT group treatment ([Barbarich et al. 2004](#)). Olanzapine was initiated at a dosage of 1.25–5.00 mg/day, with upward titration as needed, balancing sedation and side effects against efficacy. Although patients showed improvement in weight as well as in Beck Depression Inventory (BDI) and Spielberger State-Trait Anxiety Inventory (STAI) scores, the lack of a control group limited the validity of these results ([Barbarich et al. 2004](#)). A trial of 15 women with anorexia nervosa randomly assigned to either olanzapine or chlorpromazine in a balanced block design found that olanzapine reduced anorexic ruminations (as measured by the impaired control over mental activities subscale of the Padua Inventory). There was no difference in weight gain between the two groups. However, this study was somewhat limited by its lack of blinding ([Mondraty et al. 2005](#)). A case series evaluating low-dosage olanzapine treatment in 13 adolescent girls with restricting-type anorexia nervosa ([Leggero et al. 2010](#)) found improvements in weight and reductions in hyperactivity in the 7 girls who were olanzapine responders (defined as improvement of at least 50% in Eating Attitudes Test–26 scores).

Results of randomized double-blind, placebo-controlled trials have been mixed. In a 10-week trial of 34 women with anorexia nervosa, [Bissada et al. \(2008\)](#) found significant increases in weight and reductions in obsessive symptoms among those treated with olanzapine. Similarly, in an 8-week study of 23 outpatient women with anorexia nervosa, end-of-treatment body mass index was greater in women receiving olanzapine as compared with placebo. Psychological symptoms improved equally in both groups

([Attia et al. 2011](#)). However, a trial of olanzapine versus placebo in 20 adolescent girls with anorexia found no difference in median body weight from baseline at either week 5 or week 10. The two groups showed similar improvements in eating attitudes, psychological functioning, and resting energy expenditure ([Kafantaris et al. 2011](#)). A planned fourth clinical trial of adolescent girls was discontinued owing to inability to adequately recruit subjects, primarily because potential subjects did not meet study criteria (71% of those screened) and eligible subjects declined participation due to concerns about medication use (74% of those eligible) ([Norris et al. 2010](#)).

Given that weight gain is a prominent side effect of olanzapine, studies have begun to examine the mechanisms underlying this effect and the possibility that olanzapine might be useful as a weight-gain agent. In a double-blind, placebo-controlled trial investigating whether olanzapine might induce weight gain through modulation of ghrelin and leptin (hormones associated with satiety), patients with anorexia received olanzapine concurrently with CBT, with levels of ghrelin and leptin assessed over 3 months. Although both the olanzapine patients and the placebo patients gained weight, there was no statistical difference between the groups in amount of weight gained or in leptin or ghrelin levels, which remained unchanged over the course of the study ([Brambilla et al. 2007](#)).

The role of olanzapine as an augmentation to psychotherapy in anorexia nervosa is limited at best. The majority of studies using the most rigorous methods did not find psychological improvement for patients after olanzapine augmentation. However, in patients for whom timely weight gain is medically imperative, there may be a limited role for olanzapine. Trials have been small, with



mixed results; further research is required to clarify the potential benefits and risks for patients.

## **Posttraumatic Stress Disorder**

Posttraumatic stress disorder (PTSD) is characterized by disproportionate and disturbing symptoms of fear persisting for longer than 1 month after a severe trauma. For some patients, psychosis can occur, leading to intense feelings of horror and helplessness. This phenomenon led investigators to consider a potential role for olanzapine in a broader treatment plan for PTSD patients.

A limited number of small studies have examined olanzapine's potential utility in the treatment of PTSD. In a double-blind, placebo-controlled augmentation trial of olanzapine in 19 patients with PTSD who were minimally responsive to 12 weeks of SSRI treatment, olanzapine produced limited symptomatic improvements compared with placebo on measures of PTSD, depression, and sleep ([Stein et al. 2002](#)). However, overall clinical improvement with olanzapine was no different from that with placebo, and patients receiving olanzapine had an average weight gain of 13 pounds. In a 6-week open-trial comparison of olanzapine versus fluphenazine as monotherapy in male patients with combat-related PTSD and psychosis, olanzapine was significantly more efficacious than fluphenazine in reducing symptoms on the PANSS (negative, general, psychopathology subscale, supplementary items), Watson's PTSD subscales (avoidance, increased arousal), and a variety of global impression scales (Clinical Global Impression Severity Scale [CGI-S], Clinical Global Impression Improvement Scale [CGI-I], Patient Global Impression Improvement Scale [PGI-I]) when evaluated at 3 and 6 weeks. The two medications produced



similar improvements on PANSS positive and Watson's trauma re-experiencing subscale scores. An additional 3 weeks of treatment did not increase the efficacy of either drug ([Pivac et al. 2004](#)). In a small double-blind, randomized, placebo-controlled trial in patients with non-combat-related PTSD, olanzapine-treated patients demonstrated significantly greater improvement on the Clinician Administered PTSD Scale over 8 weeks of treatment compared with those treated with placebo ([Carey et al. 2012](#)).

## **Obsessive-Compulsive Disorder**

Obsessive-compulsive disorder (OCD) is characterized by recurrent, unwanted, and anxiety-inducing thoughts and repetitive behaviors that a person feels driven to perform in response to those thoughts. At times, obsessive thoughts can become sufficiently divorced from reality that they resemble or overlap with psychosis.

A few double-blind, placebo-controlled clinical trials have examined olanzapine's potential efficacy in augmentation of traditional SSRI treatment in OCD patients. The first such trial enrolled 26 patients who had not responded to traditional SSRI therapy. Patients received olanzapine or placebo augmentation for 6 weeks, with biweekly assessment on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Six (46%) of the 13 olanzapine-treated patients showed symptom response (defined as a 25% or greater reduction on Y-BOCS scores), compared with none of the placebo-treated patients ([Bystritsky et al. 2004](#)). In the second trial, partial responders or nonresponders to fluoxetine received an additional 6 weeks of either olanzapine or placebo augmentation. Both groups improved, but there were no differences between groups in

the extent or timing of improvement as measured by Y-BOCS scores ([Shapira et al. 2004](#)). Findings of more recent studies provide further confirmation that olanzapine is effective in only a limited set of OCD patients, such as those with primarily hoarding or symmetry-based symptoms; the data do not support the drug's first-line use in OCD overall ([Matsunaga et al. 2009](#)). Given the mixed results and small sample sizes of the existing studies, it is clear that further research is needed to establish the benefit, if any, of olanzapine augmentation in the treatment of OCD patients.

---

## Side Effects and Toxicology

---

### Neurological and Extrapyrarnidal Adverse Effects

Adverse effects of olanzapine reported in clinical use are consistent with findings in preclinical studies, which predicted few neurological effects. In Phase II and III clinical trials, olanzapine-treated patients generally showed an improvement in EPS from baseline, reflecting the fact that most of the subjects had previously taken first-generation antipsychotics. In a large multinational comparison study ([Tollefson et al. 1997](#)), olanzapine produced fewer treatment-emergent neurological adverse effects than haloperidol, including parkinsonism (14% vs. 38%) and akathisia (12% vs. 40%). In a comprehensive meta-analysis, the relative risk (RR) of EPS for olanzapine was 0.39 compared with haloperidol ([Leucht et al. 2009](#)).

Antiparkinsonian medication is sometimes required when patients are treated with olanzapine, although the need for such medication may be lower with olanzapine than with antipsychotics having greater potency at the dopamine D<sub>2</sub> receptor. In one study ([Volavka et al. 2002](#)), antiparkinsonian agents were prescribed to 13% of both clozapine-treated subjects and olanzapine-treated subjects, compared with 32% of risperidone-treated patients. In a meta-analysis of randomized controlled trials, [Komossa et al. \(2010\)](#) found that olanzapine incurred a modestly higher risk of EPS (as measured by use of antiparkinsonian medication) compared with quetiapine (RR=2.05) but a lower EPS risk compared with risperidone (RR=0.78) and ziprasidone (RR=0.70).

Evidence now exists for phenotypic variation in the risk of EPS among olanzapine-treated patients. A meta-analysis of 4,831 subjects compared the incidence of olanzapine-induced EPS in schizophrenia versus bipolar patients. Parkinsonism was significantly higher among schizophrenia patients (13.9% vs. 3.1%), and this difference remained significant after adjustment for gender. There were no differences between groups on measures of akathisia or use of antiparkinsonian medication ([Motesafi et al. 2012](#)).

The reduction of EPS is predictive of decreased risk of tardive dyskinesia, the most problematic of the common adverse effects of classic antipsychotics. The accumulated experience with second-generation antipsychotics indicates that tardive dyskinesia is 10- to 15-fold less common with these agents than with conventional agents, with an annual rate of 0.52% for olanzapine-treated patients compared with 7.45% for haloperidol-treated patients, based on pooled data from long-term comparison trials ([Beasley et al. 1999](#)). [Miller et al. \(2008\)](#) examined data from the

previously described CATIE study. After exclusion of subjects who met criteria for tardive dyskinesia at baseline, there was no difference in incidence of tardive dyskinesia over 1 year between patients treated with olanzapine and patients treated with any other antipsychotic (perphenazine, quetiapine, risperidone, or ziprasidone).

## Weight Gain and Other Metabolic Effects

Weight gain and associated dyslipidemia are among the most significant major adverse effects found during treatment with olanzapine. Weight gain is a serious concern, because persons with schizophrenia are more likely than the general population to be obese, and weight gain may contribute to nonadherence to antipsychotic treatment, leading to increased risk for relapse. With the reduced risk of neurological side effects attached to second-generation antipsychotic agents, metabolic effects have emerged as a major risk for patients and a focus of consideration for clinicians.

The relative degree of weight gain associated with first- and second-generation antipsychotics was studied in a comprehensive meta-analysis by [Allison et al. \(1999\)](#). Estimates of weight change associated with standardized dosages over 10 weeks were calculated from published data on 81 studies. Clozapine produced the greatest weight gain (4.45 kg), followed by olanzapine (4.15 kg). By comparison, risperidone was associated with a gain of 2.1 kg and haloperidol was associated with a gain of 1.08 kg, whereas patients lost 0.74 kg while taking placebo. In long-term treatment, 30%–50% of patients gain more than 7% of

body weight, with low pretreatment weight and good clinical response associated with more weight gain ([Russell and Mackell 2001](#)). In a large database of British patients, use of olanzapine conferred a fivefold increase in the risk of dyslipidemia over an untreated control condition and a threefold increase over conventional antipsychotics, whereas risperidone did not increase the risk ([Koro et al. 2002b](#)).

The risk for metabolic dysfunction appears to be present even before patients receive antipsychotics, and risk is further compounded by antipsychotic medication use. In a sample of 404 patients with first-episode psychosis enrolled in community health centers, patients with no previous exposure to antipsychotics had lower levels of non-high-density lipoprotein (HDL) cholesterol but were more likely to carry diagnoses of obesity and hypertension compared with patients with any lifetime exposure to antipsychotic medication (average exposure = 47.3 days) ([Correll et al. 2014](#)). Furthermore, longer duration of antipsychotic treatment was associated with greater abnormalities in triglycerides and cholesterol (both HDL and non-HDL) and lower systolic blood pressure. In this study, which allowed treatment with any antipsychotic or no medication, patients receiving olanzapine had a significantly increased risk for elevated triglycerides, insulin, and homeostasis model assessment for insulin resistance (HOMA-IR) compared with patients receiving other antipsychotic medications ([Correll et al. 2014](#)).

Studies using metformin, an agent known to decrease hepatic glucose output, have tested its potential to help patients either lose weight or remain at the same weight while receiving olanzapine or other second-generation antipsychotics. In a double-blind, placebo-controlled trial

([Baptista et al. 2006](#)), patients were given 10 mg of olanzapine and randomly assigned to receive either metformin or placebo for 14 weeks. No differences between groups were seen in body mass index or waist circumference. There was a modest improvement in overall glucose levels and in HOMA-IR, but no change was seen in lipid levels. A follow-up study conducted by the same group ([Baptista et al. 2007](#)) demonstrated similar results, although in the second study, small differences in weight gain between the groups were found, with the metformin group losing an average of 1.5 kg and showing decreased leptin levels, whereas the placebo group maintained a consistent weight.

Investigators from the Use of Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia (METS) Study randomly assigned 148 clinically stable overweight outpatients with schizophrenia or schizoaffective disorder to up to 2,000 mg of metformin or placebo daily ([Jarskog et al. 2013](#)). Patients were taking either one or two of any of the FDA-approved antipsychotic medications. All patients received weekly diet and exercise counseling. After 16 weeks, metformin-treated patients had lost significantly more weight than placebo-treated patients (6.6 lbs. vs. 2.2 lbs.). The metformin group also showed significant reductions in triglyceride levels ( $-7.0$  mg/dL vs.  $+13.2$  mg/dL) as well as modest reductions in hemoglobin A1c, a measure of elevated blood glucose ( $-0.06\%$  vs.  $+0.011\%$ ), with a time-by-treatment interaction, suggesting that the benefits of metformin increase with time. There were no significant differences in fasting glucose or insulin levels ([Jarskog et al. 2013](#)).

In a double-blind, placebo-controlled trial in adolescents who had gained weight after 1 year of treatment with a

second-generation antipsychotic (olanzapine, risperidone, or quetiapine), the addition of metformin resulted in statistical reductions in waist circumference and body mass index and stabilization of weight gain ([Klein et al. 2006](#)). HOMA-IR scores were significantly decreased, and the number of subjects requiring referral for a glucose tolerance test was reduced, among the subjects who received metformin.

Interestingly, a recent small study of first-episode schizophrenia patients started on olanzapine found that daily supplementation with melatonin attenuated increases in weight and abdominal obesity as compared with olanzapine and placebo, and additionally improved scores on the PANSS. There was also a trend for attenuation of hypertriglyceridemia ([Modabbernia et al. 2014](#)).

Weight gain is an even greater concern in the treatment of children and adolescents, who may be exposed to medication for a longer time than adults. In a study evaluating weight gain among hospitalized adolescents after 12 weeks of treatment with olanzapine ( $n=21$ ), risperidone ( $n=21$ ), or haloperidol ( $n=8$ ), patients in the olanzapine group gained an average of  $7.2\pm6.3$  kg, approximately twice the amount gained in the risperidone group ( $3.9\pm4.8$  kg) and more than 6 times the amount gained in the haloperidol group ( $1.1\pm3.3$  kg) ([Ratzoni et al. 2002](#)). In a double-blind multisite trial comparing first- and second-generation antipsychotic medications among children and adolescents, the olanzapine arm was discontinued because of weight gain without evidence of improved efficacy over risperidone or molindone ([Sikich et al. 2008](#)). A further study of olanzapine in adolescents demonstrated a statistically significant difference in symptom improvement ratings for olanzapine over placebo.



As in previous studies, significantly more weight gain occurred in the adolescents on olanzapine ([Kryzhanovskaya et al. 2009b](#)).

Changes in weight, lipids, and insulin metabolism raise serious concerns for diabetes and related complications. Cases reported to the FDA Drug Surveillance System and published cases of olanzapine-associated diabetes and hyperglycemia were reviewed by [Koller and Doraiswamy \(2002\)](#). Two hundred eighty-nine cases were identified, of which 225 (78%) involved new-onset diabetes and 100 (35%) involved ketosis or acidosis; in 23 (8%) cases, the patient died. Most cases developed within 6 months of initiation of olanzapine therapy. Many cases occurred during the first month of therapy, indicating that weight gain alone did not mediate the occurrence of diabetes-related problems. On the basis of the temporal relation between the appearance of metabolic changes and the introduction and withdrawal of olanzapine, the young age of patients affected, and the number of reports, the authors concluded that the data suggested that olanzapine was causally related to the development or worsening of diabetes. A similar conclusion about clozapine and diabetes had been reported previously ([Koller et al. 2001](#)). Because case studies and reports by clinicians to regulatory agencies may reflect reporting bias, controlled studies comparing the development of metabolic disorders are needed to clarify whether these are related to the underlying psychosis, causally related to drug treatment in general, or specifically related to individual agents.

Studies using large health system databases have linked antipsychotic treatment with subsequent diagnoses of diabetes or use of hypoglycemic agents. These studies show an increased risk of development of type 2 diabetes among



individuals using olanzapine or clozapine relative to those using risperidone or typical antipsychotics or compared with matched untreated persons ([Gianfrancesco et al. 2002](#); [Koro et al. 2002a](#); [Sernyak et al. 2002](#)).

In addition to olanzapine's association with weight gain and type 2 diabetes, it has also been linked to diabetic ketoacidosis (DKA), a condition more often associated with type 1 than type 2 diabetes mellitus. Reports of this connection first appeared in the literature in 1999 ([Gatta et al. 1999](#); [Goldstein et al. 1999](#); [Lindenmayer and Patel 1999](#)). In a review of California Medicaid data on cases of risperidone- and olanzapine-associated DKA, [Ramaswamy et al. \(2007\)](#) found a higher incidence of DKA with olanzapine treatment than with risperidone treatment and noted that the risk increased with duration of treatment with olanzapine. By contrast, a multicenter retrospective cohort study using administrative health data (encompassing the records of 725,489 patients) from Canada and the United Kingdom ([Lipscombe et al. 2014](#)) found no increased risk of hyperglycemic emergency associated with initiation of olanzapine versus risperidone.

## Other Side Effects

Among other side effects reported with olanzapine, sedation is frequent at the start of therapy but diminishes as patients develop tolerance for this side effect. In long-term treatment, the incidence of sedation is about 15%, similar to that of haloperidol. Prolactin elevations observed during olanzapine treatment occur early in the course of treatment, and levels are much lower than those seen with risperidone or typical antipsychotics. Leukopenia is rare

and occurs at a rate similar to that seen with other first- and second-generation antipsychotics, but olanzapine does not cause agranulocytosis, even in patients who developed this effect while taking clozapine. In animal toxicology studies and in clinical trials of olanzapine, no QTc prolongation was observed, and other cardiovascular effects are rarely of clinical importance ([Cadario 2000](#)).

## Safety in Overdose

Reviews of case series and reports of olanzapine toxicity in adults describe predominantly circulatory and central nervous system effects, including coma, psychomotor agitation, hypertension and hypotension, tachycardia and bradycardia, hyperthermia and hypothermia, miosis and mydriasis, and QTC prolongation (QTC prolongation only with >1,040-mg ingestion and in mixed overdoses) ([Ciszowski et al. 2011](#); [Tan et al. 2009](#)). Olanzapine overdose was rarely fatal in the aforementioned case reports, and a systematic study of second-generation antipsychotic overdose found that of 422 olanzapine overdoses, there were no fatalities and 14% required ventilation ([Berling et al. 2016](#)). There are very few data describing olanzapine overdose in children. Available case report data are consistent with adult presentations of EPS and elevated prolactin levels ([Tanoshima et al. 2013](#)) and circulatory and neurological symptoms ([McAllister et al. 2012](#); [Singh et al. 2012](#); [Theisen et al. 2005](#)).

## Use in Pregnancy

Exposure to second-generation antipsychotics was associated with gestational diabetes in a Swedish birth cohort study ([Bodén et al. 2012](#)). The risk was similar for medications known to have severe anabolic effects (olanzapine and clozapine) and other antipsychotic medications. Fetuses exposed to antipsychotic medication in utero were more likely than those not exposed to be born small for gestational age, but this association was not robust to adjustment for maternal factors. Because of the difficulty in studying medication use during pregnancy, data on antipsychotic use during pregnancy are extremely sparse. No specific fetal abnormalities have been reported with olanzapine, although there is some evidence suggesting an association between antipsychotic use in pregnancy and neonatal respiratory distress and withdrawal symptoms ([Kulkarni et al. 2015](#)). Further research is needed to aid clinicians in maximizing infant and maternal well-being.

---

## Drug-Drug Interactions

---

Olanzapine is metabolized primarily via glucuronidation and via oxidation by CYP1A2 (see section “Pharmacokinetics and Disposition” earlier in this chapter). Other drugs that affect the activity of these metabolic pathways would therefore be expected to affect olanzapine pharmacokinetics. Indeed, drugs that inhibit CYP1A2 activity have been shown to decrease olanzapine clearance, thereby increasing olanzapine plasma concentrations.

Fluvoxamine, a known inhibitor of CYP1A2, has been shown to inhibit olanzapine metabolism in several studies.

In an 11-day study of 10 healthy male smokers, coadministration of fluvoxamine (50–100 mg/day) with olanzapine (2.5–7.5 mg/day for 8 days [beginning on day 4]) resulted in an 84% increase in olanzapine peak serum concentrations ( $C_{\max}$ ) and a 119% increase in  $AUC_{0-24}$  compared with placebo coadministered with olanzapine. No change in half-life was observed in either olanzapine or 4'-*N*-desmethylolanzapine, suggesting that fluvoxamine inhibited olanzapine's first-pass metabolism ([Maenpaa et al. 1997](#)).

Fluoxetine and imipramine, although not known to be significant inhibitors of CYP1A2, when coadministered with olanzapine have been associated with small but statistically significant changes in olanzapine pharmacokinetics. Coadministration of fluoxetine with olanzapine resulted in a 15% decrease in olanzapine clearance and an 18% increase in  $C_{\max}$ , with no significant difference in olanzapine half-life ([Callaghan et al. 1999](#)). Coadministration of imipramine with olanzapine resulted in an approximately 14% increase in olanzapine  $C_{\max}$  and a non-statistically significant increase in olanzapine AUC of 19% ([Callaghan et al. 1997](#)).

Inducers of the CYP1A2 enzyme increase olanzapine clearance, thereby decreasing olanzapine systemic exposure. Carbamazepine, an inducer of several CYP enzymes (including 1A2), affects olanzapine disposition. A study in healthy volunteers reported that a single 10-mg dose of olanzapine taken after 2 weeks of pretreatment with carbamazepine (200 mg twice daily) had significantly higher clearance and apparent volume of distribution—but significantly lower  $C_{\max}$ , AUC, and half-life—compared with a single 10-mg dose taken before carbamazepine pretreatment ([Lucas et al. 1998](#)).

Smoking, also known to induce CYP1A2, can affect olanzapine disposition. A study comparing 19 male smokers with 30 male nonsmokers found that olanzapine clearance in smokers was 23% higher than that in nonsmokers ([Callaghan et al. 1999](#)). A population pharmacokinetic analysis of 910 patients receiving olanzapine found that clearance among nonsmokers was 37% lower in men and 48% lower in women than it was in the corresponding group of smokers ([Patel et al. 1996](#)). A smaller analysis of healthy volunteers also found higher drug clearances among smokers ([Patel et al. 1995](#)). The polycyclic aromatic hydrocarbons in cigarette smoke are responsible for inducing the aryl hydrocarbon hydroxylases, thereby leading to enzymatic induction ([Desai et al. 2001](#)). For this reason, dosage adjustments may be needed when a patient who smokes is placed in a smoke-free inpatient unit, even if adequate nicotine replacement is provided. Conversely, when there is a sudden increase in cigarette consumption (often associated with stress or impending relapse), a dosage increase may be needed to prevent an abrupt worsening of symptoms.

In vitro studies suggest that olanzapine does not significantly inhibit the activity of CYP 1A2, 3A, 2D6, 2C9, or 2C19 ([Ring et al. 1996a](#)). In vivo studies suggest that olanzapine does not affect the disposition of aminophylline ([Macias et al. 1998](#)), diazepam, alcohol, imipramine ([Callaghan et al. 1997](#)), warfarin, biperiden, or lithium ([Callaghan et al. 1999](#); [Demolle et al. 1995](#)).

---

## Conclusion

---

From review of the research focused on olanzapine, it is clear that this compound, which has been approved for use in the United States since 1997, has wide utility and some distinct advantages compared with traditional antipsychotics. In addition to its positive effects on a broad group of symptoms in schizophrenia, olanzapine is approved for the treatment of mania, both acute and long term, in bipolar disorder. Recent research has shown that olanzapine may be beneficial for disorders beyond psychosis (e.g., borderline personality disorder, anorexia nervosa, PTSD, OCD). The extension of olanzapine's uses is in many ways made possible by its low rate of movement disorders. Olanzapine's low risk of dystonia, parkinsonism, and tardive dyskinesia has led to its greater acceptability in chronic schizophrenia and has encouraged clinicians to prescribe it for other conditions, although concerns about metabolic side effects limit the drug's overall utility.

As noted in the earlier section "Side Effects and Toxicology," olanzapine is not free of adverse effects. Weight gain and metabolic disturbances are of significant concern and are the focus of intense research in both pathophysiology and prevention/treatment. Because of these concerns, the FDA does not recommend olanzapine as a first-line agent in young people.

In addition to providing better treatment for schizophrenia and other disorders, olanzapine promotes actions in the brain that have revealed new directions for research on the pathophysiological mechanisms underlying psychiatric disease. As noted previously, investigation of olanzapine's effects on glutamate, neurotensin, neuregulin, and other neurotransmitters may improve our understanding of the pathophysiology of these diseases and open new avenues of treatment.

---

# References

---

- Aichhorn W, Whitworth AB, Weiss EM, Marksteiner J: Second-generation antipsychotics: is there evidence for sex differences in pharmacokinetic and adverse effect profiles? *Drug Saf* 29(7):587-598, 2006 16808551
- Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156(11):1686-1696, 1999 10553730
- Alvarez E, Ciudad A, Olivares JM, et al: A randomized, 1-year follow-up study of olanzapine and risperidone in the treatment of negative symptoms in outpatients with schizophrenia. *J Clin Psychopharmacol* 26(3):238-249, 2006 16702888
- Amsterdam JD, Shults J: Comparison of fluoxetine, olanzapine, and combined fluoxetine plus olanzapine initial therapy of bipolar type I and type II major depression—lack of manic induction. *J Affect Disord* 87(1):121-130, 2005 15923042
- Aravagiri M, Ames D, Wirshing WC, Marder SR: Plasma level monitoring of olanzapine in patients with schizophrenia: determination by high-performance liquid chromatography with electrochemical detection. *Ther Drug Monit* 19(3):307-313, 1997 9200772
- Attia E, Kaplan AS, Walsh BT, et al: Olanzapine versus placebo for out-patients with anorexia nervosa. *Psychol Med* 41(10):2177-2182, 2011 21426603
- Baker RW, Kinon BJ, Maguire GA, et al: Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. *J Clin Psychopharmacol* 23(4):342-348, 2003 12920409
- Bakshi VP, Swerdlow NR, Braff DL, Geyer MA: Reversal of isolation rearing-induced deficits in prepulse inhibition by Seroquel and olanzapine. *Biol Psychiatry* 43(6):436-445, 1998 9532349

- Baldwin DS, Montgomery SA: First clinical experience with olanzapine (LY 170053): results of an open-label safety and dose-ranging study in patients with schizophrenia. *Int Clin Psychopharmacol* 10(4):239-244, 1995 8748045
- Baptista T, Martínez J, Lacruz A, et al: Metformin for prevention of weight gain and insulin resistance with olanzapine: a double-blind placebo-controlled trial. *Can J Psychiatry* 51(3):192-196, 2006 16618011
- Baptista T, Rangel N, Fernández V, et al: Metformin as an adjunctive treatment to control body weight and metabolic dysfunction during olanzapine administration: a multicentric, double-blind, placebo-controlled trial. *Schizophr Res* 93(1-3):99-108, 2007 17490862
- Barak Y, Shamir E, Zemishlani H, et al: Olanzapine vs. haloperidol in the treatment of elderly chronic schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry* 26(6):1199-1202, 2002 12452546
- Barbarich NC, McConaha CW, Gaskill J, et al: An open trial of olanzapine in anorexia nervosa. *J Clin Psychiatry* 65(11):1480-1482, 2004 15554759
- Beasley CM Jr, Sanger T, Satterlee W, et al: Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. *Psychopharmacology (Berl)* 124(1-2):159-167, 1996a 8935812
- Beasley CM Jr, Tollefson G, Tran P, et al: Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 14(2):111-123, 1996b 8822534
- Beasley CM Jr, Hamilton SH, Crawford AM, et al: Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol* 7(2):125-137, 1997 9169300
- Beasley CM, Dellva MA, Tamura RN, et al: Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-



- term treatment with olanzapine or haloperidol. *Br J Psychiatry* 174:23-30, 1999 10211147
- Benzel I, Bansal A, Browning BL, et al: Interactions among genes in the ErbB-Neuregulin signalling network are associated with increased susceptibility to schizophrenia. *Behav Brain Funct* 3:31, 2007 17598910
- Bergstrom RF, Callaghan JT, Cerimele BJ, et al: Pharmacokinetics of olanzapine in elderly and young (abstract). *Pharm Res* 12 (9 suppl):S358, 1995
- Berling I, Buckley NA, Isbister GK: The antipsychotic story: changes in prescriptions and overdose without better safety. *Br J Clin Pharmacol* 82(1):249-254, 2016 26945707
- Bissada H, Tasca GA, Barber AM, Bradwejn J: Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 165(10):1281-1288, 2008 18558642
- Bodén R, Lundgren M, Brandt L, et al: Antipsychotics during pregnancy: relation to fetal and maternal metabolic effects. *Arch Gen Psychiatry* 69(7):715-721, 2012 22752236
- Boules M, Shaw A, Fredrickson P, Richelson E: Neurotensin agonists: potential in the treatment of schizophrenia. *CNS Drugs* 21(1):13-23, 2007 17190526
- Boules MM, Fredrickson P, Muehlmann AM, Richelson E: Elucidating the role of neurotensin in the pathophysiology and management of major mental disorders. *Behav Sci (Basel)* 4(2):125-153, 2014 25379273
- Brambilla F, Monteleone P, Maj M: Olanzapine-induced weight gain in anorexia nervosa: involvement of leptin and ghrelin secretion? *Psychoneuroendocrinology* 32(4):402-406, 2007 17395395
- Breier A, Meehan K, Birkett M, et al: A double-blind, placebo-controlled dose-response comparison of

- intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry* 59(5):441-448, 2002 11982448
- Brooks JO, Hoblyn JC: Neurocognitive costs and benefits of psychiatric medication in older adults: invited review. *J Geriatr Psychiatry Neurol* 20(4):199-214, 2007 18004007
- Brooks JO, Karnik N, Hoblyn JC: High initial dosing of olanzapine for stabilization of acute agitation: a retrospective case series. *J Pharm Technol* 24(1):7-11, 2008 doi: 10.1177/875512250802400103
- Brown EB, McElroy SL, Keck PE Jr, et al: A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry* 67(7): 1025-1033, 2006 16889444
- Bymaster FP, Calligaro DO, Falcone JF, et al: Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 14(2):87-96, 1996 8822531
- Bystritsky A, Ackerman DL, Rosen RM, et al: Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry* 65(4):565-568, 2004 15119922
- Cadario B: Olanzapine (Zyprexa): suspected serious reactions. *CMAJ* 163(1):85-86, 89-90, 2000 10920744
- Callaghan JT, Cerimele BJ, Kassahun KJ, et al: Olanzapine: interaction study with imipramine. *J Clin Pharmacol* 37(10):971-978, 1997 9505989
- Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM: Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 37(3):177-193, 1999 10511917
- Carey P, Suliman S, Ganesan K, et al: Olanzapine monotherapy in posttraumatic stress disorder: efficacy

- in a randomized, double-blind, placebo-controlled study. *Hum Psychopharmacol* 27(4):386-391, 2012 22730105
- Chagnon YC, Roy MA, Bureau A, et al: Differential RNA expression between schizophrenic patients and controls of the dystrobrevin binding protein 1 and neuregulin 1 genes in immortalized lymphocytes. *Schizophr Res* 100(1-3): 281-290, 2008 18234478
- Ciszowski K, Sein Anand J, Wilimowska J, Jawień W: [The clinical picture of acute olanzapine poisonings] (in Polish). *Przegl Lek* 68(8):426-433, 2011 22010430
- Ciudad A, Olivares JM, Bousoño M, et al: Improvement in social functioning in outpatients with schizophrenia with prominent negative symptoms treated with olanzapine or risperidone in a 1 year randomized, open-label trial. *Prog Neuropsychopharmacol Biol Psychiatry* 30(8): 1515-1522, 2006 16820255
- Conley RR, Tamminga CA, Bartko JJ, et al: Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *Am J Psychiatry* 155(7):914-920, 1998 9659857
- Correll CU, Robinson DG, Schooler NR, et al: Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry* 71(12):1350-1363, 2014 25321337
- Corya SA, Williamson D, Sanger TM, et al: A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety* 23(6):364-372, 2006 16710853
- Coyle JT: Glutamate and schizophrenia: beyond the dopamine hypothesis. *Cell Mol Neurobiol* 26(4-6):365-384, 2006 16773445
- De Deyn PP, Carrasco MM, Deberdt W, et al: Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients

- with Alzheimer's disease. *Int J Geriatr Psychiatry* 19(2):115-126, 2004 14758577
- Delay J, Bernitzer P: Le traitement des psychoses par une methode neuroleptique derivee de l'hibernotherapie, in *Congres de Medecins Alienistes et Neurologistes de France*. Edited by Ossa PC. Paris, Masson, 1952, pp 497-502
- Demolle D, Onkelinx C, Müller-Oerlinghausen B: Interaction between olanzapine and lithium in healthy male volunteers (abstract 486). *Therapie* 50 (suppl), 1995
- Deng C, Pan B, Hu CH, et al: Differential effects of short- and long-term antipsychotic treatment on the expression of neuregulin-1 and ErbB4 receptors in the rat brain. *Psychiatry Res* 225(3):347-354, 2015 25576368
- Desai HD, Seabolt J, Jann MW: Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs* 15(6):469-494, 2001 11524025
- Detke HC, DelBello MP, Landry J, Usher RW: Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 54(3):217-224, 2015 25721187
- Dulawa SC, Geyer MA: Psychopharmacology of prepulse inhibition in mice. *Chin J Physiol* 39(3):139-146, 1996 8955560
- Eli Lilly: Zyprexa (olanzapine) tablets: prescribing information. Indianapolis, IN, Eli Lilly, 2015. Available at: <http://pi.lilly.com/us/zyprexa-pi.pdf>. Accessed August 2, 2016.
- Essock SM, Covell NH, Davis SM, et al: Effectiveness of switching antipsychotic medications. *Am J Psychiatry* 163(12):2090-2095, 2006 17151159
- Farah A: Atypicality of atypical antipsychotics. *Prim Care Companion J Clin Psychiatry* 7(6):268-274, 2005 16498489

- Farah A: Atypicality of atypical antipsychotics revisited. *Curr Psych Reviews* 9(4):316-324, 2013
- Farde L, Nordström AL: PET analysis indicates atypical central dopamine receptor occupancy in clozapine-treated patients. *Br J Psychiatry Suppl* (17):30-33, 1992 1358126
- Farde L, Nordström AL, Wiesel FA, et al: Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiatry* 49(7):538-544, 1992 1352677
- Gareri P, De Fazio P, De Fazio S, et al: Adverse effects of atypical antipsychotics in the elderly: a review. *Drugs Aging* 23(12): 937-956, 2006 17154659
- Gatta B, Rigalleau V, Gin H: Diabetic ketoacidosis with olanzapine treatment. *Diabetes Care* 22(6):1002-1003, 1999 10372259
- Gianfrancesco FD, Grogg AL, Mahmoud RA, et al: Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry* 63(10):920-930, 2002 12416602
- Goldberg SC, Schulz SC, Schulz PM, et al: Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. *Arch Gen Psychiatry* 43(7):680-686, 1986 3521531
- Goldstein LE, Sporn J, Brown S, et al: New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics* 40(5):438-443, 1999 10479950
- Gosselin G, Oberling P, Di Scala G: Antagonism of amphetamine-induced disruption of latent inhibition by the atypical antipsychotic olanzapine in rats. *Behav Pharmacol* 7(8):820-826, 1996 11224476

- Gossen D, de Suray JM, Vandenhende F, et al: Influence of fluoxetine on olanzapine pharmacokinetics. *AAPS PharmSci* 4(2):E11, 2002 12102620
- Green MF: Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry* 67(10): e12, 2006 17107235
- Grothe DR, Calis KA, Jacobsen L, et al: Olanzapine pharmacokinetics in pediatric and adolescent inpatients with childhood-onset schizophrenia. *J Clin Psychopharmacol* 20(2):220-225, 2000 10770461
- Gruber SH, Angelucci F, Nomikos GG, Mathé AA: Effects of olanzapine on extracellular concentrations and tissue content of neurotensin in rat brain regions. *Eur Neuropsychopharmacol* 21(12):918-927, 2011 21316929
- Gurpegui M, Alvarez E, Bousoño M, et al: Effect of olanzapine or risperidone treatment on some cognitive functions in a one-year follow-up of schizophrenia outpatients with prominent negative symptoms. *Eur Neuropsychopharmacol* 17(11):725-734, 2007 17543505
- Guttmacher MS, Goldberg SC, Klerman GL: Phenothiazine in treatment of acute schizophrenia. *Arch Gen Psychiatry* 10(3):246-261, 1964 14089354
- Hägg S, Spigset O, Lakso HA, Dahlqvist R: Olanzapine disposition in humans is unrelated to CYP1A2 and CYP2D6 phenotypes. *Eur J Clin Pharmacol* 57(6-7):493-497, 2001 11699614
- Hawkins KA, Keefe RS, Christensen BK, et al: Neuropsychological course in the prodrome and first episode of psychosis: findings from the PRIME North America Double Blind Treatment Study. *Schizophr Res* 105(1-3):1-9, 2008 18774696
- Hwang JP, Yang CH, Lee TW, Tsai SJ: The efficacy and safety of olanzapine for the treatment of geriatric psychosis. *J Clin Psychopharmacol* 23(2):113-118, 2003 12640211

- Jardemark KE, Liang X, Arvanov V, Wang RY: Subchronic treatment with either clozapine, olanzapine or haloperidol produces a hyposensitive response of the rat cortical cells to N-methyl-D-aspartate. *Neuroscience* 100(1):1-9, 2000 10996453
- Jarskog LF, Hamer RM, Catellier DJ, et al; METS Investigators: Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. *Am J Psychiatry* 170(9):1032-1040, 2013 23846733
- Jensen PS, Buitelaar J, Pandina GJ, et al: Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. *Eur Child Adolesc Psychiatry* 16(2):104-120, 2007 17075688
- Kafantaris V, Leigh E, Hertz S, et al: A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol* 21(3):207-212, 2011 21663423
- Kales HC, Kim HM, Zivin K, et al: Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry* 169(1):71-79, 2014 22193526
- Kane JM, Detke HC, Naber D, et al: Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry* 167(2): 181-189, 2010 20008947
- Kantrowitz JT, Malhotra AK, Cornblatt B, et al: High dose D-serine in the treatment of schizophrenia. *Schizophr Res* 121(1-3): 125-130, 2010 20541910
- Kapur S, Remington G: Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry* 50(11): 873-883, 2001 11743942
- Kapur S, Zipursky RB, Remington G, et al: 5-HT<sub>2</sub> and D<sub>2</sub> receptor occupancy of olanzapine in schizophrenia: a

- PET investigation. *Am J Psychiatry* 155(7):921-928, 1998 9659858
- Kapur S, Zipursky RB, Remington G: Clinical and theoretical implications of 5-HT<sub>2</sub> and D<sub>2</sub> receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 156(2):286-293, 1999 9989565
- Kapur S, Zipursky R, Jones C, et al: A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D<sub>2</sub> receptor occupancy. *Arch Gen Psychiatry* 57(6):553-559, 2000 10839333
- Kapur S, Arenovich T, Agid O, et al: Evidence for onset of antipsychotic effects within the first 24 hours of treatment. *Am J Psychiatry* 162(5):939-946, 2005 15863796
- Kassahun K, Mattiuz E, Nyhart E Jr, et al: Disposition and biotransformation of the antipsychotic agent olanzapine in humans. *Drug Metab Dispos* 25(1):81-93, 1997 9010634
- Kaur T, Cadenhead KS: Treatment implications of the schizophrenia prodrome. *Curr Top Behav Neurosci* 4:97-121, 2010 21312398
- Kelly DL, Conley RR, Tamminga CA: Differential olanzapine plasma concentrations by sex in a fixed-dose study. *Schizophr Res* 40(2):101-104, 1999 10593449
- Kennedy J, Deberdt W, Siegal A, et al: Olanzapine does not enhance cognition in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. *Int J Geriatr Psychiatry* 20(11): 1020-1027, 2005 16250069
- Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmüller B: Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. *Neurosci Lett* 20(3):379-382, 1980 6108541
- Kinon BJ, Noordsy DL, Liu-Seifert H, et al: Randomized, double-blind 6-month comparison of olanzapine and



quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning. *J Clin Psychopharmacol* 26(5):453-461, 2006 16974184

Klein DJ, Cottingham EM, Sorter M, et al: A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *Am J Psychiatry* 163(12):2072-2079, 2006 17151157

Koller EA, Doraiswamy PM: Olanzapine-associated diabetes mellitus. *Pharmacotherapy* 22(7):841-852, 2002 12126218

Koller E, Schneider B, Bennett K, Dubitsky G: Clozapine-associated diabetes. *Am J Med* 111(9):716-723, 2001 11747852

Komossa K, Rummel-Kluge C, Hunger H, et al: Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* (3):CD006654, 2010 20238348

Koro CE, Fedder DO, L'Italien GJ, et al: Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 325(7358):243, 2002a 12153919

Koro CE, Fedder DO, L'Italien GJ, et al: An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry* 59(11):1021-1026, 2002b 12418935

Krystal JH, Karper LP, Seibyl JP, et al: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51(3):199-214, 1994 8122957

- Kryzhanovskaya LA, Robertson-Plouch CK, Xu W, et al: The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder: a pooled analysis of 4 clinical trials. *J Clin Psychiatry* 70(2):247-258, 2009a 19210948
- Kryzhanovskaya L, Schulz SC, McDougale C, et al: Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 48(1):60-70, 2009b 19057413
- Kulkarni J, Storch A, Baraniuk A, et al: Antipsychotic use in pregnancy. *Expert Opin Pharmacother* 16(9):1335-1345, 2015 26001182
- Lauriello J, Lambert T, Andersen S, et al: An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. *J Clin Psychiatry* 69(5):790-799, 2008 18452346
- Leggero C, Masi G, Brunori E, et al: Low-dose olanzapine monotherapy in girls with anorexia nervosa, restricting subtype: focus on hyperactivity. *J Child Adolesc Psychopharmacol* 20(2):127-133, 2010 20415608
- Leucht S, Pitschel-Walz G, Abraham D, Kissling W: Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res* 35(1):51-68, 1999 9988841
- Leucht S, Corves C, Arbter D, et al: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 373(9657):31-41, 2009 19058842
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353(12):1209-1223, 2005 16172203

- Lindenmayer JP, Patel R: Olanzapine-induced ketoacidosis with diabetes mellitus. *Am J Psychiatry* 156(9):1471, 1999 10484968
- Lipscombe LL, Austin PC, Alessi-Severini S, et al; Canadian Network for Observational Drug Effect Studies (CNODES) Investigators: Atypical antipsychotics and hyperglycemic emergencies: multicentre, retrospective cohort study of administrative data. *Schizophr Res* 154(1-3):54-60, 2014 24581419
- Lucas RA, Gilfillan DJ, Bergstrom RF: A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanism. *Eur J Clin Pharmacol* 54(8):639-643, 1998 9860152
- Macias WL, Bergstrom RF, Cerimele BJ, et al: Lack of effect of olanzapine on the pharmacokinetics of a single aminophylline dose in healthy men. *Pharmacotherapy* 18(6):1237-1248, 1998 9855322
- Maenpaa J, Wrighton S, Bergstrom R, et al: Pharmacokinetic (PK) and pharmacodynamic (PD) interactions between fluvoxamine and olanzapine (abstract). *Clin Pharmacol Ther* 61(2):225, 1997
- Mamo D, Kapur S, Keshavan M, et al: D2 receptor occupancy of olanzapine pamoate depot using positron emission tomography: an open-label study in patients with schizophrenia. *Neuropsychopharmacology* 33(2):298-304, 2008 17443131
- Markowitz JS, DeVane CL, Malcolm RJ, et al: Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. *J Clin Pharmacol* 46(2):164-171, 2006 16432268
- Matsunaga H, Nagata T, Hayashida K, et al: A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory

- obsessive-compulsive disorder. *J Clin Psychiatry* 70(6):863-868, 2009 19422759
- McAllister RK, Tutt CD, Colvin CS: Lipid 20% emulsion ameliorates the symptoms of olanzapine toxicity in a 4-year-old. *Am J Emerg Med* 30(6):1012.e1-1012.e2, 2012 21641141
- McEvoy JP, Lieberman JA, Stroup TS, et al; CATIE Investigators: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 163(4):600-610, 2006 16585434
- McEvoy JP, Lieberman JA, Perkins DO, et al: Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry* 164(7):1050-1060, 2007 17606657
- McGlashan TH, Zipursky RB, Perkins D, et al: Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry* 163(5):790-799, 2006 16648318
- Meehan K, Zhang F, David S, et al: A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol* 21(4):389-397, 2001 11476123
- Mei L, Nave KA: Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. *Neuron* 83(1):27-49, 2014 24991953
- Miller DD, Caroff SN, Davis SM, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry* 193(4):279-288, 2008 18827289

- Modabbernia A, Heidari P, Soleimani R, et al: Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. *J Psychiatr Res* 53:133-140, 2014 24607293
- Moghaddam B, Javitt D: From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* 37(1):4-15, 2012 21956446
- Mondraty N, Birmingham CL, Touyz S, et al: Randomized controlled trial of olanzapine in the treatment of cognitions in anorexia nervosa. *Australas Psychiatry* 13(1):72-75, 2005 15777417
- Moore NA: Behavioural pharmacology of the new generation of antipsychotic agents. *Br J Psychiatry Suppl* 174 (38 suppl 138):5-11, 1999 10884895
- Moteshefi H, Zhornitsky S, Brunelle S, Stip E: Comparing tolerability of olanzapine in schizophrenia and affective disorders: a meta-analysis. *Drug Saf* 35(10):819-836, 2012 22967188
- Ninan I, Jardemark KE, Wang RY: Olanzapine and clozapine but not haloperidol reverse subchronic phencyclidine-induced functional hyperactivity of N-methyl-D-aspartate receptors in pyramidal cells of the rat medial prefrontal cortex. *Neuropharmacology* 44(4):462-472, 2003 12646283
- Norris ML, Spettigue W, Buchholz A, et al: Factors influencing research drug trials in adolescents with anorexia nervosa. *Eat Disord* 18(3):210-217, 2010 20419525
- Patel BR, Nyhart EH, Callaghan JT, et al: Combined population pharmacokinetic analysis of olanzapine in healthy volunteers (abstract). *Pharm Res* 12 (9 suppl):S360, 1995
- Patel BR, Kurtz DL, Callaghan JT, et al: Effects of smoking and gender on population pharmacokinetics of

- olanzapine (OL) in a phase III clinical trial (abstract). Pharm Res 13 (9 suppl):S408, 1996
- Pivac N, Kozaric-Kovacic D, Muck-Seler D: Olanzapine versus fluphenazine in an open trial in patients with psychotic combat-related post-traumatic stress disorder. Psychopharmacology (Berl) 175(4):451-456, 2004 15064916
- Ramaswamy K, Kozma CM, Nasrallah H: Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. Drug Saf 30(7):589-599, 2007 17604410
- Ratzoni G, Gothelf D, Brand-Gothelf A, et al: Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. J Am Acad Child Adolesc Psychiatry 41(3):337-343, 2002 11886029
- Ring BJ, Binkley SN, Vandenbranden M, Wrighton SA: In vitro interaction of the antipsychotic agent olanzapine with human cytochromes P450 CYP2C9, CYP2C19, CYP2D6 and CYP3A. Br J Clin Pharmacol 41(3):181-186, 1996a 8866916
- Ring BJ, Catlow J, Lindsay TJ, et al: Identification of the human cytochromes P450 responsible for the in vitro formation of the major oxidative metabolites of the antipsychotic agent olanzapine. J Pharmacol Exp Ther 276(2):658-666, 1996b 8632334
- Robertson GS, Fibiger HC: Effects of olanzapine on regional C-Fos expression in rat forebrain. Neuropsychopharmacology 14(2):105-110, 1996 8822533
- Rosenheck RA, Leslie DL, Sindelar J, et al; CATIE Study Investigators: Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. Am J Psychiatry 163(12): 2080-2089, 2006 17151158
- Russell JM, Mackell JA: Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. CNS Drugs 15(7):537-551, 2001 11510624

- Sanger TM, Grundy SL, Gibson PJ, et al: Long-term olanzapine therapy in the treatment of bipolar I disorder: an open-label continuation phase study. *J Clin Psychiatry* 62(4):273-281, 2001 11379842
- Schneider LS, Dagerman K, Insel PS: Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 14(3):191-210, 2006a 16505124
- Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 355(15):1525-1538, 2006b 17035647
- Schulz SC: Pharmacologic treatment of schizophrenia. *Psychiatr Clin North Am* 6:51-71, 1999
- Schulz SC, Cornelius K: Statement 6: Second-generation antipsychotics are effective mood stabilizers. *Curr Psychiatry* 9 (suppl):S37-S43, 2010
- Schulz SC, Camlin KL, Berry SA, Jesberger JA: Olanzapine safety and efficacy in patients with borderline personality disorder and comorbid dysthymia. *Biol Psychiatry* 46(10):1429-1435, 1999 10578457
- Schulz SC, Zanarini MC, Bateman A, et al: Olanzapine for the treatment of borderline personality disorder: variable dose 12-week randomised double-blind placebo-controlled study. *Br J Psychiatry* 193(6):485-492, 2008 19043153
- Seeman P: Atypical antipsychotics: mechanism of action. *Can J Psychiatry* 47(1):27-38, 2002 11873706
- Sernyak MJ, Leslie DL, Alarcon RD, et al: Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 159(4): 561-566, 2002 11925293
- Shapira NA, Ward HE, Mandoki M, et al: A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biol Psychiatry* 55(5):553-555, 2004 15023585

- Sharma RP, Janicak PG, Bissette G, Nemeroff CB: CSF neurotensin concentrations and antipsychotic treatment in schizophrenia and schizoaffective disorder. *Am J Psychiatry* 154(7):1019-1021, 1997 9210757
- Sharpley AL, Vassallo CM, Cowen PJ: Olanzapine increases slow-wave sleep: evidence for blockade of central 5-HT(2C) receptors in vivo. *Biol Psychiatry* 47(5):468-470, 2000 10704958
- Shi L, Namjoshi MA, Swindle R, et al: Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial. *Clin Ther* 26(1):125-134, 2004 14996525
- Sikich L, Hamer RM, Bashford RA, et al: A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology* 29(1):133-145, 2004 14583740
- Sikich L, Frazier JA, McClellan J, et al: Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *Am J Psychiatry* 165(11):1420-1431, 2008 18794207
- Singh LK, Praharaj SK, Sahu M: Nonfatal suicidal overdose of olanzapine in an adolescent. *Curr Drug Saf* 7(4):328-329, 2012 23062245
- Soler J, Pascual JC, Campins J, et al: Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *Am J Psychiatry* 162(6):1221-1224, 2005 15930077
- Soloff PH, George A, Nathan RS, et al: Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. *Arch Gen Psychiatry* 43(7):691-697, 1986 3521532



- Stein MB, Kline NA, Matloff JL: Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry* 159(10): 1777-1779, 2002 12359687
- Stephenson CM, Pilowsky LS: Psychopharmacology of olanzapine. A review. *Br J Psychiatry Suppl* 174(38):52-58, 1999 10884900
- Stockton ME, Rasmussen K: Electrophysiological effects of olanzapine, a novel atypical antipsychotic, on A9 and A10 dopamine neurons. *Neuropsychopharmacology* 14(2):97-105, 1996a 8822532
- Stockton ME, Rasmussen K: Olanzapine, a novel atypical antipsychotic, reverses D-amphetamine-induced inhibition of midbrain dopamine cells. *Psychopharmacology (Berl)* 124(1-2):50-56, 1996b 8935800
- Street JS, Clark WS, Gannon KS, et al; The HGEU Study Group: Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 57(10):968-976, 2000 11015815
- Street JS, Clark WS, Kadam DL, et al: Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. *Int J Geriatr Psychiatry* 16 (suppl 1):S62-S70, 2001 11748789
- Swartz MS, Perkins DO, Stroup TS, et al; CATIE Investigators: Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *Am J Psychiatry* 164(3):428-436, 2007 17329467
- Tan HH, Hoppe J, Heard K: A systematic review of cardiovascular effects after atypical antipsychotic

medication overdose. *Am J Emerg Med* 27(5):607-616, 2009 19497468

Tanoshima R, Chandranipapongse W, Colantonio D, et al: Acute olanzapine overdose in a toddler: a case report. *Ther Drug Monit* 35(5):557-559, 2013 24052061

Tauscher J, Küfferle B, Asenbaum S, et al: In vivo 123I IBZM SPECT imaging of striatal dopamine-2 receptor occupancy in schizophrenic patients treated with olanzapine in comparison to clozapine and haloperidol. *Psychopharmacology (Berl)* 141(2):175-181, 1999 9952042

Thase ME, Corya SA, Osuntokun O, et al: A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry* 68(2):224-236, 2007 17335320

Theisen FM, Grabarkiewicz J, Fegbeutel C, et al: Olanzapine overdose in children and adolescents: two case reports and a review of the literature. *J Child Adolesc Psychopharmacol* 15(6):986-995, 2005 16379519

Theisen FM, Haberhausen M, Firnges MA, et al: No evidence for binding of clozapine, olanzapine and/or haloperidol to selected receptors involved in body weight regulation. *Pharmacogenomics J* 7(4):275-281, 2007 16983399

Tohen M, Sanger TM, McElroy SL, et al; Olanzapine HGEH Study Group: Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry* 156(5):702-709, 1999 10327902

Tohen M, Jacobs TG, Grundy SL, et al; The Olanzapine HGGW Study Group: Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 57(9):841-849, 2000 10986547

Tohen M, Baker RW, Altshuler LL, et al: Olanzapine versus divalproex in the treatment of acute mania. *Am J Psychiatry* 159(6):1011-1017, 2002 12042191

- Tohen M, Vieta E, Calabrese J, et al: Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 60(11): 1079-1088, 2003 14609883
- Tohen M, Greil W, Calabrese JR, et al: Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry* 162(7):1281-1290, 2005 15994710
- Tohen M, Kryzhanovskaya L, Carlson G, et al: Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry* 164(10):1547-1556, 2007 17898346
- Tollefson GD, Sanger TM: Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. *Am J Psychiatry* 154(4):466-474, 1997 9090332
- Tollefson GD, Beasley CM Jr, Tran PV, et al: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 154(4):457-465, 1997 9090331
- Tollefson GD, Birkett MA, Kiesler GM, Wood AJ; Lilly Resistant Schizophrenia Study Group: Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine. *Biol Psychiatry* 49(1):52-63, 2001 11163780
- Torgersen S, Kringlen E, Cramer V: The prevalence of personality disorders in a community sample. *Arch Gen Psychiatry* 58(6):590-596, 2001 11386989
- Tran PV, Tollefson GD, Sanger TM, et al: Olanzapine versus haloperidol in the treatment of schizoaffective disorder. Acute and long-term therapy. *Br J Psychiatry* 174:15-22, 1999 10211146

- Volavka J, Czobor P, Sheitman B, et al: Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry* 159(2):255-262, 2002 11823268
- Zacher JL, Roche-Desilets J: Hypotension secondary to the combination of intramuscular olanzapine and intramuscular lorazepam. *J Clin Psychiatry* 66(12):1614-1615, 2005 16401168
- Zanarini MC, Frankenburg FR: Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry* 62(11):849-854, 2001 11775043
- Zanarini MC, Frankenburg FR, Parachini EA: A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry* 65(7):903-907, 2004 15291677
- Zanarini MC, Schulz SC, Detke HC, et al: A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 72(10):1353-1362, 2011 21535995
- Zanarini MC, Schulz SC, Detke H, et al: Open-label treatment with olanzapine for patients with borderline personality disorder. *J Clin Psychopharmacol* 32(3):398-402, 2012 22544004

## CHAPTER 27

# Quetiapine

Peter F. Buckley, M.D.

Adriana E. Foster, M.D.

Matthew Byerly, M.D.

---

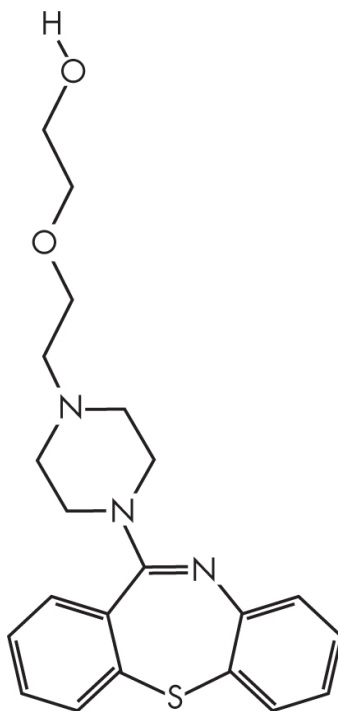
### History and Discovery

Quetiapine is a second-generation antipsychotic (SGA) developed and subsequently marketed by AstraZeneca. In preclinical trials, quetiapine showed the features associated with antipsychotic efficacy, as well as a low rate of motor effects ([Goldstein 1999](#); [Nemeroff et al. 2002](#)). Quetiapine was approved in 1997 by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia; it was subsequently approved in Europe and in other countries worldwide. Additional approvals and indications for quetiapine's use in bipolar disorder, as well as approval of an extended-release formulation of quetiapine, have followed ([Möller et al. 2007](#); [Peuskens et al. 2007](#)). The extended-release formulation has an additional indication as adjunctive treatment for major depression in patients who show inadequate response to antidepressants alone.

---

### Structure-Activity Relations

Quetiapine is an SGA of the dibenzothiazepine class ([Figure 27-1](#)). Its complex neuropharmacology includes a relatively low binding profile for dopamine type 2 ( $D_2$ ) receptors ([Kapur et al. 2000](#)). Indeed, considering the idea that an antipsychotic needs to occupy 60% or more of  $D_2$  receptors in order to be clinically efficacious ([Kapur et al. 2000](#)), quetiapine's low  $D_2$  binding—typically, approximately 30%—is noteworthy.



**FIGURE 27-1.** Chemical structure of quetiapine

Source. PubChem Compound Database, National Center for Biotechnology Information. Available at: <http://www.ncbi.nlm.nih.gov/pccompound>.

In attempting to reconcile this apparently subtherapeutic  $D_2$  receptor antagonism with the well-recorded efficacy of quetiapine as an antipsychotic, [Kapur et al. \(2000\)](#) proposed an elegant *kiss and run hypothesis* to explain quetiapine's mechanisms of action. In a series of studies, they found that when  $D_2$  receptor occupancy with quetiapine was measured with positron emission tomography at shorter intervals (4 hours and 6 hours) than the conventional 12 hours after the last dose was taken, quetiapine did indeed show high  $D_2$  occupancy. In contrast to other antipsychotics, quetiapine demonstrated a more rapid "run-off" from  $D_2$  receptors; that is, there was rapid dissociation of the  $D_2$  receptors ([Kapur et al. 2000](#)).

Like clozapine, quetiapine has strong binding at 5-hydroxytryptamine (serotonin) type 2 ( $5-HT_2$ ) receptors. This profile contrasts with its relatively weak affinity for other subclasses of the serotonin receptor family ([Nemeroff et al. 2002](#)). Quetiapine also has strong affinity for  $\alpha_1$ -noradrenergic receptors. This antagonism may relate to its propensity to induce postural hypotension—especially during rapid dosage titration. Additionally, quetiapine has strong antagonism at histamine type 1 ( $H_1$ ) receptors. This most likely relates to its sedative effect.  $H_1$  receptor antagonism also appears to be a key contributor to weight gain during quetiapine therapy ([Kim et al. 2007](#)).

---

## Pharmacokinetics and Disposition

---

Quetiapine's absorption in the gastrointestinal tract is unaffected by food. With the tablet formulation, peak blood levels are achieved in about 2 hours, with effective plasma levels

sustained for approximately 6 hours ([DeVane and Nemeroff 2001](#)). Although this provides the basis for the usual clinical regimen of twice-daily dosing, a short-term trial comparing once-daily dosing with twice-daily dosing demonstrated that the two regimens were equivalent in terms of efficacy and tolerability ([Chengappa et al. 2003b](#)). A positron emission tomography study ([Mamo et al. 2008](#)) found comparable plasma levels and D<sub>2</sub> receptor occupancy between the immediate-release (IR) and the extended-release (XR) formulation.

Quetiapine is metabolized by cytochrome P450 (CYP) 3A4 to inactive metabolites. Coadministration with drugs that alter CYP3A4 activity is likely to result in clinically significant interactions. For example, the anticonvulsants carbamazepine and phenytoin are CYP3A4 inducers, and in their presence quetiapine dosages may need to be increased because of accelerated drug clearance ([Potkin et al. 2002a, 2002b](#); [Strakowski et al. 2002](#)). Ritonavir, erythromycin, ketoconazole, and nefazodone are potent inhibitors of CYP3A4, and their concomitant use with quetiapine requires caution.

Clinical trials ([Kahn et al. 2007](#); [Lindenmayer et al. 2008](#)) comparing the efficacy and tolerability of the XR formulation with the regular IR formulation indicated that quetiapine XR given once daily (at dosages of 400–800 mg/day) was effective for the treatment of schizophrenia and, on average, was similar in efficacy and tolerability to treatment with quetiapine IR. Quetiapine is excreted in the kidneys and is not affected by gender or smoking status. The metabolism of quetiapine is reduced by approximately 30% with advancing age ([Goldstein 1999](#)). Quetiapine is available only in tablet formulations; there are no liquid or intramuscular preparations.

---

## Indications and Efficacy

---

Quetiapine in the XR and IR formulations is FDA approved for the following indications in adults: treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex; acute treatment of depressive episodes associated with bipolar I or II disorder; and maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex. The XR formulation is also approved for use as an adjunct to antidepressant therapy in the treatment of major depressive disorder in adults.

In addition, quetiapine is efficacious in the treatment of schizophrenia and bipolar disorder in pediatric populations ([Barzman et al. 2006](#); [DelBello et al. 2007](#); [McConville et al. 2000](#)). The IR formulation is FDA approved for the treatment of schizophrenia in adolescents (ages 13–17 years) and the acute treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents (ages 10–17 years).

There are also reports of quetiapine's efficacy in treating anxiety disorders, obsessive-compulsive disorder (OCD), borderline personality disorder, and Parkinson's disease. These uses have not been approved by the FDA. The use of any medication (in this case quetiapine) in situations that are not FDA-approved indications is not recommended in clinical practice.

## Schizophrenia

Registration and early trials of quetiapine ([Arvanitis and Miller 1997](#); [Borison et al. 1996](#); [Copolov et al. 2000](#); [King et al. 1998](#); [Peuskens and Link 1997](#); [Small et al. 1997](#))

demonstrated that quetiapine is an efficacious antipsychotic for the treatment of schizophrenia. Short-term (6-week) trials compared quetiapine, haloperidol, and placebo using quetiapine at flexible daily dosages of  $\leq 250$  mg or  $\leq 750$  mg (Small et al. 1997) or fixed daily dosages of 75 mg, 150 mg, 300 mg, 600 mg, or 750 mg (Arvanitis and Miller 1997); the latter trial found that 300 mg/day was superior (but not statistically significantly so) to the lower and higher dosages and was the only dosage demonstrating efficacy for negative symptoms (Arvanitis and Miller 1997). These studies established a range of effective dosages for quetiapine and also suggested that dosages of  $\geq 250$  mg/day were superior to lower dosages.

Subsequent studies helped refine quetiapine dosing strategies. An 8-week fixed-dosage comparison trial of quetiapine at 600 mg/day versus haloperidol at 20 mg/day showed similar efficacy for the two drugs in patients who were partial responders to first-generation antipsychotics (FGAs) (Emsley et al. 2000). A study comparing a rapid titration strategy (beginning at 200 mg/day, increasing to 800 mg/day by day 4) with a more conventional dosing strategy (50 mg/day on day 1, increasing up to 400 mg/day by day 5) showed similar efficacy and tolerability for the two strategies (Pae et al. 2007). Growing evidence from more recent studies (Honer et al. 2012; Lindenmayer et al. 2011) discourages the use of very-high-dosage quetiapine, and data are still lacking to indicate that dosages above 300–400 mg/day are more efficacious.

Most studies comparing quetiapine with either an FGA or another SGA have reported similar efficacy for the agents in treating schizophrenia (Emsley et al. 2000; Peuskens and Link 1997; Small et al. 1997). A 4-month open-label trial of quetiapine and risperidone showed overall comparability between the two agents (Mullen et al. 2001). An 8-week comparative trial of quetiapine (with an average dosage of 525 mg/day) and risperidone (with an average dosage of 5.2 mg/day) also found the drugs similar in efficacy (Zhong et al. 2006). Quetiapine-treated patients had fewer extrapyramidal side effects (EPS), lower prolactin levels, and fewer sexual side effects. Whereas weight gain was similar in both treatment groups, quetiapine was more sedating and was more frequently associated with dry mouth than was risperidone. A 6-month study comparing quetiapine and risperidone reported better efficacy for risperidone (Potkin et al. 2006), with quetiapine associated with more polypharmacy. A 6-month double-blind comparative trial of quetiapine and olanzapine (Kinon et al. 2006) reported that quetiapine-treated patients were less likely to complete the study, although relapse rates were comparable overall in the two treatment groups. More weight gain occurred in olanzapine recipients. As yet, no studies have directly compared quetiapine with aripiprazole, iloperidone, asenapine, or lurasidone in the treatment of schizophrenia.

The most extensive comparative evaluation of quetiapine and other SGAs comes from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). In the Phase I study, more quetiapine-treated patients than olanzapine-treated patients had discontinued treatment by 18 months (78% vs. 64%), and a similar (not statistically significant) trend was seen in comparisons of quetiapine versus risperidone, ziprasidone, or perphenazine (Lieberman et al. 2005). In the Phase II study, discontinuation rates favored clozapine and olanzapine over risperidone and quetiapine (McEvoy et al. 2006). The results from the tolerability pathways were mixed and showed similar efficacy for quetiapine versus other agents (Stroup et al. 2007). The findings relating to quetiapine's relative adverse-effects profile in this formative study are presented in the section "Side Effects and Toxicology." Another interesting analysis from the CATIE schizophrenia studies (Stroup et al. 2007) examined how those patients originally assigned to the perphenazine arm of the Phase I study fared. In this analysis, switching to quetiapine was more efficacious than switching



to any of the other agents. Many of the efficacy and tolerability differences among agents observed in the CATIE schizophrenia studies have been attributed to differential dosing profiles.

An analogous comparative trial of quetiapine, risperidone, and olanzapine was conducted with patients experiencing a first episode of psychosis—the Comparison of Atypicals in First Episode Psychosis (CAFE) study. Here, discontinuation rates were similar across drugs over the 1-year trial ([McEvoy et al. 2007](#)). Two recent studies inform the comparative efficacy and tolerability of quetiapine in adolescents with psychosis (and related conditions) ([Arango et al. 2014](#); [Pérez-Iglesias et al. 2014](#)). [Pérez-Iglesias et al. \(2014\)](#) found that quetiapine increased weight and cholesterol levels over 3 months. Similarly, [Arango et al. \(2014\)](#) found that quetiapine increased weight (less so than olanzapine, more so than risperidone) over 6 months in children and adolescents, although in this study, there was no rise in cholesterol in quetiapine-treated patients.

The use of quetiapine in patients with prodromal features of schizophrenia has not yet been studied. A small study of quetiapine in schizophrenia patients with comorbid substance abuse was inconclusive ([Brunette et al. 2009](#)).

## Mood Disorders

There is evidence that quetiapine is an effective and well-tolerated antipsychotic for treating patients with bipolar mania and bipolar depression. [Bowden et al. \(2005\)](#) demonstrated that quetiapine was superior to placebo in the treatment of mania. In this multicenter study, significantly more patients treated with quetiapine than with placebo met criteria for response (greater than 50% decrease from baseline score on the Young Mania Rating Scale) at 7, 21, and 84 days. Building on initial evidence for mood effects that was derived from observations on mood assessment items in the pivotal schizophrenia trials, the Quetiapine Experience with Safety and Tolerability (QUEST) study compared quetiapine with risperidone in a 4-month open-label, flexible-dose trial ([Mullen et al. 2001](#)). This study included patients with schizophrenia, schizoaffective disorder, bipolar disorder, and depression. At week 16, the mean dosage of quetiapine was 317 mg/day, and the mean dosage of risperidone was 4.5 mg/day. Mean improvement on the Hamilton Rating Scale for Depression was significantly greater in quetiapine recipients than in risperidone recipients.

[Calabrese et al. \(2005\)](#) and [Thase et al. \(2006\)](#) have studied quetiapine use in patients with bipolar depression. In an 8-week trial, [Calabrese et al. \(2005\)](#) compared two dosages of quetiapine (300 mg/day and 600 mg/day) with placebo. Both dosages were efficacious, with improvements observed across the full range of depressive and anxiety symptoms. Fifty-eight percent of patients met a priori criteria for treatment response. Additionally, this antidepressant effect was observed with a once-daily dosage regimen. In a subsequent similar study ([Thase et al. 2006](#)) of the same two dosages (300 mg/day and 600 mg/day), quetiapine was again compared with placebo in an 8-week trial in patients with bipolar depression. Again, both dosages of quetiapine showed efficacy across a broad range of depressive symptoms. These two studies led to FDA approval of quetiapine for treating bipolar depression.

Two large 8-week international multicenter studies—Efficacy of Monotherapy Seroquel in BipOLar DEpression (EMBOLDEN) I ([Young et al. 2010](#)) and II ([McElroy et al. 2010](#))—compared quetiapine 300 mg/day and 600 mg/day with lithium 600–1,800 mg/day and placebo (EMBOLDEN I) and with paroxetine 20 mg/day and placebo (EMBOLDEN II) in bipolar patients with a major depressive episode. In the first study ([Young et al. 2010](#)),

quetiapine at both dosages, but not lithium, led to significant improvement in symptoms of depression and anxiety. Compared with patients receiving placebo, patients treated with quetiapine 300 mg/day and 600 mg/day showed significant improvement on the Sheehan Disability Scale. In the second study ([McElroy et al. 2010](#)), quetiapine 300 mg/day and 600 mg/day, but not paroxetine 20 mg/day, led to significant improvement in depressive and anxiety symptoms. Neither lithium nor paroxetine led to significant functional improvement over placebo in these studies. In both studies, a small subgroup of patients with rapid-cycling bipolar disorder did not improve significantly from baseline with any of the drugs administered (quetiapine, lithium, or paroxetine).

In a long-term naturalistic study ([Ketter et al. 2010](#)) of quetiapine administered to 96 patients with bipolar disorder in a clinical setting, 38.5% of patients continued taking quetiapine for 328 days without the addition of other psychotropics, whereas 22.9% of patients continued taking quetiapine for 613 days with the addition of another psychotropic, most often for depression. In a small double-blind, placebo-controlled pilot study ([DelBello et al. 2009](#)) of quetiapine 300–600 mg/day in depressed adolescents with bipolar disorder, quetiapine neither differentiated from placebo nor induced significant change in symptoms from baseline to endpoint on measures of depressive, anxiety, or manic symptoms or clinical global impressions of bipolar severity. [Bourin et al. \(2014\)](#) reported superior efficacy when lithium was added to quetiapine XR, and this combination was well tolerated.

[Dorée et al. \(2007\)](#) reported that in a pilot study ( $n=20$ ), quetiapine was an efficacious augmenting agent for antidepressant treatment in major depression. [Anderson et al. \(2009\)](#) also reported on quetiapine's efficacy as an adjunctive treatment for patients with refractory depression. Quetiapine XR monotherapy at a mean daily dosage of 162.2 mg was shown to decrease symptoms of major depression at 8 weeks versus placebo ([Bortnick et al. 2011](#)). [Cutler et al. \(2009\)](#) reported that quetiapine XR 300 mg/day led to significantly higher rates of response and remission versus placebo in major depression, whereas quetiapine XR 150 mg/day had a significant effect only on response versus placebo. Quetiapine at dosages of 150–300 mg/day is now approved by the FDA as an adjunct to antidepressant treatment for a major depressive episode. In one of the studies leading to FDA approval of quetiapine XR for this indication, [El-Khalili et al. \(2010\)](#) demonstrated that quetiapine XR at 300 mg/day led to significant improvement in symptoms of depression from the first week of treatment when compared with placebo. In a review of registration studies for the major depression indication, [McIntyre et al. \(2009\)](#) concluded that quetiapine XR provides rapid and sustained relief of major depressive symptoms. [Weisler et al. \(2012\)](#) also reported substantial improvement in depressive symptoms in two 6-week clinical trials of quetiapine XR. Remission at 6 weeks was achieved by 23.5% of patients taking 150 mg/day and by 28.8% of patients taking 300 mg/day of quetiapine. [Lin et al. \(2014\)](#) used a national insurance database from Taiwan to compare in a mirror image design the effect of augmentation of antidepressant therapy over 1 year in patients with major depressive disorder. Quetiapine, olanzapine, and aripiprazole augmentations were each effective in reducing health care utilization. [Masi et al. \(2015\)](#) reported improvement from and tolerability of quetiapine in a small open-label study comparing quetiapine and risperidone in adolescents with bipolar disorder and comorbid conduct disorder.

## Anxiety Disorders

The sedative/calming effect of quetiapine was well described in a variety of product registration trials ([Chengappa et al. 2003a](#); [Weiden et al. 2006](#)), and studies in bipolar I disorder and bipolar depression ([Calabrese et al. 2005](#); [Hirschfeld et al. 2006](#); [Thase et al. 2006](#)) demonstrated improvements in anxiety symptoms with quetiapine.

In a small 8-week study ([Vaishnavi et al. 2007](#)) of social phobia treatment, there was no significant difference in Brief Social Phobia Scale scores between the quetiapine and placebo groups, although people who took quetiapine did show a robust response as measured by Clinical Global Impression—Improvement Scale (CGI-I) scores.

Two small studies of quetiapine augmentation in patients with generalized anxiety disorder (GAD) who had not responded to antidepressant therapy ([Katzman et al. 2008](#); [Simon et al. 2008](#)) yielded contradictory results. A large double-blind, randomized, placebo-controlled study of monotherapy for GAD ([Bandelow et al. 2010](#)) compared quetiapine XR 50 mg/day or 150 mg/day, paroxetine 20 mg/day, and placebo. Significant separation from placebo on the primary outcome variable (mean reduction in Hamilton Anxiety Scale (Ham-A) total score) was seen for quetiapine XR 50 mg/day and 150 mg/day as early as 4 days into treatment, but not for paroxetine. After 8 weeks of treatment, both quetiapine 150 mg/day and paroxetine 20 mg/day had higher anxiety remission rates (Ham-A score  $\leq 7$ ) compared with placebo. Weight gain greater than or equal to 7% of body weight was noted in a higher percentage of patients treated with quetiapine than of those taking placebo. In a parallel-group, double-blind, placebo-controlled study by [Katzman et al. \(2011\)](#), 432 patients with GAD were randomly assigned to continue treatment long term with quetiapine XR (50 mg/day, 150 mg/day, or 300 mg/day) or to switch to placebo after an open-label run-in and stabilization period. During the randomized treatment period (from the point of random assignment to the end of the study), quetiapine XR significantly increased the time to occurrence of an anxiety event and decreased anxiety symptoms compared with placebo.

An analysis of the tolerability of quetiapine in patients with various disorders showed that patients with GAD, bipolar depression, or refractory major depression had significantly higher rates of discontinuation due to adverse effects versus placebo than did patients with schizophrenia or mania when treated with quetiapine XR dosages of  $\geq 300$  mg/day ([Wang et al. 2011](#)). In a systematic review and meta-analysis of all available trials of SGA medications, quetiapine was observed to have the most robust effect on anxiety symptoms ([LaLonde and Van Lieshout 2011](#)). The antianxiety effects of quetiapine were observed at lower dosages (typically 150 mg/day) than those used in schizophrenia studies, and the effects included overall improvement as well as remission. However, quetiapine was also associated with weight gain and high rates of medication discontinuation in these studies of anxiety disorder ([LaLonde and Van Lieshout 2011](#)). In three 8-week studies of quetiapine XR, [Stein et al. \(2011\)](#) reported rates of study discontinuation due to side effects of 13%, 16%, and 24% for quetiapine dosages of 50 mg/day, 150 mg/day, and 300 mg/day, respectively. In an 8-week placebo-controlled comparative trial of quetiapine XR and escitalopram, comparable improvements in anxiety symptoms, occurring early in the study, were observed with quetiapine and escitalopram ([Merideth et al. 2012](#)). In a more “real-world” population of patients with bipolar depression with substantial comorbidities (especially GAD), quetiapine XR showed no advantages over placebo in an 8-week trial ([Gao et al. 2014](#)).

At present, the FDA has not approved quetiapine for use in any anxiety disorders.

## Other Disorders

Several small studies of quetiapine augmentation (at dosages up to 400 mg/day) of SSRI pharmacotherapy in refractory OCD yielded contradictory results ([Atmaca et al. 2002](#); [Carey et al. 2005](#); [Fineberg et al. 2005](#)); although improvement in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores was noted in patients treated with quetiapine, the response to quetiapine did not differentiate from placebo. Quetiapine's efficacy as an augmenting agent with antidepressants in treatment-resistant OCD was recently reviewed in a meta-analysis of five double-blind randomized controlled trials (RCTs) ([Komossa et al. 2010](#)). Adjunctive quetiapine was not superior to placebo in reducing Y-BOCS scores by 25% (the criterion for response in these studies), but it did reduce the Y-BOCS score significantly by the endpoint compared with placebo. A small case series also showed that adjunctive quetiapine response may be enduring ([Dell'Osso et al. 2006](#)). [Veale et al. \(2014\)](#) conducted a meta-analysis of SGAs in OCD. In contrast to benefits seen with risperidone or aripiprazole, there was no effect seen with augmentation with either quetiapine or olanzapine.

Quetiapine has been studied in the treatment of posttraumatic stress disorder ([Ahearn et al. 2006](#); [Byers et al. 2010](#); [Hamner et al. 2003](#); [Kozaric-Kovacic and Pivac 2007](#); [Sokolski et al. 2003](#); [Stathis et al. 2005](#)). All but one of the studies ([Stathis et al. 2005](#)) involved quetiapine being administered to veterans as an adjunctive agent added to selective serotonin reuptake inhibitors (SSRIs), other antidepressants, sedative-anxiolytics, or anticonvulsants. All were open-label studies, and with the exception of a retrospective chart review comparing quetiapine with the  $\alpha_1$  receptor antagonist prazosin ([Byers et al. 2010](#)), none had a comparison group. The average quetiapine dosage used in these studies was 100–335 mg/day administered for 6–8 weeks. Quetiapine decreased symptoms of avoidance, hyperarousal, and recollection in the populations studied.

## Other Conditions and Patient Populations

Quetiapine has also been used in elderly populations. In a 1-year open-label trial of quetiapine treatment in 151 elderly patients (mean age 76.8 years) with psychotic disorders ([McManus et al. 1999](#)), 52% of patients showed symptom improvement (as measured by a 20% or greater decline in Brief Psychiatric Rating Scale total score). Seventy percent of patients had some organic condition, predominantly Alzheimer's disease, with the remaining patients having a diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder. Quetiapine was well tolerated at a mean dosage of 100 mg/day. A 10-week study comparing two dosages of quetiapine (100 mg/day and 200 mg/day) with placebo in nursing home residents with dementia and agitation ([Zhong et al. 2007](#)) reported that only the 200 mg/day quetiapine dosage was efficacious in treating agitation. Quetiapine (100 mg/day) was also compared with risperidone (1.0 mg/day), olanzapine (5.5 mg/day), and placebo over 36 weeks in the CATIE Alzheimer's disease study ([Schneider et al. 2006](#)). Overall, no effect on the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale was seen with any of the agents, and there were no differences between agents in time to discontinuation.

In contrast to the encouraging findings from open-label studies of quetiapine for Parkinson's-associated psychosis, four of five later double-blind RCTs ([Kurlan et al. 2007](#); [Ondo et al. 2005](#); [Rabey et al. 2007](#); [Shotbolt et al. 2009](#)) found no benefit for quetiapine in this population. The single positive RCT ([Fernandez et al. 2009](#)) was small ( $N=16$ ) and excluded patients with delusions, which appear to be more difficult to treat than hallucinations in Parkinson's disease ([Shotbolt et al. 2010](#)).

Agitation is a core aspect of several conditions. [Currier et al. \(2006\)](#) reported an interesting study of quetiapine in agitated patients in the emergency department. Here, Currier and colleagues reported that quetiapine could be used as an acute antiagitation agent if the dosage titration is judicious. Postural hypotension was observed in this study. Other studies of quetiapine and agitation report benefits in treating hostility both in adults with schizophrenia ([Chengappa et al. 2003a](#)) or bipolar disorder ([Buckley et al. 2007](#)) and in children with hostile behaviors ([Barzman et al. 2006](#); [Findling et al. 2007](#)).

[Black et al. \(2014\)](#) examined low-dosage quetiapine (150 mg/day) and moderate-dosage quetiapine (300 mg/day) versus placebo in an 8-week, double-blind trial of inpatients with borderline personality disorder. Both dosages of quetiapine were effective across a range of symptoms in these patients, although there were more side effects with moderate-dosage quetiapine.

## Side Effects and Toxicology

To illustrate the profile of adverse effects typically seen with quetiapine, we have tabulated the results from an 8-week RCT ([Zhong et al. 2006](#)) ([Table 27-1](#)) in which quetiapine was compared with risperidone. Overall, quetiapine was well tolerated, with only 6% of patients discontinuing treatment because of adverse effects.

**TABLE 27-1. Comparative side-effect profile of quetiapine versus risperidone: adverse effects present in  $\geq 5\%$  of patients in an 8-week study**

Adverse effect	Quetiapine ( <i>n</i> =338; median dosage=525 mg/day)	Risperidone ( <i>n</i> =334; median dosage=5.2 mg/day)	<i>P</i> value <sup>a</sup>
	<i>n</i> (%)	<i>n</i> (%)	
Somnolence	89 (26.3)	66 (19.7)	0.044
Headache	51 (15.1)	56 (16.7)	0.599
Weight gain	48 (14.2)	45 (13.4)	0.824
Dizziness	48 (14.2)	32 (9.6)	0.0737
Dry mouth	41 (12.1)	17 (5.1)	<0.01
Dyspepsia	22 (6.5)	26 (7.8)	0.552
Nausea	21 (6.2)	22 (6.6)	0.876
Pain	21 (6.2)	24 (7.2)	0.536
Asthenia	17 (5.0)	14 (4.2)	0.714
Agitation	17 (5.0)	10 (3.0)	0.238
Pharyngitis	15 (4.4)	24 (7.2)	0.140
Akathisia	13 (3.8)	28 (8.4)	0.016
Vomiting	13 (3.8)	18 (5.4)	0.364
Dystonia	1 (0.3)	18 (5.4)	<0.001

<sup>a</sup>Fisher exact test, unadjusted.

Source. Adapted from [Zhong et al. 2006](#).



Overall, the adverse-effect profile of the XR formulation of quetiapine is similar to that of the IR formulation.

## Somnolence, Sedation, and Dizziness

Somnolence is a common side effect of quetiapine that most likely relates to its antihistaminergic activity. Although somnolence occurs early in treatment and generally decreases over time, it may persist in some patients. It may also cause patients to stop taking their medication, because sedation is generally a poorly tolerated side effect. In the bipolar depression study by [Calabrese et al. \(2005\)](#), somnolence was observed in 24% of patients taking quetiapine at a dosage of 300 mg/day and in 27% of patients taking 600 mg/day. In the long-term study by [Ketter et al. \(2010\)](#), sedation was present in 19.8% of patients. Dizziness is another troublesome side effect, and it may be associated with postural hypotension, an effect that is of even greater concern. As with sedation, dizziness can sometimes cause discontinuation of quetiapine therapy.

## Metabolic Effects

There is major concern about antipsychotic-induced weight gain and metabolic disturbances ([Allison et al. 1999](#); [Newcomer 2005](#); [Newcomer et al. 2002](#)). Quetiapine is clearly associated with weight gain, although the weight gain effect is not as great as that seen with clozapine or olanzapine. On the other hand, the weight-effects profile of quetiapine is not as favorable as that of ziprasidone or aripiprazole ([Newcomer 2005](#)) or that of the newer agents asenapine and lurasidone ([Allergan 2015](#); [Sunovion 2013](#)).

In the 8-week comparative study by [Zhong et al. \(2006\)](#), weight gain that was clinically significant (a 7% increase above baseline weight) was observed in 10.4% of patients taking quetiapine and in 10.5% of patients taking risperidone. In the Phase I CATIE study, quetiapine had a moderate effect on weight (and other aspects of the metabolic profile) compared with other agents ([Lieberman et al. 2005](#)). Those data are shown in [Table 27-2](#). In the first-episode CAFE study, quetiapine had a less favorable weight-effects profile compared with olanzapine or risperidone. Eighty percent of patients taking quetiapine gained weight, compared with 50% of those taking olanzapine and 2% of those taking risperidone. Interestingly, females taking quetiapine were less likely than males to gain weight in this 1-year study of patients treated for their first episode of psychosis ([Patel et al. 2009](#)). It is also important to consider quetiapine’s propensity to induce weight gain among bipolar patients (especially because these patients may also be taking lithium or valproic acid). In the 8-week EMBOLDEN I ([Young et al. 2010](#)) and EMBOLDEN II ([McElroy et al. 2010](#)) trials, weight gain of more than 7% body weight was present in 4.6% and 9%, respectively, of patients taking quetiapine 300 mg/day versus 8.3% and 11.3%, respectively, of those taking quetiapine 600 mg/day. In EMBOLDEN I and EMBOLDEN II, the average weight gains in quetiapine-treated patients were 0.6 kg and 1.1 kg, respectively, for the 300-mg/day groups and 0.8 kg and 1.7 kg, respectively, for the 600-mg/day groups.

**TABLE 27-2. Comparative metabolic profiles of antipsychotics in the Phase I CATIE schizophrenia trial: change from baseline**

Olanzapine	Quetiapine	Perphenazine	Risperidone	Ziprasidone	P value
------------	------------	--------------	-------------	-------------	---------

	Olanzapine	Quetiapine	Perphenazine	Risperidone	Ziprasidone	<i>P</i> value
Weight gain >7%, <i>n</i> /total <i>N</i> (%)	92/307 (30)	49/305 (16)	29/243 (12)	42/300 (14)	12/161 (7)	<0.001
Weight change (lb), mean±SE	9.4±0.9	1.1±0.9	−2.0±1.10	0.8±0.9	−1.6±1.10	<0.001
Blood glucose change (mg/dL), exposure- adjusted mean±SE	13.7±2.50	7.5±2.5	5.4±2.8	6.6±2.5	2.9±3.4	0.5
Glycosylated Hb (%), exposure- adjusted mean±SE	0.40±0.07	0.04±0.08	0.09±0.09	0.07±0.08	0.11±0.09	0.0
Cholesterol (mg/dL), exposure- adjusted mean±SE	9.4±2.4	6.6±2.4	1.5±2.7	−1.3±2.40	−8.2±3.20	<0.001
Triglycerides (mg/dL), exposure- adjusted mean±SE	40.5±8.90	21.2±9.20	9.2±10.1	−2.4±9.10	−16.5±12.20	<0.001

*Note.* Hb=hemoglobin; SE=standard error. *P* values for laboratory values and for the change in weight are based on ranked analysis of covariance with adjustment for whether patient had a recent exacerbation in the preceding 3 months and the duration of exposure to the study drug in FIM. Mean values for metabolic factors (other than weight change) were also adjusted for duration of exposure to study drug.

Source. Adapted from [Lieberman et al. 2005](#).

In the bipolar depression study by [Calabrese et al. \(2005\)](#), the mean changes in glucose levels were 6 mg/dL and 3 mg/dL with quetiapine dosages of 600 mg/day and 300 mg/day, respectively. In the comparative study of quetiapine and risperidone in the treatment of schizophrenia ([Zhong et al. 2006](#)), the mean changes from baseline in fasting glucose

levels were 1.8 mg/dL with quetiapine and 5.6 mg/dL with risperidone. The metabolic profile of quetiapine appeared moderate in the Phase I CATIE schizophrenia study (see [Table 27-2](#)). [Newcomer et al. \(2009\)](#) conducted a euglycemic clamp study of quetiapine and found little evidence of insulin insensitivity. A recent meta-analysis by the Cochrane group involving head-to-head comparisons of SGAs ([Komossa et al. 2010](#)) found that quetiapine was associated with significantly greater cholesterol elevations than risperidone (mean difference 8.61 mg/dL) and ziprasidone (mean difference 16.01 mg/dL). In the CATIE Phase I trial ([Lieberman et al. 2005](#)), which included patients with chronic schizophrenia, quetiapine led to a mean change from baseline fasting triglyceride levels of +19.2 mg/dL, whereas a mean change of +42.9 mg/dL was observed for olanzapine, +8.3 mg/dL for perphenazine, -2.6 mg/dL for risperidone, and -18.1 mg/dL for ziprasidone. In a population of young patients with early psychosis treated with quetiapine, olanzapine, or risperidone, the CAFE study ([Patel et al. 2009](#)) found that elevations in fasting triglyceride levels at 52 weeks were significantly greater in quetiapine-treated patients than in risperidone-treated patients (44.3 vs. 8.2 ng/mL, respectively). [Correll et al. \(2014\)](#) reported baseline results from the pragmatic study Recovery After an Initial Schizophrenia Episode (RAISE). All patients were in their first episode of psychosis, with less than 6 months of exposure to antipsychotics. Use of quetiapine was associated with a high ratio of triglycerides to high-density lipoprotein (HDL) cholesterol. The extent to which patients traverse during treatment from a normative metabolic state to dysregulation is also informative. In the first-episode CAFE study, treatment-emergent metabolic syndrome was observed among 51 patients (13.4% of the population in a study where 4.3% met metabolic syndrome criteria at study onset), with a distribution of 22 patients taking olanzapine, 18 taking quetiapine, and 11 taking risperidone ([Patel et al. 2009](#)). Another recent study of antipsychotic use in adolescents found an elevated risk of type 2 diabetes mellitus, with longer duration of antipsychotic exposure and olanzapine use conferring greater risk ([Correll et al. 2014](#)). In another first-episode comparative study, [Pérez-Iglesias et al. \(2014\)](#) found that first-episode patients treated with quetiapine, aripiprazole, or ziprasidone gained weight over 12 weeks of treatment, with >7% weight increase noted for 32% of patients receiving quetiapine, 45% of those receiving aripiprazole, and 23% of those receiving ziprasidone. Quetiapine and aripiprazole were also associated with greater increases in total cholesterol and low-density lipoprotein (LDL) cholesterol. Overall, quetiapine appears to carry a risk of causing weight gain and other metabolic disturbances. The potential that quetiapine may preferentially raise triglycerides is noteworthy, given that this effect could be a harbinger for later insulin resistance. This observation merits further consideration and vigilance over time.

Quetiapine is associated with a low risk of raising prolactin levels ([Hamner et al. 1996](#); [Lieberman et al. 2005](#); [Small et al. 1997](#); [Zhong et al. 2006](#)).

## Extrapyramidal Side Effects

The low-EPS advantage of quetiapine is compelling and consistent across studies. In the Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication (SPECTRUM) switch study ([Larmo et al. 2005](#)), switching to quetiapine from haloperidol, olanzapine, or risperidone was associated with a robust reduction in EPS. This low propensity for EPS was also seen in the bipolar depression studies ([Calabrese et al. 2005](#); [Thase et al. 2006](#)).



## Cardiovascular Effects

Quetiapine's prescribing information ([AstraZeneca 2013a, 2013b](#)) carries a warning similar to that required in the prescribing information of many other antipsychotics concerning cardiovascular risks. The CATIE trial found no evidence of a heightened QTc risk with quetiapine relative to other SGAs and perphenazine ([Lieberman et al. 2005](#)). A curious and unsubstantiated claim is that quetiapine might have abuse potential ([Pierre et al. 2005](#); [Pinta and Taylor 2007](#)). This observation merits further consideration and vigilance.

## Other Effects

The potential of quetiapine to induce cataracts was studied in a pragmatic follow-up trial of patients ( $N=37$ ; mean age 23 years) with first-episode psychosis that included regular slit-lamp ophthalmological examinations ([Whitehorn et al. 2004](#)). After exposure to quetiapine 500–600 mg/day for a mean of 22.4 months, none of the patients developed any ocular changes. Most clinicians do not obtain specialist eye examinations when prescribing quetiapine.

Abnormalities in thyroid hormone levels were observed in the large premarketing trials of quetiapine ([Arvanitis and Miller 1997](#)). A small RCT did find lower total thyroid hormone levels with quetiapine use, but no significant changes in free thyroxine ( $T_4$ ) or thyroid-stimulating hormone (TSH) levels ([Kelly and Conley 2005](#)).

## Use During Pregnancy

As is the case with all SGAs, there is little information about the effects of quetiapine during pregnancy. A prospective study by [McKenna et al. \(2005\)](#) examined a sample of pregnant women in Canada, Israel, and England treated with SGAs, which was matched to a comparison group of pregnant women who were not exposed to these agents. Among them were 36 women treated with quetiapine. The pregnancy outcomes in the exposed and comparison groups were not significantly different, with the exceptions of the rate of low birth weight, which was 10% in exposed babies versus 2% in the comparison group ( $P=0.05$ ), and the rate of therapeutic abortions, which was 9.9% in exposed women versus 1.3% in the comparison group ( $P=0.003$ ). These findings suggest that atypical antipsychotics as a group are not associated with an increased risk for major malformations.

---

## Conclusion

---

Quetiapine is now a well-established and widely prescribed antipsychotic. As detailed earlier, there is strong evidence for its efficacy in all of the current FDA-approved indications. Quetiapine is also used extensively under circumstances not approved by the FDA (i.e., off-label use), and evidence for its efficacy in some of these uses has been reviewed in this chapter. Additional clinical trials of quetiapine are ongoing (<https://clinicaltrials.gov>).

---

## References

---

- Ahearn EP, Mussey M, Johnson C, et al: Quetiapine as an adjunctive treatment for post-traumatic stress disorder: an 8-week open-label study. *Int Clin Psychopharmacol* 21(1):29-33, 2006 16317314
- Allergan: Saphris (asenapine) sublingual tablets, full prescribing information. March 2015. Available at: [http://www.allergan.com/assets/pdf/saphris\\_pi](http://www.allergan.com/assets/pdf/saphris_pi). Accessed April 3, 2016.
- Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156(11):1686-1696, 1999 10553730
- Anderson IM, Sarsfield A, Haddad PM: Efficacy, safety and tolerability of quetiapine augmentation in treatment resistant depression: an open-label, pilot study. *J Affect Disord* 117(1-2):116-119, 2009 19171384
- Arango C, Giráldez M, Merchán-Naranjo J, et al: Second-generation antipsychotic use in children and adolescents: a six-month prospective cohort study in drug-naïve patients. *J Am Acad Child Adolesc Psychiatry* 53(11):1179-1190, 1190.e1-1190.e4, 2014 25440308
- Arvanitis LA, Miller BG: Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry* 42(4):233-246, 1997 9270900
- AstraZeneca: Seroquel (quetiapine fumarate) tablets, full prescribing information. October 2013a. Available at: <http://www.azpicentral.com/seroquel/seroquel.pdf>. Accessed April 3, 2016.
- AstraZeneca: Seroquel XR (quetiapine fumarate) extended-release tablets, full prescribing information. October 2013b. Available at: <http://www.azpicentral.com/seroquel-xr/seroquelxr.pdf>. Accessed April 3, 2016.
- Atmaca M, Kuloglu M, Tezcan E, et al: Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol* 17(3):115-119, 2002 11981352
- Bandelow B, Chouinard G, Bobes J, et al: Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and active-controlled study. *Int J Neuropsychopharmacol* 13(3):305-320, 2010 19691907
- Barzman DH, DelBello MP, Adler CM, et al: The efficacy and tolerability of quetiapine versus divalproex for the treatment of impulsivity and reactive aggression in adolescents with co-occurring bipolar disorder and disruptive behavior disorder(s). *J Child Adolesc Psychopharmacol* 16(6):665-670, 2006 17201610
- Black DW, Zanarini MC, Romine A, et al: Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 171(11):1174-1182, 2014 24968985
- Borison RL, Arvanitis LA, Miller BG; U.S. SEROQUEL Study Group: ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *J Clin Psychopharmacol* 16(2):158-169, 1996 8690831
- Bortnick B, El-Khalili N, Banov M, et al: Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in major depressive disorder: a placebo-controlled, randomized study. *J Affect Disord* 128(1-2):83-94, 2011 20691481
- Bourin MS, Severus E, Schronen JP, et al: Lithium as add-on to quetiapine XR in adult patients with acute mania: a 6-week, multicenter, double-blind, randomized, placebo-controlled study. *Int J Bipolar Disord* 2:14, 2014 25505693
- Bowden CL, Grunze H, Mullen J, et al: A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 66(1):111-121, 2005 15669897
- Brunette MF, Dawson R, O'Keefe C, et al: An open label study of quetiapine in patients with schizophrenia and alcohol disorders. *Mental Health and Substance Use* 2(3):203-211,

2009

- Buckley PF, Paulsson B, Brecher M: Treatment of agitation and aggression in bipolar mania: efficacy of quetiapine. *J Affect Disord* 100 (suppl 1):S33-S43, 2007 17376537
- Byers MG, Allison KM, Wendel CS, et al: Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. *J Clin Psychopharmacol* 30(3):225-229, 2010 20473055
- Calabrese JR, Keck PE Jr, Macfadden W, et al: A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 162(7):1351-1360, 2005 15994719
- Carey PD, Vythilingum B, Seedat S, et al: Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study [ISRCTN 83050762] (ISRCTN 83050762). *BMC Psychiatry* 5:5, 2005 15667657
- Chengappa KN, Goldstein JM, Greenwood M, et al: A post hoc analysis of the impact on hostility and agitation of quetiapine and haloperidol among patients with schizophrenia. *Clin Ther* 25(2):530-541, 2003a 12749512
- Chengappa KN, Parepally H, Brar JS, et al: A random-assignment, double-blind, clinical trial of once- vs twice-daily administration of quetiapine fumarate in patients with schizophrenia or schizoaffective disorder: a pilot study. *Can J Psychiatry* 48(3):187-194, 2003b 12728743
- Copolov DL, Link CG, Kowalczyk B: A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, 'Seroquel') and haloperidol in schizophrenia. *Psychol Med* 30(1):95-105, 2000 10722180
- Correll CU, Robinson DG, Schooler NR, et al: Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry* 71(12):1350-1363, 2014 25321337
- Currier GW, Trenton AJ, Walsh PG, et al: A pilot, open-label safety study of quetiapine for treatment of moderate psychotic agitation in the emergency setting. *J Psychiatr Pract* 12(4):223-228, 2006 16883147
- Cutler AJ, Montgomery SA, Feifel D, et al: Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. *J Clin Psychiatry* 70(4):526-539, 2009 19358790
- DelBello MP, Adler CM, Whitsel RM, et al: A 12-week single-blind trial of quetiapine for the treatment of mood symptoms in adolescents at high risk for developing bipolar I disorder. *J Clin Psychiatry* 68(5):789-795, 2007 17503991
- DelBello MP, Chang K, Welge JA, et al: A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord* 11(5):483-493, 2009 19624387
- Dell'Osso B, Mundo E, Altamura AC: Quetiapine augmentation of selective serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a six-month follow-up case series. *CNS Spectr* 11(11):879-883, quiz 885, 2006 17075559
- DeVane CL, Nemeroff CB: Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet* 40(7):509-522, 2001 11510628
- Dorée JP, Des Rosiers J, Lew V, et al: Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. *Curr Med Res Opin* 23(2):333-341, 2007 17288688
- El-Khalili N, Joyce M, Atkinson S, et al: Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. *Int J Neuropsychopharmacol* 13(7):917-932, 2010 20175941
- Emsley RA, Raniwalla J, Bailey PJ, et al; PRIZE Study Group: A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a

- demonstrated, partial response to conventional antipsychotic treatment. *Int Clin Psychopharmacol* 15(3):121-131, 2000 10870870
- Fernandez HH, Okun MS, Rodriguez RL, et al: Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study. *Int J Neurosci* 119(12):2196-2205, 2009 19916848
- Findling RL, Reed MD, O'Riordan MA, et al: A 26-week open-label study of quetiapine in children with conduct disorder. *J Child Adolesc Psychopharmacol* 17(1): 1-9, 2007 17343549
- Fineberg NA, Sivakumaran T, Roberts A, et al: Adding quetiapine to SRI in treatment-resistant obsessive-compulsive disorder: a randomized controlled treatment study. *Int Clin Psychopharmacol* 20(4):223-226, 2005 15933483
- Gao K, Wu R, Kemp DE, et al: Efficacy and safety of quetiapine-XR as monotherapy or adjunctive therapy to a mood stabilizer in acute bipolar depression with generalized anxiety disorder and other comorbidities: a randomized, placebo-controlled trial. *J Clin Psychiatry* 75(10):1062-1068, 2014 25007003
- Goldstein JM: Quetiapine fumarate (Seroquel): a new atypical antipsychotic. *Drugs Today (Barc)* 35(3):193-210, 1999 12973385
- Hamner MB, Arvanitis LA, Miller BG, et al: Plasma prolactin in schizophrenia subjects treated with Seroquel (ICI 204,636). *Psychopharmacol Bull* 32(1):107-110, 1996 8927658
- Hamner MB, Deitsch SE, Brodrick PS, et al: Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. *J Clin Psychopharmacol* 23(1):15-20, 2003 12544370
- Hirschfeld RM, Weisler RH, Raines SR, et al; BOLDER Study Group: Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: a secondary analysis from a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 67(3):355-362, 2006 16649820
- Honer WG, MacEwan GW, Gendron A, et al; STACK Study Group: A randomized, double-blind, placebo-controlled study of the safety and tolerability of high-dose quetiapine in patients with persistent symptoms of schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 73(1):13-20, 2012 21733490
- Kahn RS, Schulz SC, Palazov VD, et al; Study 132 Investigators: Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 68(6):832-842, 2007 17592906
- Kapur S, Zipursky R, Jones C, et al: A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry* 57(6):553-559, 2000 10839333
- Katzman MA, Vermani M, Jacobs L, et al: Quetiapine as an adjunctive pharmacotherapy for the treatment of non-remitting generalized anxiety disorder: a flexible-dose, open-label pilot trial. *J Anxiety Disord* 22(8):1480-1486, 2008 18455360
- Katzman MA, Brawman-Mintzer O, Reyes EB, et al: Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. *Int Clin Psychopharmacol* 26(1):11-24, 2011 20881846
- Kelly DL, Conley RR: Thyroid function in treatment-resistant schizophrenia patients treated with quetiapine, risperidone, or fluphenazine. *J Clin Psychiatry* 66(1):80-84, 2005 15669892
- Ketter TA, Brooks JO 3rd, Hoblyn JC, et al: Long-term effectiveness of quetiapine in bipolar disorder in a clinical setting. *J Psychiatr Res* 44(14):921-929, 2010 20378127
- Kim SF, Huang AS, Snowman AM, et al: From the Cover: Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci U S A* 104(9):3456-3459, 2007 17360666

- King DJ, Link CG, Kowalczyk B: A comparison of bd and tid dose regimens of quetiapine (Seroquel) in the treatment of schizophrenia. *Psychopharmacology (Berl)* 137(2):139-146, 1998 9630000
- Kinon BJ, Noordsy DL, Liu-Seifert H, et al: Randomized, double-blind 6-month comparison of olanzapine and quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning. *J Clin Psychopharmacol* 26(5):453-461, 2006 16974184
- Komossa K, Depping AM, Meyer M, et al: Second-generation antipsychotics for obsessive compulsive disorder. *Cochrane Database Syst Rev* (12):CD008141, 2010 21154394
- Kozaric-Kovacic D, Pivac N: Quetiapine treatment in an open trial in combat-related post-traumatic stress disorder with psychotic features. *Int J Neuropsychopharmacol* 10(2):253-261, 2007 16945162
- Kurlan R, Cummings J, Raman R, Thal L; Alzheimer's Disease Cooperative Study Group: Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology* 68(17):1356-1363, 2007 17452579
- LaLonde CD, Van Lieshout RJ: Treating generalized anxiety disorder with second generation antipsychotics: a systematic review and meta-analysis. *J Clin Psychopharmacol* 31(3):326-333, 2011 21508847
- Larmo I, de Nayer A, Windhager E, et al; Spectrum Study Group: Efficacy and tolerability of quetiapine in patients with schizophrenia who switched from haloperidol, olanzapine or risperidone. *Hum Psychopharmacol* 20(8):573-581, 2005 16175656
- Lieberman JA, Stroup TS, McEvoy JP, et al: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353(12):1209-1223, 2005 16172203
- Lin CY, Tsai GE, Wang HS, et al: Effectiveness of aripiprazole, olanzapine, quetiapine, and risperidone augmentation treatment for major depressive disorder: a nationwide population-based study. *J Clin Psychiatry* 75(9):e924-e931, 2014 25295435
- Lindenmayer JP, Brown D, Liu S, et al: The efficacy and tolerability of once-daily extended release quetiapine fumarate in hospitalized patients with acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled study. *Psychopharmacol Bull* 41(3):11-35, 2008 18779774
- Lindenmayer JP, Citrome L, Khan A, et al: A randomized, double-blind, parallel-group, fixed-dose, clinical trial of quetiapine at 600 versus 1200 mg/d for patients with treatment-resistant schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 31(2):160-168, 2011 21346616
- Mamo DC, Uchida H, Vitcu I, et al: Quetiapine extended-release versus immediate-release formulation: a positron emission tomography study. *J Clin Psychiatry* 69(1): 81-86, 2008 18312041
- Masi G, Milone A, Stawinoga A, et al: Efficacy and safety of risperidone and quetiapine in adolescents with bipolar II disorder comorbid with conduct disorder. *J Clin Psychopharmacol* 35(5):587-590, 2015 26226481
- McConville BJ, Arvanitis LA, Thyrum PT, et al: Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. *J Clin Psychiatry* 61(4):252-260, 2000 10830145
- McElroy SL, Weisler RH, Chang W, et al; EMBOLDEN II (Trial D1447C00134) Investigators: A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry* 71(2):163-174, 2010 20122366
- McEvoy JP, Lieberman JA, Stroup TS, et al; CATIE Investigators: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 163(4):600-610, 2006 16585434
- McEvoy JP, Lieberman JA, Perkins DO, et al: Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-

- blind 52-week comparison. *Am J Psychiatry* 164(7):1050-1060, 2007 17606657
- McIntyre RS, Muzina DJ, Adams A, et al: Quetiapine XR efficacy and tolerability as monotherapy and as adjunctive treatment to conventional antidepressants in the acute and maintenance treatment of major depressive disorder: a review of registration trials. *Expert Opin Pharmacother* 10(18):3061-3075, 2009 19954275
- McKenna K, Koren G, Tetelbaum M, et al: Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 66(4):444-449, quiz 546, 2005 15816786
- McManus DQ, Arvanitis LA, Kowalczyk BB: Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. Seroquel Trial 48 Study Group. *J Clin Psychiatry* 60(5):292-298, 1999 10362435
- Merideth C, Cutler AJ, She F, et al: Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: a randomized, placebo controlled and active-controlled study. *Int Clin Psychopharmacol* 27(1):40-54, 2012 22045039
- Möller H, Johnson S, Meulien D, et al: Once-daily quetiapine sustained release (SR) is effective and well tolerated in patients with schizophrenia switched from the same total daily dose of quetiapine immediate release (IR). *Schizophr Bull* 33(2):449, 2007
- Mullen J, Jibson MD, Sweitzer D: A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: the quetiapine experience with safety and tolerability (QUEST) study. *Clin Ther* 23(11):1839-1854, 2001 11768836
- Nemeroff CB, Kinkead B, Goldstein J: Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. *J Clin Psychiatry* 63 (suppl 13):5-11, 2002 12562141
- Newcomer JW: Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 19 (suppl 1):1-93, 2005 15998156
- Newcomer JW, Haupt DW, Fucetola R, et al: Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry* 59(4):337-345, 2002 11926934
- Newcomer JW, Ratner RE, Eriksson JW, et al: A 24-week, multicenter, open-label, randomized study to compare changes in glucose metabolism in patients with schizophrenia receiving treatment with olanzapine, quetiapine, or risperidone. *J Clin Psychiatry* 70(4):487-499, 2009 19358783
- Ondo WG, Tintner R, Vong KD, et al: Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 20(8):958-963, 2005 15800937
- Pae CU, Kim JJ, Lee CU, et al: Rapid versus conventional initiation of quetiapine in the treatment of schizophrenia: a randomized, parallel-group trial. *J Clin Psychiatry* 68(3):399-405, 2007 17388709
- Patel JK, Buckley PF, Woolson S, et al; CAFE Investigators: Metabolic profiles of second-generation antipsychotics in early psychosis: findings from the CAFE study. *Schizophr Res* 111(1-3):9-16, 2009 19398192
- Pérez-Iglesias R, Ortiz-García de la Foz V, Martínez García O, et al: Comparison of metabolic effects of aripiprazole, quetiapine and ziprasidone after 12 weeks of treatment in first treated episode of psychosis. *Schizophr Res* 159(1):90-94, 2014 25151200
- Peuskens J, Link CG: A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand* 96(4):265-273, 1997 9350955
- Peuskens J, Trivedi JK, Malyarov S, et al: Randomised, placebo-controlled, relapse-prevention study with once-daily quetiapine sustained release in patients with schizophrenia. *Eur Psychiatry* 22 (suppl 1):S132, 2007
- Pierre JM, Wirshing DA, Wirshing WC, et al: High-dose quetiapine in treatment refractory schizophrenia. *Schizophr Res* 73(2-3):373-375, 2005 15653285

- Pinta ER, Taylor RE: Quetiapine addiction? *Am J Psychiatry* 164(1):174-175, 2007 17202569
- Potkin SG, Thyrum PT, Alva G, et al; Pharmacokinetic Study Group: Effect of fluoxetine and imipramine on the pharmacokinetics and tolerability of the antipsychotic quetiapine. *J Clin Psychopharmacol* 22(2):174-182, 2002a 11910263
- Potkin SG, Thyrum PT, Alva G, et al: The safety and pharmacokinetics of quetiapine when coadministered with haloperidol, risperidone, or thioridazine. *J Clin Psychopharmacol* 22(2):121-130, 2002b 11910256
- Potkin SG, Gharabawi GM, Greenspan AJ, et al: A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophr Res* 85(1-3):254-265, 2006 16797162
- Rabey JM, Prokhorov T, Miniovitz A, et al: Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord* 22(3):313-318, 2007 17034006
- Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 355(15):1525-1538, 2006 17035647
- Shotbolt P, Samuel M, Fox C, David AS: A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. *Neuropsychiatr Dis Treat* 5:327-332, 2009 19557142
- Shotbolt P, Samuel M, David A: Quetiapine in the treatment of psychosis in Parkinson's disease. *Ther Adv Neurol Disorder* 3(6):339-350, 2010 21179595
- Simon NM, Connor KM, LeBeau RT, et al: Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. *Psychopharmacology (Berl)* 197(4):675-681, 2008 18246327
- Small JG, Hirsch SR, Arvanitis LA, et al; Seroquel Study Group: Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry* 54(6):549-557, 1997 9193196
- Sokolski KN, Denson TF, Lee RT, et al: Quetiapine for treatment of refractory symptoms of combat-related post-traumatic stress disorder. *Mil Med* 168(6):486-489, 2003 12834142
- Stathis S, Martin G, McKenna JG: A preliminary case series on the use of quetiapine for posttraumatic stress disorder in juveniles within a youth detention center. *J Clin Psychopharmacol* 25(6):539-544, 2005 16282834
- Stein DJ, Bandelow B, Merideth C, et al: Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalised anxiety disorder: an analysis of pooled data from three 8-week placebo-controlled studies. *Hum Psychopharmacol* 26(8):614-628, 2011 22143997
- Strakowski SM, Keck PE Jr, Wong YW, et al: The effect of multiple doses of cimetidine on the steady-state pharmacokinetics of quetiapine in men with selected psychotic disorders. *J Clin Psychopharmacol* 22(2):201-205, 2002 11910267
- Stroup TS, Lieberman JA, McEvoy JP, et al; CATIE Investigators: Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry* 164(3):415-427, 2007 17329466
- Sunovion: Latuda (lurasidone hydrochloride) tablets, full prescribing information. July 2013. Available at: <http://www.latuda.com/LatudaPrescribingInformation.pdf>. Accessed April 3, 2016.
- Thase ME, Macfadden W, Weisler RH, et al; BOLDER II Study Group: Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 26(6):600-609, 2006 17110817
- Vaishnavi S, Alamy S, Zhang W, et al: Quetiapine as monotherapy for social anxiety disorder: a placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry*

- 31(7):1464-1469, 2007 17698275
- Veale D, Miles S, Smallcombe N, et al: Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis. *BMC Psychiatry* 14:317, 2014 25432131
- Wang Z, Kemp DE, Chan PK, et al: Comparisons of the tolerability and sensitivity of quetiapine-XR in the acute treatment of schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and generalized anxiety disorder. *Int J Neuropsychopharmacol* 14(1):131-142, 2011 20875219
- Weiden PJ, Young AH, Buckley PF: The art and science of switching of antipsychotic medications, part 1. *J Clin Psychiatry* 67(11):e15, 2006 17201045
- Weisler RH, Montgomery SA, Earley WR, et al: Efficacy of extended release quetiapine fumarate monotherapy in patients with major depressive disorder: a pooled analysis of two 6-week, double-blind, placebo-controlled studies. *Int Clin Psychopharmacol* 27(1):27-39, 2012 22027845
- Whitehorn D, Gallant J, Woodley H, et al: Quetiapine treatment in early psychosis: no evidence of cataracts. *Schizophr Res* 71(2-3):511-512, 2004 15474924
- Young AH, McElroy SL, Bauer M, et al; EMBOLDEN I (Trial 001) Investigators: A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 71(2):150-162, 2010 20122369
- Zhong KX, Sweitzer DE, Hamer RM, et al: Comparison of quetiapine and risperidone in the treatment of schizophrenia: a randomized, double-blind, flexible-dose, 8-week study. *J Clin Psychiatry* 67(7):1093-1103, 2006 16889453
- Zhong KX, Tariot PN, Mintzer J, et al: Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. *Curr Alzheimer Res* 4(1): 81-93, 2007 17316169



## CHAPTER 28

# Risperidone and Paliperidone

Michele Hill, M.R.C.Psych.

Donald C. Goff, M.D.

---

### History and Discovery

---

A decade before clozapine was approved for marketing in the United States, Janssen Pharmaceuticals established a program to examine the potential role of serotonergic agents in schizophrenia. Early interest in serotonergic agents stemmed from preclinical literature demonstrating that both behavioral effects of dopamine receptor agonists and haloperidol-induced catalepsy could be modulated by serotonin 2 (5-HT<sub>2</sub>) receptor antagonists; in addition, the early butyrophenone derivative pipamperone, which was observed to reduce agitation and improve social activity in patients with severe depression, was found to possess primarily 5-HT<sub>2</sub> receptor antagonist activity ([Ansoms et al. 1977](#); [Leysen et al. 1978](#)).

In 1981, Janssen Pharmaceuticals developed setoperone, a 5-HT<sub>2</sub> receptor antagonist with weak dopamine 2 (D<sub>2</sub>) receptor antagonism that displayed antipsychotic effects and efficacy for negative symptoms in a preliminary open trial ([Ceulemans et al. 1985](#)). Janssen Pharmaceuticals additionally synthesized a selective 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptor antagonist, ritanserin, which was shown to decrease extrapyramidal side effects (EPS) when combined with haloperidol in rat studies. Ritanserin also was active in animal models of anxiety ([Colpaert et al. 1985](#); [Meert and Colpaert 1986](#)) and partially ameliorated the behavioral effects of lysergic acid diethylamide (LSD) ([Colpaert et al. 1985](#)). In placebo-controlled trials in patients with chronic schizophrenia, addition of ritanserin to first-generation antipsychotics (FGAs) improved negative symptoms and EPS ([Bersani et al. 1990](#); [Duinkerke et al. 1993](#); [Gelders 1989](#); [Reyntjens et al. 1986](#)). Concluding that 5-HT<sub>2</sub> receptor antagonism might improve the effectiveness of D<sub>2</sub> blockers, particularly for negative symptoms, and reduce EPS, but that it was not sufficiently effective as monotherapy, Paul Janssen and colleagues undertook development of risperidone, which combined potent 5-HT<sub>2A</sub> and D<sub>2</sub> receptor blockade.

After extensive preclinical characterization ([Janssen et al. 1988](#)), risperidone was first studied in clinical trials in 1986 and received U.S. Food and Drug Administration (FDA) approval for marketing in the United States in 1994. By the time risperidone became available to clinicians, the prominence of theories citing 5-HT<sub>2</sub> enhancement of D<sub>2</sub> receptor antagonism as a primary mechanism for clozapine's atypical properties ([Meltzer et al. 1989](#)), and the evidence from registration trials of reduced EPS and greater efficacy

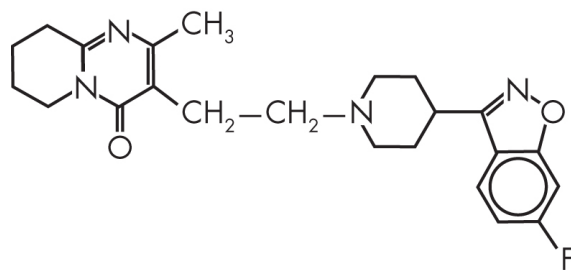
compared with high-dose haloperidol, resulted in considerable enthusiasm for the first of the “serotonin-dopamine antagonists.” Risperidone was rapidly incorporated into clinical practice in the United States, where within 2 years it became the most frequently prescribed antipsychotic agent. In 2003, risperidone microspheres (Consta) received FDA approval as the first long-acting second-generation antipsychotic (SGA) designed for intramuscular (IM) injection. In December 2006, Janssen Pharmaceuticals introduced paliperidone (9-hydroxyrisperidone), the active metabolite of risperidone, formulated as an extended-release tablet marketed under the brand name Invega. Extended-release paliperidone is approved for the treatment of schizophrenia and schizoaffective disorder. A long-acting depot preparation, paliperidone palmitate (Sustenna), received FDA approval for schizophrenia in 2009 and for schizoaffective disorder in 2014; it was the first once-monthly depot formulation of an SGA to become available in the United States. In May 2015, a new formulation of paliperidone with a 3-month injection interval, paliperidone palmitate 3-month formulation (PP3M; Invega Trinza), was approved by the FDA for the treatment of schizophrenia under its priority review process. This formulation’s 3-month schedule provides the longest dosing interval available for patients with schizophrenia.

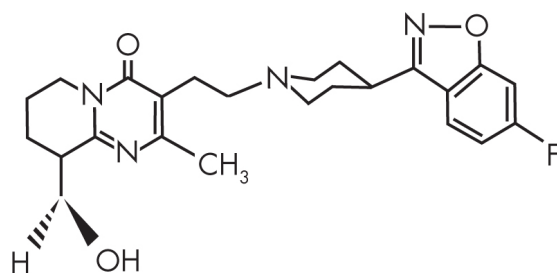
---

## Pharmacological Profile

---

Risperidone, or 3-[2-(4-[6-fluoro-1,2-benzisoxazol-3-yl]-1-piperidinyl)ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, is a benzisoxazole derivative characterized by very high affinity for 5-HT<sub>2A</sub> receptors and moderately high affinity for D<sub>2</sub>, histamine 1 (H<sub>1</sub>), and  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors (Figure 28-1). In vitro, the affinity of risperidone for 5-HT<sub>2A</sub> receptors is roughly 10- to 20-fold greater than that for D<sub>2</sub> receptors (Leysen et al. 1994; Schotte et al. 1996); in vivo binding to rat striatal D<sub>2</sub> receptors occurs at a dosage 10 times higher than does binding to 5-HT<sub>2A</sub> receptors (Leysen et al. 1994). The affinity for 5-HT<sub>2A</sub> receptors is more than 100-fold greater than for other serotonin receptor subtypes. Risperidone’s active metabolite 9-hydroxyrisperidone (paliperidone) (Figure 28-2) has a similar receptor affinity profile, although paliperidone has lower affinity for  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors. Both risperidone and paliperidone display a high affinity for 5-HT<sub>2A</sub> receptors in rat brain tissue and for cloned human receptors expressed in COS-7 cells (Leysen et al. 1994). Risperidone binds to 5-HT<sub>2A</sub> receptors with approximately 20-fold greater affinity compared with clozapine and 170-fold greater affinity compared with haloperidol (Leysen et al. 1994).





**FIGURE 28-2.** Chemical structure of paliperidone.

The affinity of risperidone for  $D_2$  receptors is approximately 50-fold greater than that of clozapine and approximately 20%–50% that of haloperidol (Leysen et al. 1994) (Table 28-1). Binding affinity for  $D_2$  receptors was similar in rat mesolimbic and striatal tissue and in the long and short forms of cloned human  $D_2$  receptors expressed in embryonic kidney cells (Leysen et al. 1993a). The affinities of risperidone and paliperidone for dopamine<sub>4</sub> ( $D_4$ ) and dopamine<sub>1</sub> ( $D_1$ ) receptors are similar to those of clozapine and haloperidol (Leysen et al. 1994). Risperidone and paliperidone have essentially no affinity for muscarinic acetylcholine receptors and modest  $H_1$  receptor activity. Unlike haloperidol, risperidone does not bind to sigma sites (Leysen et al. 1994). However, compared with other agents, including paliperidone, risperidone has a relatively high affinity for  $\alpha_2$ -adrenergic receptors that is substantially greater than that of clozapine or any FGA and that approaches the affinity of phentolamine (Richelson 1996). The affinity of risperidone for  $\alpha_1$ -adrenergic receptors is roughly comparable to that of chlorpromazine and approximately 5 to 10 times greater than that of clozapine (Leysen et al. 1993b; Richelson 1996). The median effective dose ( $ED_{50}$ ) of risperidone required to inhibit  $D_2$ -mediated apomorphine-induced stereotypies in rats is 0.5 mg/kg; at this dose, approximately 40% of  $D_2$  receptors are occupied, as are 80% of 5-HT<sub>2A</sub> receptors, 50% of  $H_1$  receptors, 38% of  $\alpha_1$ -adrenergic receptors, and 10% of  $\alpha_2$ -adrenergic receptors (Leysen et al. 1994).

**TABLE 28-1. Receptor-binding affinities ( $K_i$  values, in nM) of representative antipsychotics in cloned human receptors and rat brain**

	Paliperidone	Risperidone	Haloperidol	Clozapine
Dopaminergic				
$D_2^a$	4.8	5.9	2.2	190
$D_1^a$	670	620	270	540
Serotonergic				
5-HT <sub>2A</sub> <sup>a</sup>	1.0	0.52	200	9.6
5-HT <sub>1A</sub> <sup>a</sup>	590	420	1,500	140
Adrenergic				
$\alpha_1^b$	4.0	2.3	19	23

<sup>a</sup>Cloned human receptor.

<sup>b</sup>Rat brain.

Source. Adapted from Schotte et al. 1996.

	Paliperidone	Risperidone	Haloperidol	Clozapine
$\alpha_2^b$	17	7.5	>5,000	160
H <sub>1</sub> histaminergic <sup>a</sup>	32	27	790	0.23
Muscarinic <sup>b</sup>	3,570	>5,000	4,670	34

<sup>a</sup>Cloned human receptor.

<sup>b</sup>Rat brain.

Source. Adapted from [Schotte et al. 1996](#).

Several groups have studied the occupancy of D<sub>2</sub> and 5-HT<sub>2</sub> receptors in patients with schizophrenia, employing positron emission tomography (PET) or single-photon emission computed tomography (SPECT) ligand-binding techniques. [Kapur et al. \(1999\)](#) used PET to measure D<sub>2</sub> occupancy with <sup>11</sup>C-labeled raclopride and 5-HT<sub>2</sub> occupancy with <sup>18</sup>F-labeled setoperone in patients with chronic schizophrenia maintained on a stable clinician-determined dose of risperidone. The PET was performed 12–14 hours after the last dose of risperidone. Occupancy of D<sub>2</sub> receptors ranged from 63% to 89%; 50% occupancy was calculated to occur with a daily risperidone dose of 0.8 mg. Patients treated with risperidone (6 mg/day) exhibited a mean D<sub>2</sub> occupancy of 79%, which was consistent with the mean occupancy of 82% that was previously reported by [Nyberg et al. \(1999\)](#) and would be expected to exceed the putative threshold for EPS in some patients. A similar degree of D<sub>2</sub> occupancy was calculated to occur with olanzapine at approximately 30 mg daily ([Kapur et al. 1999](#)). A maximal 5-HT<sub>2</sub> occupancy of greater than 95% was achieved with risperidone at daily doses as low as 2–4 mg. In a small sample of patients treated biweekly for at least 10 weeks with risperidone microspheres (Consta), [Remington et al. \(2006\)](#) found that the 25-mg dose produced a mean D<sub>2</sub> occupancy of 54% (preinjection) and 71% (postinjection), whereas the 50-mg dose produced occupancy levels of 65% (preinjection) and 74% (postinjection). [Arakawa et al. \(2008\)](#) found a D<sub>2</sub> occupancy of 58% with paliperidone at 3 mg/day and 77% with 9 mg/day, consistent with clinical estimates that paliperidone is roughly half as potent as risperidone, perhaps due to reduced bioavailability ([de Leon et al. 2010](#)).

Preclinical characterization of risperidone in rats revealed more potent antiserotonergic activity compared with ritanserin in all tests ([Janssen et al. 1988](#)). For example, in reversal of tryptophan-induced effects in rats, risperidone was 6.4 times more potent than ritanserin for reversal of peripheral 5-HT<sub>2</sub>-mediated effects and 2.4 times more potent for reversal of centrally mediated 5-HT<sub>2</sub> effects ([Janssen et al. 1988](#)). Risperidone was also found to completely block discrimination of LSD, in contrast to the partial attenuation observed with ritanserin ([Meert et al. 1989](#)). Although risperidone demonstrated activity in all dopamine-mediated tests, the dose-response pattern differed from that of haloperidol ([Janssen et al. 1988](#)). The two drugs were roughly equipotent for inhibition of certain dopamine effects, such as amphetamine-induced oxygen hyperconsumption, whereas the dose of risperidone necessary to cause pronounced catalepsy in rats was 18-fold higher than that of haloperidol ([Janssen et al. 1988](#)). Risperidone depressed vertical and horizontal activity in rats at a dose 2–3 times greater than that of haloperidol but required doses more than 30 times greater than those of haloperidol to depress small motor movements ([Megens et al. 1988](#)).

---

## Pharmacokinetics and Disposition

---

Risperidone is rapidly absorbed after oral administration, with peak plasma levels achieved within 1 hour ([Heykants et al. 1994](#)). In early Phase I studies, risperidone demonstrated linear pharmacokinetics at dosages between 0.5 and 25 mg/day ([Mesotten et al. 1989](#); [Roose et al. 1988](#)).

After a single dose of the extended-release formulation of paliperidone (Invega), serum concentrations gradually increase until a maximum concentration is achieved approximately 24 hours after ingestion. Absorption of paliperidone is increased by approximately 50% when taken with a meal compared with the fasting state. Extended-release paliperidone also demonstrates dose-proportional pharmacokinetics within the recommended dosing range (3–12 mg/day).

Because risperidone lacks a hydroxyl group to which an ester can be bound for a traditional oil-based depot preparation, polymer microsphere technology was used to produce a slow-release injectable formulation. Risperidone microspheres do not begin to release appreciable amounts of drug until 3 weeks after injection and continue to release drug for approximately 4 weeks, with maximal drug release occurring after about 5 weeks.

Paliperidone palmitate is an esterified form of paliperidone and is poorly soluble in water. It dissolves slowly following IM injection, after which it is hydrolyzed to active paliperidone and absorbed into the systemic circulation. Systemic availability of paliperidone begins on day 1 and can last as long as 126 days after injection. Maximum blood levels are achieved a median of 13 days after injection. A dose of 75 mg/month is recommended, but in practice the modal dose is 100 mg/month ([Attard et al. 2014](#)). IM injection in the deltoid produces blood levels approximately 28% higher than those produced with gluteal injection. The 3-month formulation of paliperidone palmitate has an extended apparent elimination half-life that permits this longer dosing interval. Risperidone is 90% plasma protein bound, whereas paliperidone is 74% plasma protein bound ([Borison et al. 1994](#)). The absolute bioavailability of risperidone is about 100%; that of extended-release paliperidone is about 28%. Paliperidone may achieve relatively lower concentrations in the brain because of its higher affinity for the extruding P-glycoprotein transporter, which limits the amount of drug crossing the blood-brain barrier ([de Leon et al. 2010](#)).

Risperidone is metabolized by hydroxylation of the tetrahydropyridopyrimidinone ring at the seven and nine positions and by oxidative *N*-dealkylation ([Mannens et al. 1993](#)). The most important metabolite, 9-hydroxyrisperidone (paliperidone), accounts for up to 31% of the dose excreted in the urine. Because hydroxylation of risperidone is catalyzed by cytochrome P450 (CYP) 2D6, the half-life of the parent compound varies according to the relative activity of this enzyme. In extensive metabolizers, which include about 90% of Caucasians and as many as 99% of Asians, the half-life of risperidone is approximately 3 hours. Approximately 60% of paliperidone is excreted unchanged in the urine, and the remainder is metabolized by at least four different pathways (dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission), none of which accounts for more than 10% of the total. The terminal half-life of 9-hydroxyrisperidone (and of extended-release paliperidone) is 23 hours. Poor metabolizers metabolize risperidone primarily via oxidative pathways; the half-life may exceed 20 hours. In extensive metabolizers, radioactivity from <sup>14</sup>C-labeled risperidone is not detectable in plasma 24 hours after a single dose, whereas 9-hydroxyrisperidone accounts for 70%–80% of radioactivity. In poor metabolizers, risperidone is primarily responsible for radioactivity after 24 hours. In the U.S. multicenter

registration trial, the correlations between risperidone dose and serum risperidone and 9-hydroxyrisperidone concentrations were 0.59 and 0.88, respectively ([Anderson et al. 1993](#)). Because of paliperidone's longer half-life, its serum concentrations at steady state are approximately 5- to 10-fold higher than risperidone concentrations in CYP2D6 extensive metabolizers treated with risperidone ([de Leon et al. 2010](#)). However, in 2D6 poor metabolizers and patients concurrently taking 2D6 inhibitors, risperidone concentrations may be higher than paliperidone concentrations.

---

## Mechanism of Action

---

As previously discussed, risperidone was developed specifically to exploit the apparent pharmacological advantages of combining 5-HT<sub>2A</sub> receptor antagonism with D<sub>2</sub> receptor blockade. Selective 5-HT<sub>2A</sub> receptor antagonists administered alone have demonstrated activity in several animal models suggestive of antipsychotic effect, including blockade of both amphetamine- and phencyclidine (PCP)-induced locomotor activity ([Schmidt et al. 1995](#)). Dizocilpine-induced disruption of prepulse inhibition is also blocked by 5-HT<sub>2A</sub> receptor antagonists, suggesting that sensory gating deficits characteristic of schizophrenia and perhaps resulting from glutamatergic dysregulation might also benefit from the 5-HT<sub>2</sub> receptor antagonism of risperidone ([Varty et al. 1999](#)). The disruption of prepulse inhibition by dizocilpine (MK-801, a noncompetitive N-methyl-D-aspartate [NMDA] receptor antagonist) is attenuated by SGAs, but not by first-generation D<sub>2</sub> receptor blockers ([Geyer et al. 1990](#)). From a study in which the selective 5-HT<sub>2A</sub> receptor antagonist M100907 was added to low-dose raclopride (a selective D<sub>2</sub> receptor blocker), [Wadenberg et al. \(1998\)](#) concluded that 5-HT<sub>2A</sub> antagonism facilitates D<sub>2</sub> receptor antagonist blockade of conditioned avoidance, another behavioral model associated with antipsychotic efficacy, but does not block conditioned avoidance when administered alone.

One mechanism by which risperidone, paliperidone, and similar atypical agents might produce enhanced efficacy for negative symptoms and cognitive deficits and reduced risk for EPS is via 5-HT<sub>2A</sub> receptor modulation of dopamine neuronal firing and cortical dopamine release. Prefrontal dopaminergic hypoactivity has been postulated to underlie negative symptoms and cognitive deficits in schizophrenia ([Goff and Evins 1998](#)); both clozapine and ritanserin have been shown to increase dopamine release in prefrontal cortex, whereas haloperidol does not ([Busatto and Kerwin 1997](#)). Following 21 days of administration, risperidone, but not haloperidol, continued to increase dopamine turnover in the dorsal striatum and prefrontal cortex ([Stathis et al. 1996](#)). Ritanserin has been shown to enhance midbrain dopamine cell firing by blocking a tonic inhibitory serotonin input ([Ugedo et al. 1989](#)). Ritanserin also normalized ventral tegmental dopamine neuron firing patterns in rats after hypofrontality was induced by experimental cooling of the frontal cortex ([Svensson et al. 1989](#)).

[Svensson et al. \(1995\)](#) performed a series of elegant studies examining the impact of atypical antipsychotics on ventral tegmental dopamine firing patterns disrupted by glutamatergic NMDA receptor antagonists. In healthy human subjects, administration of the NMDA antagonist ketamine is widely regarded as a promising model for several clinical aspects of schizophrenia, including psychosis, negative symptoms, and cognitive deficits ([Goff and Coyle 2001](#); [Krystal et al. 1994](#)). In rats, administration of the NMDA channel blockers dizocilpine or PCP increased burst firing of ventral tegmental dopamine neurons predominantly projecting to limbic structures but reduced firing of mesocortical



tract dopamine neurons and disrupted firing patterns. Administration of ritanserin or clozapine preferentially enhanced firing of dopamine neurons with cortical projections, and when added to a D<sub>2</sub> blocker, ritanserin increased dopamine release in prefrontal cortex. In addition to modulating ventral tegmental dopamine neuron firing, risperidone also blocks 5-HT<sub>2</sub> receptors on inhibitory  $\gamma$ -aminobutyric acid (GABA)-ergic interneurons, which could also influence activity of cortical pyramidal neurons that are regulated by these local inhibitory circuits (Gellman and Aghajanian 1994).

In placebo-controlled clinical trials, 5-HT<sub>2</sub> receptor antagonists have shown efficacy in reducing antipsychotic-induced parkinsonism and akathisia (Duinkerke et al. 1993; Poyurovsky et al. 1999). This effect may reflect 5-HT<sub>2A</sub> antagonist effects on nigrostriatal dopamine release. When combined with haloperidol, selective 5-HT<sub>2</sub> receptor antagonists increase dopamine metabolism in the striatum and prevent an increase in D<sub>2</sub> receptor density, thereby possibly reducing the effects of D<sub>2</sub> receptor blockade and dopamine supersensitivity (Saller et al. 1990). These agents do not affect dopamine metabolism in the absence of D<sub>2</sub> blockade.

The relative importance of 5-HT<sub>2</sub> receptor antagonist activity in producing atypical characteristics is the subject of debate. As argued by Kapur and Seeman (2001) and Seeman (2002), most SGAs have dissociation constants for the D<sub>2</sub> receptor that are larger than the dissociation constant of dopamine. This “loose binding” to the D<sub>2</sub> receptor may allow displacement by endogenous dopamine and may contribute to a reduced liability for EPS and hyperprolactinemia. Unique among atypical agents, risperidone is “tightly bound” to the D<sub>2</sub> receptor, with a dissociation constant smaller than that of dopamine (Seeman 2002). A model for atypical antipsychotic mechanisms that emphasizes D<sub>2</sub> dissociation constants would predict that the apparent atypicality of risperidone, compared with that of haloperidol, reflects the reduced D<sub>2</sub> receptor occupancy achieved by more favorable dosing rather than the intrinsic pharmacological characteristics of risperidone. According to some binding data, a comparable clinical dosage of haloperidol would be approximately 4 mg/day, rather than 20 mg/day as used in the North American multicenter registration trial (Kapur et al. 1999). Consistent with this view, benefits of risperidone for negative symptoms and EPS were less apparent when compared with lower doses of haloperidol or with lower-potency FGAs (see “Indications and Efficacy” section later in this chapter) than when compared with high-dose haloperidol (20 mg/day).

An additional mechanism possibly contributing to the enhanced efficacy of risperidone and paliperidone is their considerable  $\alpha$ -adrenergic receptor antagonism. In a placebo-controlled augmentation trial, Litman et al. (1996) demonstrated significant improvement in psychosis and negative symptoms with the  $\alpha_2$ -adrenergic receptor antagonist idazoxan when it was added to FGAs. Idazoxan has been shown to increase dopamine levels in the rat medial prefrontal cortex (Hertel et al. 1999). In aged rats (Haapalinna et al. 2000) and in patients with frontal dementias (Coull et al. 1996),  $\alpha_2$ -adrenergic receptor blockers have also been reported to improve cognitive functioning. Svensson et al. (1995) found that prazosin, an  $\alpha_1$  receptor antagonist, inhibited both the behavioral activation and the increase in mesolimbic dopamine release produced by PCP or MK-801.

In summary, risperidone and paliperidone possess at least two mechanisms that may confer atypical characteristics. 5-HT<sub>2A</sub> receptor antagonism partially protects against D<sub>2</sub> antagonist-induced neurological side effects and may improve negative symptoms and cognitive functioning via modulation of mesocortical dopamine activity. In addition, blockade of adrenoceptors may further increase prefrontal cortical activity and could

enhance antipsychotic efficacy by modulation of mesolimbic dopamine activity. Unlike other SGA agents, risperidone and paliperidone do not differ from FGAs in their dissociation constant for the D<sub>2</sub> receptor; this feature perhaps accounts for the risk of EPS at high doses, as well as their greater propensity to cause hyperprolactinemia.

## Indications and Efficacy

Risperidone is approved by the FDA for the treatment of schizophrenia, bipolar mania, and irritability associated with autism. In August 2007, the indication for schizophrenia was extended to include adolescents ages 13–17 years, and the bipolar mania indication was extended to include children 10–17 years of age. The risperidone microsphere formulation (Consta long-acting injectable [LAI]) is approved for the treatment of schizophrenia and bipolar I disorder. Extended-release oral paliperidone (Invega) is approved for the treatment of schizophrenia and schizoaffective disorder, LAI paliperidone palmitate (Sustenna) is approved for the treatment of schizophrenia and schizoaffective disorder, and paliperidone palmitate 3-month injection formulation (Invega Trinza) is approved for the treatment of schizophrenia.

## Schizophrenia

### Clinical Trial Results for Risperidone

**Eight-week trials.** In the two North American registration trials ([Chouinard et al. 1993](#); [Marder and Meibach 1994](#)), a total of 513 patients with chronic schizophrenia were randomly assigned to an 8-week double-blind, fixed-dose, placebo-controlled comparison of risperidone (2, 6, 10, or 16 mg/day) versus haloperidol (20 mg/day). Risperidone dosages of 6, 10, and 16 mg/day produced significantly greater reductions, as compared with haloperidol, in each of the five domains of the Positive and Negative Syndrome Scale (PANSS), derived by principal-components analysis ([Marder et al. 1997](#)), and significantly higher response rates, defined as a 20% reduction in the PANSS total score. Effect sizes representing the difference in change scores between risperidone (6 mg/day) and haloperidol, although statistically significant, were uniformly small by Cohen’s classification system ([Cohen 1988](#)): negative symptoms 0.31; positive symptoms 0.26; disorganized thoughts 0.22; uncontrolled hostility/excitement 0.29; and anxiety/depression 0.30 ([Table 28–2](#)). Severity of EPS was greater with haloperidol than with risperidone; further statistical analysis suggested that differences in EPS rates did not significantly influence the differences in PANSS subscale ratings ([Marder et al. 1997](#)). In fact, risperidone 10 mg/day and 16 mg/day produced improvements in negative symptoms equivalent to those seen with risperidone 6 mg/day, despite increased EPS at the higher dosages of risperidone.

**TABLE 28–2. Effect sizes on Positive and Negative Syndrome Scale (PANSS) symptom dimensions: North American trials (N=513)**

Adjusted mean change scores	Risperidone 6
-----------------------------	---------------

Source. Adapted from [Marder et al. 1997](#).



	Adjusted mean change scores			Risperidone 6	
	Placebo	Risperidone 6 mg/day	Haloperidol 20 mg/day	Effect size vs. placebo	Effect size vs. halo
PANSS total	-3.8	-18.6	-5.1	0.53	0.0
Negative	0.2	-3.4	-0.1	0.27	0.0
Positive	0.9	-5.7	-2.3	0.48	0.0
Disorganized thought	0.1	-4.6	-0.2	0.43	0.0
Hostility/excitement	0.2	-2.5	-0.1	0.47	0.0
Anxiety/depression	-0.1	-2.5	-0.6	0.36	0.0

Source. Adapted from [Marder et al. 1997](#).

When risperidone (1, 4, 8, 12, and 16 mg/day) was compared with haloperidol (10 mg/day) in a large 8-week European trial involving 1,362 subjects with schizophrenia ([Peuskens 1995](#)), PANSS subscale change scores among risperidone-treated subjects indicated a preferential response to daily doses of 4 mg and 8 mg. However, neither the risperidone group taken as a whole nor individual risperidone doses achieved significantly better outcomes than haloperidol (10 mg/day) on any measure except for EPS, suggesting that the clinical superiority of risperidone over haloperidol in previous studies may have resulted from excessively high dosing of the comparator.

**CATIE.** In the National Institute of Mental Health-funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; [Stroup et al. 2003](#)), 1,432 patients with chronic schizophrenia were randomly assigned to double-blind, flexibly dosed treatment for 18 months with risperidone, olanzapine, quetiapine, ziprasidone, or the FGA comparator perphenazine. Clinicians could adjust the dosage of each drug by prescribing 1–4 capsules daily; risperidone capsules contained 1.5 mg, and the mean daily dose administered in the study was 3.9 mg. Based on the primary outcome measure, time to all-cause discontinuation, risperidone was less effective than olanzapine (mean dosage 20 mg/day) and comparable in effectiveness to perphenazine, quetiapine, and ziprasidone ([Lieberman et al. 2005](#)). Although differences in rates of dropout due to intolerance did not reach statistical significance, risperidone consistently was the best-tolerated drug, particularly in subjects who had discontinued their first-assigned drug due to intolerance.

**Maintenance treatment.** [Csernansky et al. \(2002\)](#) randomly assigned 365 patients with stable schizophrenia or schizoaffective disorder to clinician-determined flexible dosing with risperidone or haloperidol for a minimum of 1 year. Kaplan-Meier estimates of the risk of relapse at the end of the study were 34% with risperidone versus 60% with haloperidol, a highly significant difference ( $P=0.001$ ). The LAI risperidone microsphere formulation (Consta) at fixed doses of 25 mg, 50 mg, and 75 mg administered biweekly was superior in efficacy to placebo in a 12-week trial ([Kane et al. 2003](#)), but the 75-mg dose was not developed further due to an increased rate of EPS. In a 52-week maintenance study comparing fixed doses of risperidone microspheres administered every 2 weeks, the 25-mg dose was associated with a relapse rate of 21.6% and the 50-mg dose was associated with a 14.9% relapse rate ( $P=0.06$ ) ([Simpson et al. 2006](#)). Comparisons of risperidone microspheres against oral SGAs have failed to demonstrate greater benefit with the LAI formulation. In 12-month randomized trials, the efficacy of risperidone

microspheres was similar to that of oral risperidone ( $n=50$ ; [Bai et al. 2007](#)), oral olanzapine ( $n=377$ ; [Keks et al. 2007](#)), or clinician's choice of an oral antipsychotic other than clozapine ( $n=369$ ; [Rosenheck et al. 2011](#)). By contrast, a nationwide cohort study using national databases in Norway found risperidone microspheres to be more effective in preventing readmission following a first hospitalization compared with oral risperidone and other oral antipsychotics with the exception of olanzapine and clozapine ([Tiihonen et al. 2011](#)). Because antipsychotic treatment in this naturalistic study was not randomized, conclusions are limited; nonetheless, the advantage found with depot formulations may reflect performance under typical clinical conditions.

**Cognitive functioning in schizophrenia.** Several early studies suggested that risperidone might enhance cognitive functioning, particularly verbal working memory, compared with haloperidol ([Green et al. 1997](#); [Harvey et al. 2005](#)). A large double-blind trial that examined cognitive effects in 414 chronic schizophrenia patients treated for 52 weeks with risperidone (mean dosage 5.2 mg/day), olanzapine (12.3 mg/day), and haloperidol (8.2 mg/day) found no difference between treatments on the composite cognitive score, although risperidone and olanzapine were superior to haloperidol in a secondary analysis of completers ([Keefe et al. 2006](#)). When compared with low-dose haloperidol (mean dosage 5 mg/day), no cognitive advantage was found for risperidone ([Green et al. 2002](#)). In addition, in the CATIE, neither risperidone nor any other SGA demonstrated cognitive benefit compared with the FGA agent perphenazine ([Keefe et al. 2007](#)). A study in medication-naïve patients found similar overall cognitive improvement with risperidone and olanzapine ([Cuesta et al. 2009](#)); however, another study of risperidone in medication-naïve patients reported impairments of spatial working memory ([Reilly et al. 2006](#)) and procedural memory ([Harris et al. 2009](#)).

**First-episode and treatment-refractory schizophrenia.** Risperidone has been found to be well tolerated and effective in subgroups of patients with schizophrenia, including first-episode patients and elderly patients. In a 4-month double-blind trial comparing risperidone (mean dosage 3.9 mg/day) and olanzapine (mean dosage 11.8 mg/day) in 112 first-episode patients, both treatments were well tolerated, with an overall completion rate of 72% ([Robinson et al. 2006](#)). Response rates did not differ significantly between risperidone (54%) and olanzapine (44%), although patients who responded to risperidone were significantly more likely to retain their response. A recent 12-month double-blind trial comparing oral risperidone with LAI risperidone in 86 patients with recent-onset schizophrenia showed significantly lower relapse rates in the patients receiving the depot formulation ([Subotnik et al. 2015](#)). However, another randomized controlled trial of 85 first-episode patients found oral SGAs and LAI risperidone to be equally effective and to have similar safety profiles ([Malla et al. 2013](#)). This finding implies that LAI risperidone is a safe, effective treatment option in this population, although not necessarily the treatment of first choice.

Experience in patients with treatment-resistant schizophrenia has been less consistent. In the U.S. multicenter registration study, [Marder and Meibach \(1994\)](#) found that patients who were presumed to have failed to respond to FGAs, on the basis of a history of hospitalization for at least 6 months prior to study entry, did not respond to haloperidol (20 mg/day) but did display significant response to risperidone (6 mg/day and 16 mg/day) compared with placebo. [Wirshing et al. \(1999\)](#) reported significant improvement with risperidone (6 mg/day) compared with haloperidol (15 mg/day) during a 4-week fixed-dose trial in 67 patients with schizophrenia and a history of treatment resistance. In contrast, [Volavka et al. \(2002\)](#) found no difference between high-dose risperidone (8–16 mg/day)

and haloperidol (10–20 mg/day) in patients established by history to be treatment resistant to FGAs. In the CATIE, risperidone was more effective than quetiapine but did not differ from olanzapine and ziprasidone in patients who discontinued their first-assigned SGA medication due to lack of efficacy (Stroup et al. 2006). In contrast, patients who discontinued perphenazine (for any reason) subsequently did better on quetiapine or olanzapine than they did on risperidone (Stroup et al. 2007). Two meta-analyses comparing FGAs and SGAs suggested an advantage for risperidone over older drugs (Davis et al. 2003; Leucht et al. 2009), and a recent network meta-analysis broadly confirmed this suggestion (Leucht et al. 2013).

### Clinical Trial Results for Paliperidone

In a 6-week trial in acutely ill schizophrenia patients, extended-release paliperidone (Invega) at dosages of 6, 9, and 12 mg/day was more effective than placebo (Kane et al. 2007), and in a flexibly dosed trial (9–15 mg/day), extended-release paliperidone significantly reduced relapse compared with placebo (Kramer et al. 2007). Combined results from three placebo-controlled trials involving 1,326 acutely ill schizophrenia patients found significant improvement across a daily dosage range of 3–15 mg (Meltzer et al. 2008). Three studies compared paliperidone with olanzapine 10 mg/day and found no difference in efficacy, but paliperidone was associated with more movement disorders and less weight gain (Nussbaum and Stroup 2008). The network meta-analysis by Leucht et al. (2013) concluded that paliperidone was significantly less effective than clozapine, amisulpride, and olanzapine but not risperidone, although unlike risperidone, paliperidone failed to demonstrate superiority over older drugs.

LAI paliperidone palmitate administered every 4 weeks has been demonstrated to be more effective than placebo (Hough et al. 2010; Kramer et al. 2010; Nasrallah et al. 2010; Takahashi et al. 2013) and to be similar in efficacy to risperidone microspheres administered every 2 weeks (Pandina et al. 2011), although the latter finding was not replicated in another study (Fleischhacker et al. 2012). A randomized clinical trial comparing LAI paliperidone palmitate with depot haloperidol administered in a matched loading-dose schedule (McEvoy et al. 2014) showed that the two drugs were equally effective in preventing relapse.

A Phase III clinical trial of paliperidone palmitate 3-month formulation (Invega Trinza) versus placebo was terminated early after the interim analysis clearly demonstrated the superior efficacy of PP3M (hazard ratio=3.45; 95% confidence interval=1.73–6.88;  $P<0.001$ ) (Berwaerts et al. 2015).

A second Phase III randomized, double-blind noninferiority study ( $N=1,016$ ) comparing PP3M with paliperidone palmitate 1-month formulation (PP1M) found no differences in efficacy, relapse rates, or side-effect profiles between the two formulations (Savitz et al. 2016).

## Mood Disorders

Six controlled trials of 3–4 weeks' duration that included a total of 1,343 patients have examined the efficacy of risperidone as monotherapy or in combination with a mood stabilizer for the acute treatment of bipolar mania (Rendell et al. 2006). As monotherapy and in combination, risperidone was more effective than placebo and similar in efficacy to haloperidol but produced more weight gain and fewer EPS (Rendell et al. 2006). In a placebo-controlled trial of open-label risperidone LAI microspheres in the maintenance treatment of bipolar I disorder, patients ( $n=303$ ) with manic or mixed episodes who

maintained response during a preceding 26-week period of risperidone following an initial 3-week period of oral risperidone were randomly allocated to placebo injections or continued treatment with LAI risperidone for up to 24 months. A switch to placebo injections significantly shortened the time to recurrence of manic episodes, but not depressive episodes ([Quiroz et al. 2010](#)).

Risperidone 1–2 mg/day was evaluated as an adjunct to antidepressant therapy in a 4-week placebo-controlled trial in 174 antidepressant-resistant patients with major depressive disorder recruited from 19 primary care and psychiatric centers ([Mahmoud et al. 2007](#)). Risperidone significantly lowered ratings of depressive symptoms compared with placebo. Remission rates were 25% with risperidone versus 11% with placebo ( $P=0.004$ ). Risperidone was well tolerated, with an 81% completion rate (vs. 88% with placebo).

## Autism Spectrum Disorder

Risperidone also was studied in a large 8-week placebo-controlled trial in 101 children and adolescents (ages 5–17 years) with DSM-IV ([American Psychiatric Association 1994](#))-defined autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior ([McCracken et al. 2002](#)). Flexible dosing with risperidone (range=0.5–3.5 mg/day; mean dosage=1.2 mg/day) resulted in a mean reduction of 57% in irritability, compared with a decrease of 14% in the placebo group, and the response rate was 69% with risperidone versus 12% with placebo. In a study of 32 children (ages 5–17 years) with DSM-IV autistic disorder who were treated for 4 months with open-label risperidone (mean dosage 2 mg/day), those who continued treatment with risperidone during the second study arm, an 8-week double-blind substitution trial, had much lower relapse rates compared with patients who were switched to placebo ([Research Units on Pediatric Psychopharmacology Autism Network 2005](#)). Risperidone at a mean dosage of 2 mg/day was also found to be effective compared with placebo in a study of 31 adults with DSM-IV autistic disorder or pervasive developmental disorder not otherwise specified ([McDougle et al. 1998](#)). In these studies, risperidone improved irritability and restricted, repetitive, and stereotyped behavioral problems associated with autism but was not effective for social or language deficits ([McDougle et al. 2005](#)). Risperidone at a dosage of 0.02–0.06 mg/kg was found to be well tolerated and effective for disruptive behaviors in children with low intelligence (IQ between 36 and 84) in a 6-week placebo-controlled trial ([Aman et al. 2002](#)).

## Other Disorders

### Generalized Anxiety Disorder

In a 4-week placebo-controlled add-on trial of low-dose risperidone in 417 patients with persistence of generalized anxiety disorder symptoms despite 8 weeks of anxiolytic therapy, no benefit from risperidone was found in the primary analysis; however, risperidone was associated with greater improvement in patients with moderate or severe anxiety at baseline ([Pandina et al. 2007](#)). Risperidone was highly effective for obsessive-compulsive disorder symptoms in a 6-week placebo-controlled trial in 36 adults prospectively confirmed to be nonresponsive to treatment with a selective serotonin reuptake inhibitor ([McDougle et al. 2000](#)). Symptoms of anxiety and depression also

responded to risperidone compared with placebo. Fifty percent of risperidone-treated patients responded (mean dosage 2.2 mg/day), compared with none in the placebo group.

### Alzheimer's Disease

In the CATIE–Alzheimer's Disease (CATIE-AD) study, risperidone had the longest time to discontinuation due to lack of effectiveness (27 weeks) among the agents studied; comparison results were 22 weeks for olanzapine, 9 weeks for quetiapine, and 9 weeks for placebo ([Schneider et al. 2006](#)). However, because of poor tolerability, none of the three antipsychotics differed from placebo on time to all-cause discontinuation.

## Side Effects and Toxicology

Risperidone shares class warnings with other SGAs in the United States, including the risks of tardive dyskinesia, neuroleptic malignant syndrome, and hyperglycemia and diabetes, as well as the risk of increased mortality in elderly patients with dementia-related psychosis. However, risperidone generally has been very well tolerated in clinical trials. In the U.S. multicenter trial reported by [Marder and Meibach \(1994\)](#), only headache and dizziness were significantly more frequent with risperidone (6 mg/day) compared with placebo, whereas the group receiving risperidone (16 mg/day) treatment also reported more EPS and dyspepsia than did the group receiving placebo ([Table 28-3](#)). Fatigue, sedation, accommodation disturbances, orthostatic dizziness, palpitations or tachycardia, weight gain, diminished sexual desire, and erectile dysfunction displayed a statistically significant relationship to risperidone dose, although most were not significantly elevated compared with placebo. In a flexible-dose relapse prevention study reported by [Csernansky et al. \(2002\)](#), no side effects were more frequent with risperidone, compared with haloperidol, although risperidone produced significantly greater weight gain. In a flexibly dosed, placebo-controlled trial of risperidone for children with disruptive behavior, risperidone (mean dosage 1.2 mg/day) produced more somnolence, headache, vomiting, dyspepsia, weight gain, and prolactin elevation than did placebo; most side effects were rated mild to moderate and did not adversely affect compliance ([Aman et al. 2002](#)).

**TABLE 28-3. Side effects reported by patients with schizophrenia receiving placebo, risperidone, or haloperidol in the U.S. multicenter trial**

	Percentage of patients			
	Placebo (n=66)	Risperidone 6 mg (n=64)	Risperidone 16 mg (n=64)	Haloperidol (n=66)
Insomnia	9.1	12.5	9.4	12.1
Agitation	7.6	10.9	12.5	16.7
Anxiety	1.5	7.8	4.7	1.5
Nervousness	1.5	6.3	1.6	0
Somnolence	0	3.1	9.4 <sup>a</sup>	4.5

<sup>a</sup>*P*<0.05 versus placebo.

<sup>b</sup>*P*<0.01 versus placebo.

Source. Adapted from [Marder and Meibach 1994](#).

	Percentage of patients			
	Placebo (n=66)	Risperidone 6 mg (n=64)	Risperidone 16 mg (n=64)	Haloperidol (n=66)
Extrapyramidal side effects	10.6	10.9	25.0 <sup>a</sup>	25.8 <sup>a</sup>
Headache	4.5	15.6 <sup>a</sup>	9.4	7.6
Dizziness	0	9.4 <sup>a</sup>	10.9 <sup>b</sup>	0
Dyspepsia	4.5	9.4	6.3	4.5
Vomiting	1.5	6.3	6.3	3.0
Nausea	0	6.3	3.1	1.5
Constipation	0	1.6	6.3	1.5
Rhinitis	6.1	15.6	6.3	4.5
Coughing	1.5	9.4	3.1	3.0
Sinusitis	1.5	6.3	1.6	0
Fever	0	6.3	3.1	1.5
Tachycardia	0	4.7	6.3	1.5

<sup>a</sup> $P < 0.05$  versus placebo.

<sup>b</sup> $P < 0.01$  versus placebo.

Source. Adapted from [Marder and Meibach 1994](#).

## Metabolic Effects

Weight gain with risperidone is intermediate—that is, the degree of weight gain is between that associated with agents like molindone, amisulpride, and ziprasidone, which appear to be relatively weight neutral, and that associated with agents like clozapine, olanzapine, and low-potency phenothiazines ([Rummel-Kluge et al. 2010](#); [Sikich et al. 2008](#)). In a meta-analysis of controlled trials, [Allison et al. \(1999\)](#), using a random effects model, estimated the mean weight gain at 10 weeks with risperidone to be 2.0 kg, compared with 0.5 kg with haloperidol, 3.5 kg with olanzapine, and 4.0 kg with clozapine. In the CATIE, in which risperidone had the lowest rate of discontinuation due to side effects, risperidone treatment was associated with a mean monthly weight gain of 0.4 lb, olanzapine with 2.0 lbs, and quetiapine with 0.5 lb; by contrast, perphenazine and ziprasidone were associated with a mean monthly weight *loss* of 0.2 lb and 0.3 lb, respectively ([Lieberman et al. 2005](#)). Although determining the risk for hyperglycemia is complex, and results of studies have not been completely consistent, it appears that risperidone does not produce insulin resistance to the degree associated with olanzapine and clozapine ([American Diabetes Association et al. 2004](#); [Henderson et al. 2006](#); [Lieberman et al. 2005](#)). A meta-analysis of head-to-head comparisons of SGAs found that risperidone produced more cholesterol elevation than aripiprazole and ziprasidone and less elevation than olanzapine and quetiapine ([Rummel-Kluge et al. 2010](#)). Metabolic side effects in children tend to be more severe than those in adults; for example, in one study of pediatric patients younger than 20 years, risperidone produced a mean weight gain of 5.3 kg (11.7 lb) over the 12-week treatment period ([Correll et al. 2009](#)). Metabolic side effects with paliperidone appear to be similar to those with risperidone.



## Extrapyramidal Side Effects

Significant reductions in EPS with risperidone compared with high-dose haloperidol were a consistent finding in the North American trials ([Chouinard et al. 1993](#); [Marder and Meibach 1994](#)). Measurement of EPS in the placebo group was complicated because 25% of the subjects were receiving depot antipsychotics prior to enrollment. Risperidone produced significantly fewer parkinsonian side effects than did haloperidol (20 mg/day), based on several measures, including self-report, change scores on the Extrapyramidal Symptom Rating Scale (ESRS), and use of anticholinergic medication. Patients receiving risperidone (2 mg/day and 6 mg/day) did not differ from the group receiving placebo in mean ratings of parkinsonism and in the use of anticholinergic medication. Parkinsonism change scores were significantly correlated with the risperidone dosage ( $r=0.94$ ); however, risperidone (16 mg/day) was associated with fewer parkinsonian side effects than was haloperidol. Dystonia occurred in six of the patients treated with risperidone (1.7%) versus two of the patients treated with haloperidol (2.4%). Dystonia rates did not differ between treatment groups, and the rates did not exhibit a relationship to risperidone dosage.

In the large European multicenter trial, maximum ratings of parkinsonism, hyperkinesia, and dystonia were greater with haloperidol (10 mg/day) than with all dosages of risperidone (maximum of 12 mg/day), and anticholinergic dosing was accordingly higher in the group treated with haloperidol ([Peuskens 1995](#)). Similarly, in a flexible-dose comparison of risperidone (mean dosage 4.9 mg/day) and haloperidol (mean dosage 11.7 mg/day) for prevention of relapse, EPS rates and use of anticholinergic medication significantly favored the group taking risperidone ([Csernansky et al. 2002](#)). However, in a smaller double-blind, flexible-dose trial comparing risperidone (5–15 mg/day) and the moderate-potency FGA agent perphenazine (16–48 mg/day) in 107 patients, no difference in EPS rates was observed ([Høyberg et al. 1993](#)), indicating that the potency of the comparator agent may in part determine the relative benefit of risperidone for EPS. Of interest, in a study of low-dose risperidone (mean dosage 1.2 mg/day) in children with behavioral disorders, ratings of EPS did not differ between risperidone and placebo ([Aman et al. 2002](#)). No differences in EPS ratings were found among any treatment groups in the CATIE ([Lieberman et al. 2005](#)), although discontinuation rates due to EPS significantly differed, with perphenazine producing the highest discontinuation rate (8%) and olanzapine (2%), risperidone (3%), and quetiapine (3%) producing the lowest.

The experience with tardive dyskinesia (TD) in patients treated with risperidone has been promising. [Jeste et al. \(1999\)](#) randomly treated 122 elderly patients with low-dosage haloperidol (median daily dose 1 mg) versus risperidone (median daily dose 1 mg). The very high rates of treatment-emergent TD typically found in geriatric patients make this sample a sensitive assay for TD risk. After 9 months, treatment-emergent TD rates were 30% with haloperidol versus less than 5% with risperidone. Risperidone was also noted to decrease dyskinetic movements compared with haloperidol in a Canadian multicenter trial reported by [Chouinard et al. \(1993\)](#), and it was associated with a treatment-emergent TD rate of 0.6%, compared with a rate of 2.7% with haloperidol, in a relapse prevention trial reported by [Csernansky et al. \(2002\)](#).

## Hyperprolactinemia

Unlike other SGA agents, risperidone and paliperidone substantially increase serum prolactin levels—in some studies, to a greater degree than does haloperidol ([Kearns et al.](#)

2000; Markianos et al. 1999)—although prolactin levels may decrease over time (Eberhard et al. 2007; Findling et al. 2003). The relationship between serum prolactin concentrations and clinical side effects remains somewhat unclear, however. Kleinberg et al. (1999) analyzed combined results from the North American and European multicenter registration trials, which included plasma prolactin concentrations from 841 patients and clinical ratings of symptoms associated with hyperprolactinemia from 1,884 patients. Mean prolactin levels significantly correlated with risperidone dosage; risperidone 6 mg/day produced elevations roughly comparable to those seen with haloperidol 20 mg/day and significantly higher than those seen with haloperidol 10 mg/day. The combined incidence of amenorrhea and galactorrhea in women, which varied between 8% and 12%, was similar for all dosages of risperidone and haloperidol (10 mg/day). Because symptom frequencies were available only for 14 women treated with placebo, comparisons with placebo were not informative. Sexual dysfunction or gynecomastia occurred in 15% of men treated with risperidone (4–6 mg/day), compared with 14% of men treated with haloperidol (10 mg/day) and 8% of men in the placebo group. Compared with placebo, ejaculatory dysfunction was significantly more frequent only in the group treated with risperidone (12–16 mg/day). Mean plasma prolactin levels were not significantly related to clinical side effects for either men or women. Decreased libido also did not differ between treatment groups and did not correlate with plasma prolactin levels. In the CATIE, prolactin levels increased by a mean of 15.4 ng/mL with risperidone, compared with a 0.4-ng/mL mean elevation with perphenazine and decreases of 4.5–9.3 ng/mL with the other SGAs (Lieberman et al. 2005). Despite having significantly higher serum prolactin concentrations, patients treated with risperidone did not report significantly higher rates of sexual dysfunction, gynecomastia, galactorrhea, or irregular menses.

Two reports of clinical trials with extended-release paliperidone have indicated low levels of prolactin-related side effects (1% and 4%) (Kane et al. 2007; Kramer et al. 2007). However, in the one publication that reported prolactin levels, substantial increases in mean plasma prolactin concentrations were observed (males: 17.4 ng/mL at baseline to 45.3 ng/mL at week 6; females: 38.0 ng/mL to 124.5 ng/mL) (Kane et al. 2007). A 13-week comparison of paliperidone palmitate with risperidone microspheres reported that paliperidone palmitate was associated with moderately higher elevations from baseline in prolactin levels compared with risperidone (women: 21.8 vs. 15.6 ng/mL; men: 9.4 vs. 6.0 ng/mL) (Pandina et al. 2011); however, another study found that the proportion of patients with abnormally elevated prolactin levels was higher in the group receiving LAI risperidone than in that receiving paliperidone palmitate (Fleischhacker et al. 2012). Two preliminary studies with risperidone found that plasma prolactin concentrations correlated with 9-hydroxyrisperidone (paliperidone) concentrations and not with risperidone concentrations (Melkersson 2006; Troost et al. 2007). The ratio of 9-hydroxyrisperidone levels to risperidone levels also correlated with prolactin concentration (Troost et al. 2007); in agreement with this finding, rapid metabolizers of CYP2D6 were found to have higher prolactin concentrations than poor metabolizers (Troost et al. 2007).

## Cardiovascular Effects

Because of relatively high affinities for adrenoreceptors, risperidone would be expected to produce orthostatic hypotension. However, by following a 3- to 7-day dosage escalation schedule, initial postural hypotension and tachycardia have been avoided in clinical trials, with only rare cases of hypotension and syncope reported (Chouinard et al. 1993; Marder



and Meibach 1994). Risperidone has very modest effects on cardiac conduction. No significant prolongation of the QTc interval was detected at dosages of up to 25 mg/day in early safety trials, and no relationship between QTc interval and risperidone dose was apparent (Mesotten et al. 1989). In the CATIE, risperidone was associated with the least QTc prolongation (mean 0.2 msec) and quetiapine with the most (mean 5.9 msec), although differences were not statistically significant (Lieberman et al. 2005). A mean QTc prolongation of 10 msec, measured after peak absorption of risperidone (16 mg/day), was found in a study comparing SGAs and FGAs, according to data filed with the FDA by Pfizer Inc. (Harrigan et al. 2004). In a retrospective cohort study of Medicaid enrollees in Tennessee, risperidone was associated with a 2.9-fold increase in rate of sudden cardiac death, compared with a 1.61-fold increase with haloperidol and a 3.67-fold increase with clozapine (Ray et al. 2009).

## High Dose and Overdose

Mesotten et al. (1989) reported the results of a safety trial involving 17 inpatients with psychosis in which, following a washout of previous medication, risperidone was started at 10 mg/day, and the dosage was then increased weekly by 5 mg/day to a maximum of 25 mg/day. Despite extremely high doses, sedation was the only prominent side effect. Although risperidone does not bind significantly to muscarinic cholinergic receptors, transient dry mouth, blurred vision, and urinary retention were observed in individual subjects. Palpitations occurred in two subjects. Heart rate significantly increased during the trial, and blood pressure slightly decreased; however, no cases of significant hypotension were reported. An endocrine battery, including plasma triiodothyronine, thyroid-stimulating hormone, growth hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, and cortisol levels, was performed, and only prolactin was found to be affected. Reported overdoses with risperidone have generally been benign, with moderate QT prolongation and no serious cardiac complications (Brown et al. 1993; Lo Vecchio et al. 1996).

---

## Drug-Drug Interactions

---

Because CYP2D6 status affects the half-life of risperidone and the relative ratio of risperidone to 9-hydroxyrisperidone in plasma, the total serum concentration of the “active moiety,” or the sum of the concentrations of risperidone and 9-hydroxyrisperidone, may be significantly increased with addition of a CYP2D6 inhibitor (e.g., fluoxetine) in rapid metabolizers but not in poor metabolizers (Bondolfi et al. 2002; Spina et al. 2002). In one study of 9 patients treated with risperidone, addition of fluoxetine resulted in a 75% increase in blood levels of the active moiety (risperidone+9-hydroxyrisperidone); two patients developed parkinsonian side effects (Spina et al. 2002). Paliperidone plasma concentrations are not influenced by CYP2D6 status, nor are paliperidone plasma concentrations likely to be affected by drug-drug interactions. It has been hypothesized that the addition of a CYP2D6 inhibitor (e.g., fluoxetine) could decrease risperidone-induced prolactin elevation by increasing the ratio of risperidone to 9-hydroxyrisperidone (Troost et al. 2007), although this has not been rigorously tested.

---

## Conclusion

---

Risperidone was the first antipsychotic agent developed specifically to exploit the clinical advantages of combined  $D_2$  and  $5-HT_{A2}$  receptor antagonism.  $\alpha$ -Adrenergic antagonism additionally may contribute to the antipsychotic and cognition-enhancing effects of risperidone. Risperidone's active metabolite, paliperidone, is pharmacologically quite similar to the parent drug and comprises roughly 80%–90% of the serum concentration of the active moiety (risperidone + paliperidone) in most patients treated with risperidone. Risperidone and paliperidone are generally quite well tolerated, producing moderate weight gain and mild sedation. Initial dosage titration is necessary to prevent orthostatic blood pressure changes and dizziness, although this may be less necessary with extended-release paliperidone. EPS are dose related and are typically less common with risperidone than with haloperidol but more common with risperidone compared with other SGAs. Risperidone and paliperidone markedly elevate prolactin levels, although the relationship between plasma prolactin concentrations and clinical symptoms is complex. The efficacy of risperidone was initially established in comparison with high-dose haloperidol, against which it was significantly more effective for all five symptom clusters derived from the PANSS. However, the magnitude of difference in effect size was not large for individual symptom clusters. In the CATIE, risperidone (at a mean daily dosage of 3.9 mg) did not differ from perphenazine in rates of discontinuation due to lack of effectiveness but was less effective than olanzapine (Lieberman et al. 2005). The risperidone microspheres product was the first FDA-approved SGA long-acting IM formulation, and paliperidone palmitate was the first SGA depot formulation that could be administered at an interval of every 4 weeks. PP3M is the first depot antipsychotic that can be administered on a quarterly schedule. Overall, risperidone and paliperidone are well-tolerated SGA agents with efficacy comparable to that of most other agents in their class.

---

## References

---

- Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156(11):1686–1696, 1999 10553730
- Aman MG, De Smedt G, Derivan A, et al; Risperidone Disruptive Behavior Study Group: Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry* 159(8):1337–1346, 2002 12153826
- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity: Consensus development conference on antipsychotic drugs and diabetes and obesity. *Diabetes Care* 27(2):596–601, 2004 14747245
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Anderson CB, True JE, Ereshefsky L, et al: Risperidone dose, plasma levels, and response. Presentation at the 146th annual meeting of the American Psychiatric Association, San Francisco, CA, May 22–27, 1993
- Ansoms C, Backer-Dierick GD, Vereecken JL: Sleep disorders in patients with severe mental depression: double-blind placebo-controlled evaluation of the value of pipamperone (Dipiperon). *Acta Psychiatr Scand* 55(2):116–122, 1977 320830
- Arakawa R, Ito H, Takano A, et al: Dose-finding study of paliperidone ER based on striatal and extrastriatal dopamine  $D_2$  receptor occupancy in patients with schizophrenia.

- Psychopharmacology (Berl) 197(2):229-235, 2008 18058087
- Attard A, Olofinjana O, Cornelius V, et al: Paliperidone palmitate long-acting injection-prospective year-long follow-up of use in clinical practice. *Acta Psychiatr Scand* 130(1):46-51, 2014 24117209
- Berwaerts J, Liu Y, Gopal S, et al: Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. *JAMA Psychiatry* 72(8):830-839, 2015 25820612
- Bai YM, Ting Chen T, Chen JY, et al: Equivalent switching dose from oral risperidone to risperidone long-acting injection: a 48-week randomized, prospective, single-blind pharmacokinetic study. *J Clin Psychiatry* 68(8):1218-1225, 2007 17854246
- Bersani G, Grispi A, Marini S, et al: 5-HT<sub>2</sub> antagonist ritanserin in neuroleptic-induced parkinsonism: a double-blind comparison with orphenadrine and placebo. *Clin Neuropharmacol* 13(6):500-506, 1990 2125857
- Bondolfi G, Eap CB, Bertschy G, et al: The effect of fluoxetine on the pharmacokinetics and safety of risperidone in psychotic patients. *Pharmacopsychiatry* 35(2):50-56, 2002 11985287
- Borison RL, Diamond B, Pathiraja A, Meibach RC: Pharmacokinetics of risperidone in chronic schizophrenic patients. *Psychopharmacol Bull* 30(2):193-197, 1994 7530379
- Brown K, Levy H, Brenner C, et al: Overdose of risperidone. *Ann Emerg Med* 22(12):1908-1910, 1993 7694530
- Busatto GF, Kerwin RW: Perspectives on the role of serotonergic mechanisms in the pharmacology of schizophrenia. *J Psychopharmacol* 11(1):3-12, 1997 9097883
- Ceulemans DL, Gelders YG, Hoppenbrouwers ML, et al: Effect of serotonin antagonism in schizophrenia: a pilot study with setoperone. *Psychopharmacology (Berl)* 85(3):329-332, 1985 3923519
- Chouinard G, Jones B, Remington G, et al: A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 13(1):25-40, 1993 7683702
- Cohen J: *Statistical Power Analysis for the Behavioral Sciences*, 2nd Edition. Hillsdale, NJ, Lawrence Erlbaum, 1988
- Colpaert FC, Meert TF, Niemegeers CJ, Janssen PA: Behavioral and 5-HT antagonist effects of ritanserin: a pure and selective antagonist of LSD discrimination in rat. *Psychopharmacology (Berl)* 86(1-2):45-54, 1985 2862659
- Correll CU, Manu P, Olshanskiy V, et al: Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents (erratum in *JAMA* 302:2322, 2009). *JAMA* 302(16):1765-1773, 2009 19861668
- Coull JT, Sahakian BJ, Hodges JR: The alpha(2) antagonist idazoxan remediates certain attentional and executive dysfunction in patients with dementia of frontal type. *Psychopharmacology (Berl)* 123(3):239-249, 1996 8833417
- Csernansky JG, Mahmoud R, Brenner R; Risperidone-USA-79 Study Group: A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 346(1):16-22, 2002 11777998
- Cuesta MJ, Jalón EG, Campos MS, Peralta V: Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis. *Br J Psychiatry* 194(5):439-445, 2009 19407274
- Davis JM, Chen N, Glick ID: A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 60(6): 553-564, 2003 12796218
- de Leon J, Wynn G, Sandson NB: The pharmacokinetics of paliperidone versus risperidone. *Psychosomatics* 51(1):80-88, 2010 20118446
- Duinkerke SJ, Botter PA, Jansen AA, et al: Ritanserin, a selective 5-HT<sub>2</sub>/1C antagonist, and negative symptoms in schizophrenia. A placebo-controlled double-blind trial. *Br J Psychiatry* 163:451-455, 1993 7902766
- Eberhard J, Lindström E, Holstad M, Levander S: Prolactin level during 5 years of risperidone treatment in patients with psychotic disorders. *Acta Psychiatr Scand* 115(4): 268-276, 2007 17355517

- Findling RL, Kusumakar V, Daneman D, et al: Prolactin levels during long-term risperidone treatment in children and adolescents. *J Clin Psychiatry* 64(11):1362-1369, 2003 14658952
- Fleischhacker WW, Gopal S, Lane R, et al: A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. *Int J Neuropsychopharmacol* 15(1):107-118, 2012 21777507
- Gelders YG: Thymosthenic agents, a novel approach in the treatment of schizophrenia. *Br J Psychiatry Suppl* 155(5):33-36, 1989 2481482
- Gellman RL, Aghajanian GK: Serotonin<sub>2</sub> receptor-mediated excitation of interneurons in piriform cortex: antagonism by atypical antipsychotic drugs. *Neuroscience* 58(3):515-525, 1994 7513386
- Geyer MA, Swerdlow NR, Mansbach RS, Braff DL: Startle response models of sensorimotor gating and habituation deficits in schizophrenia. *Brain Res Bull* 25(3):485-498, 1990 2292046
- Goff DC, Coyle JT: The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry* 158(9):1367-1377, 2001 11532718
- Goff DC, Evins AE: Negative symptoms in schizophrenia: neurobiological models and treatment response. *Harv Rev Psychiatry* 6(2):59-77, 1998 10370450
- Green MF, Marshall BD Jr, Wirshing WC, et al: Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *Am J Psychiatry* 154(6):799-804, 1997 9167507
- Green MF, Marder SR, Glynn SM, et al: The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. *Biol Psychiatry* 51(12):972-978, 2002 12062881
- Haapalinna A, Sirviö J, MacDonald E, et al: The effects of a specific alpha(2)-adrenoceptor antagonist, atipamezole, on cognitive performance and brain neurochemistry in aged Fisher 344 rats. *Eur J Pharmacol* 387(2):141-150, 2000 10650154
- Harrigan EP, Miceli JJ, Anziano R, et al: A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol* 24(1):62-69, 2004 14709949
- Harris MS, Wiseman CL, Reilly JL, et al: Effects of risperidone on procedural learning in antipsychotic-naïve first-episode schizophrenia. *Neuropsychopharmacology* 34(2):468-476, 2009 18536701
- Harvey PD, Rabinowitz J, Eerdekens M, Davidson M: Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry* 162(10):1888-1895, 2005 16199835
- Henderson DC, Copeland PM, Borba CP, et al: Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *J Clin Psychiatry* 67(5):789-797, 2006 16841629
- Hertel P, Fagerquist MV, Svensson TH: Enhanced cortical dopamine output and antipsychotic-like effects of raclopride by alpha<sub>2</sub> adrenoceptor blockade. *Science* 286(5437):105-107, 1999 10506554
- Heykants J, Huang ML, Mannens G, et al: The pharmacokinetics of risperidone in humans: a summary. *J Clin Psychiatry* 55 (suppl):13-17, 1994 7520903
- Høyberg OJ, Fensbo C, Remvig J, et al: Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. *Acta Psychiatr Scand* 88(6):395-402, 1993 7508675
- Hough D, Gopal S, Vijapurkar U, et al: Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res* 116(2-3):107-117, 2010 19959339
- Janssen PA, Niemegeers CJ, Awouters F, et al: Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S<sub>2</sub> and dopamine-D<sub>2</sub> antagonistic properties. *J Pharmacol Exp Ther* 244(2): 685-693, 1988 2450200

- Jeste DV, Lacro JP, Bailey A, et al: Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. *J Am Geriatr Soc* 47(6): 716-719, 1999 10366172
- Kane JM, Eerdekens M, Lindenmayer JP, et al: Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 160(6):1125-1132, 2003 12777271
- Kane J, Canas F, Kramer M, et al: Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res* 90(1-3):147-161, 2007 17092691
- Kapur S, Seeman P: Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? a new hypothesis. *Am J Psychiatry* 158(3): 360-369, 2001 11229973
- Kapur S, Zipursky RB, Remington G: Clinical and theoretical implications of 5-HT<sub>2</sub> and D<sub>2</sub> receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 156(2):286-293, 1999 9989565
- Kearns AE, Goff DC, Hayden DL, Daniels GH: Risperidone-associated hyperprolactinemia. *Endocr Pract* 6(6):425-429, 2000 11155212
- Keefe RS, Young CA, Rock SL, et al; HGGN Study Group: One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. *Schizophr Res* 81(1):1-15, 2006 16202565
- Keefe RS, Bilder RM, Davis SM, et al; CATIE Investigators; Neurocognitive Working Group: Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry* 64(6):633-647, 2007 17548746
- Keks NA, Ingham M, Khan A, Karcher K: Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. Randomised, controlled, open-label study. *Br J Psychiatry* 191:131-139, 2007 17666497
- Kleinberg DL, Davis JM, de Coster R, et al: Prolactin levels and adverse events in patients treated with risperidone. *J Clin Psychopharmacol* 19(1):57-61, 1999 9934944
- Kramer M, Simpson G, Maciulis V, et al: Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 27(1):6-14, 2007 17224706
- Kramer M, Litman R, Hough D, et al: Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. *Int J Neuropsychopharmacol* 13(5):635-647, 2010 19941696
- Krystal JH, Karper LP, Seibyl JP, et al: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51(3):199-214, 1994 8122957
- Leucht S, Corves C, Arbter D, et al: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 373(9657):31-41, 2009 19058842
- Leucht S, Cipriani A, Spineli L, et al: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382(9896):951-962, 2013 23810019
- Leysen JE, Niemegeers CJE, Tollenaere JP, Laduron PM: Serotonergic component of neuroleptic receptors. *Nature* 272(5649): 168-171, 1978 564466
- Leysen JE, Gommeren W, Mertens J, et al: Comparison of in vitro binding properties of a series of dopamine antagonists and agonists for cloned human dopamine D<sub>2S</sub> and D<sub>2L</sub> receptors and for D<sub>2</sub> receptors in rat striatal and mesolimbic tissues, using [<sup>125</sup>I] 2'-iodospiperone. *Psychopharmacology (Berl)* 110(1-2):27-36, 1993a 7870895
- Leysen JE, Janssen PM, Schotte A, et al: Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and

- clinical effects: role of 5HT<sub>2</sub> receptors. *Psychopharmacology (Berl)* 112 (1 suppl):S40-S54, 1993b 7530377
- Leysen JE, Janssen PM, Megens AA, Schotte A: Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. *J Clin Psychiatry* 55 (suppl):5-12, 1994 7520908
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353(12):1209-1223, 2005 16172203
- Litman RE, Su TP, Potter WZ, et al: Idazozan and response to typical neuroleptics in treatment-resistant schizophrenia. Comparison with the atypical neuroleptic, clozapine. *Br J Psychiatry* 168(5):571-579, 1996 8733795
- Lo Vecchio F, Hamilton RJ, Hoffman RJ: Risperidone overdose (letter). *Am J Emerg Med* 14(1):95-96, 1996 8630169
- Mahmoud RA, Pandina GJ, Turkoz I, et al: Risperidone for treatment-refractory major depressive disorder: a randomized trial. *Ann Intern Med* 147(9):593-602, 2007 17975181
- Malla A, Chue P, Jordan G, et al: An exploratory open-label randomized trial comparing risperidone long acting injectable (RLAI) with oral antipsychotic medication in the treatment of early psychosis. *Clin Schizophr Relat Psychoses* 17:1-26, 2013 23773886
- Mannens G, Huang M-L, Meuldermans W, et al: Absorption, metabolism, and excretion of risperidone in humans. *Drug Metab Dispos* 21(6):1134-1141, 1993 7507814
- Marder SR, Meibach RC: Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 151(6):825-835, 1994 7514366
- Marder SR, Davis JM, Chouinard G: The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 58(12): 538-546, 1997 9448657
- Markianos M, Hatzimanolis J, Lykouras L: Gonadal axis hormones in male schizophrenic patients during treatment with haloperidol and after switch to risperidone. *Psychopharmacology (Berl)* 143(3): 270-272, 1999 10353429
- McCracken JT, McGough J, Shah B, et al; Research Units on Pediatric Psychopharmacology Autism Network: Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 347(5):314-321, 2002 12151468
- McDougle CJ, Holmes JP, Carlson DC, et al: A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Arch Gen Psychiatry* 55(7):633-641, 1998 9672054
- McDougle CJ, Epperson CN, Pelton GH, et al: A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 57(8):794-801, 2000 10920469
- McDougle CJ, Scahill L, Aman MG, et al: Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *Am J Psychiatry* 162(6):1142-1148, 2005 15930063
- McEvoy JP, Byerly M, Hamer RM, et al: Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA* 311(19):1978-1987, 2014 24846035
- Meert TF, Colpaert FC: Effects of 5-HT<sub>2</sub>-antagonists in two conflict procedures that involve exploratory behavior. *Psychopharmacology (Berl)* 88(4):445-450, 1986 2871580
- Meert TF, de Haes P, Janssen PA: Risperidone (R 64 766), a potent and complete 5-HT<sub>2</sub> antagonist in drug discrimination by rats. *Psychopharmacology (Berl)* 97(2):206-212, 1989 2471220
- Megens AA, Awouters FHL, Niemegeers CJE: Differential effects of the new antipsychotic risperidone on large and small motor movements in rats: a comparison with haloperidol. *Psychopharmacology (Berl)* 95(4):493-496, 1988 2463650
- Melkersson KI: Prolactin elevation of the antipsychotic risperidone is predominantly related to its 9-hydroxy metabolite. *Hum Psychopharmacol* 21(8):529-532, 2006

17094165

- Meltzer HY, Bastani B, Ramirez L, Matsubara S: Clozapine: new research on efficacy and mechanism of action. *Eur Arch Psychiatry Neurol Sci* 238(5-6):332-339, 1989 2569975
- Meltzer HY, Bobo WV, Nuamah IF, et al: Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week, placebo-controlled studies. *J Clin Psychiatry* 69(5):817-829, 2008 18466043
- Mesotten F, Suy E, Pietquin M, et al: Therapeutic effect and safety of increasing doses of risperidone (R 64766) in psychotic patients. *Psychopharmacology (Berl)* 99(4):445-449, 1989 2480616
- Nasrallah HA, Gopal S, Gassmann-Mayer C, et al: A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. *Neuropsychopharmacology* 35(10):2072-2082, 2010 20555312
- Nussbaum AM, Stroup TS: Paliperidone for treatment of schizophrenia. *Schizophr Bull* 34(3):419-422, 2008 18375569
- Nyberg S, Eriksson B, Oxenstierna G, et al: Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. *Am J Psychiatry* 156(6):869-875, 1999 10360125
- Pandina GJ, Canuso CM, Turkoz I, et al: Adjunctive risperidone in the treatment of generalized anxiety disorder: a double-blind, prospective, placebo-controlled, randomized trial. *Psychopharmacol Bull* 40(3):41-57, 2007 18007568
- Pandina G, Lane R, Gopal S, et al: A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 35(1): 218-226, 2011 21092748
- Peuskens J; Risperidone Study Group: Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 166(6):712-726, discussion 727-733, 1995 7545060
- Poyurovsky M, Shardorodsky M, Fuchs C, et al: Treatment of neuroleptic-induced akathisia with the 5-HT2 antagonist mianserin. Double-blind, placebo-controlled study. *Br J Psychiatry* 174:238-242, 1999 10448449
- Quiroz JA, Yatham LN, Palumbo JM, et al: Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry* 68(2):156-162, 2010 20227682
- Ray WA, Chung CP, Murray KT, et al: Atypical antipsychotic drugs and the risk of sudden cardiac death (erratum in *N Engl J Med* 361:1814, 2009). *N Engl J Med* 360(3):225-235, 2009 19144938
- Reilly JL, Harris MS, Keshavan MS, Sweeney JA: Adverse effects of risperidone on spatial working memory in first-episode schizophrenia. *Arch Gen Psychiatry* 63(11):1189-1197, 2006 17088499
- Remington G, Mamo D, Labelle A, et al: A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. *Am J Psychiatry* 163(3): 396-401, 2006 16513859
- Rendell JM, Gijssman HJ, Bauer MS, et al: Risperidone alone or in combination for acute mania. *Cochrane Database Syst Rev* (1):CD004043, 2006 16437472
- Research Units on Pediatric Psychopharmacology Autism Network: Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry* 162(7):1361-1369, 2005 15994720
- Reyntjens A, Gelders YG, Hoppenbrouwers M, et al: Thymostenic effects of ritanserin (R55 667), a centrally active serotonin-5-HT2 receptor blocker. *Drug Dev Res* 8(1-4):205-211, 1986
- Richelson E: Preclinical pharmacology of neuroleptics: focus on new generation compounds. *J Clin Psychiatry* 57 (suppl 11):4-11, 1996 8941166
- Robinson DG, Woerner MG, Napolitano B, et al: Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes.

- Am J Psychiatry 163(12):2096-2102, 2006 17151160
- Roose K, Gelders Y, Heylen S: Risperidone (R64 766) in psychotic patients. A first clinical therapeutic exploration. *Acta Psychiatr Belg* 88(3):233-241, 1988 2466393
- Rosenheck RA, Krystal JH, Lew R, et al: Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* 364(9):842-851, 2011 21366475
- Rummel-Kluge C, Komossa K, Schwarz S, et al: Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 123(2-3):225-233, 2010 20692814
- Saller CF, Czupryna MJ, Salama AI: 5-HT<sub>2</sub> receptor blockade by ICI 169,369 and other 5-HT<sub>2</sub> antagonists modulates the effects of D-2 dopamine receptor blockade. *J Pharmacol Exp Ther* 253(3):1162-1170, 1990 2141636
- Savitz AJ, Xu H, Gopal S, et al: Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. *Int J Neuropsychopharmacol* 19(7):1-14, 2016 26902950
- Schmidt CJ, Sorensen SM, Kehne JH, et al: The role of 5-HT<sub>2A</sub> receptors in antipsychotic activity. *Life Sci* 56(25):2209-2222, 1995 7791509
- Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 355(15):1525-1538, 2006 17035647
- Schotte A, Janssen PF, Gommeren W, et al: Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. *Psychopharmacology (Berl)* 124(1-2):57-73, 1996 8935801
- Seeman P: Atypical antipsychotics: mechanism of action. *Can J Psychiatry* 47(1):27-38, 2002 11873706
- Sikich L, Frazier JA, McClellan J, et al: Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study (erratum in *Am J Psychiatry* 165:1495, 2008). *Am J Psychiatry* 165(11):1420-1431, 2008 18794207
- Simpson GM, Mahmoud RA, Lasser RA, et al: A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 67(8):1194-1203, 2006 16965196
- Spina E, Avenoso A, Scordo MG, et al: Inhibition of risperidone metabolism by fluoxetine in patients with schizophrenia: a clinically relevant pharmacokinetic drug interaction. *J Clin Psychopharmacol* 22(4):419-423, 2002 12172343
- Stathis P, Antoniou K, Papadopoulou-Daifotis Z, et al: Risperidone: a novel antipsychotic with many "atypical" properties? *Psychopharmacology (Berl)* 127(3):181-186, 1996 8912395
- Stroup TS, McEvoy JP, Swartz MS, et al: The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophr Bull* 29(1):15-31, 2003 12908658
- Stroup TS, Lieberman JA, McEvoy JP, et al; CATIE Investigators: Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 163(4):611-622, 2006 16585435
- Stroup TS, Lieberman JA, McEvoy JP, et al; CATIE Investigators: Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry* 164(3):415-427, 2007 17329466
- Subotnik KL, Casaus LR, Ventura J, et al: Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. *JAMA Psychiatry* 72(8):822-829, 2015 26107752



- Svensson TH, Tung C-S, Grenhoff J: The 5-HT<sub>2</sub> antagonist ritanserin blocks the effect of pre-frontal cortex inactivation on rat A10 dopamine neurons in vivo. *Acta Physiol Scand* 136(3):497-498, 1989 2568733
- Svensson TH, Mathé JM, Andersson JL, et al: Mode of action of atypical neuroleptics in relation to the phencyclidine model of schizophrenia: role of 5-HT<sub>2</sub> receptor and alpha 1-adrenoceptor antagonism [corrected]. *J Clin Psychopharmacol* 15 (1 suppl 1):11S-18S, 1995 7730496
- Takahashi N, Takahashi M, Saito T, et al: Randomized, placebo-controlled, double-blind study assessing the efficacy and safety of paliperidone palmitate in Asian patients with schizophrenia. *Neuropsychiatr Dis Treat* 8:1889-1898, 2013 24353421
- Tiihonen J, Haukka J, Taylor M, et al: A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia (erratum in *Am J Psychiatry* 169:223, 2012). *Am J Psychiatry* 168(6):603-609, 2011 21362741
- Troost PW, Lahuis BE, Hermans MH, et al: Prolactin release in children treated with risperidone: impact and role of CYP2D6 metabolism. *J Clin Psychopharmacol* 27(1):52-57, 2007 17224713
- Ugedo L, Grenhoff J, Svensson TH: Ritanserin, a 5-HT<sub>2</sub> receptor antagonist, activates midbrain dopamine neurons by blocking serotonergic inhibition. *Psychopharmacology (Berl)* 98(1):45-50, 1989 2524859
- Varty GB, Bakshi VP, Geyer MA: M100907, a serotonin 5-HT<sub>2A</sub> receptor antagonist and putative antipsychotic, blocks dizocilpine-induced prepulse inhibition deficits in Sprague-Dawley and Wistar rats. *Neuropsychopharmacology* 20(4):311-321, 1999 10088132
- Volavka J, Czobor P, Sheitman B, et al: Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry* 159(2): 255-262, 2002 11823268
- Wadenberg ML, Hicks PB, Richter JT, Young KA: Enhancement of antipsychoticlike properties of raclopride in rats using the selective serotonin<sub>2A</sub> receptor antagonist MDL 100,907. *Biol Psychiatry* 44(6): 508-515, 1998 9777184
- Wirshing DA, Marshall BD Jr, Green MF, et al: Risperidone in treatment-refractory schizophrenia. *Am J Psychiatry* 156(9): 1374-1379, 1999 10484947

# CHAPTER 29

## Aripiprazole and Brexpiprazole

Rolando Gonzalez, M.D.

Martin T. Strassnig, M.D.

---

### History and Discovery

---

In this chapter, we review the preclinical and clinical pharmacology of aripiprazole and brexpiprazole, two novel atypical (second-generation) antipsychotics. Aripiprazole is a dihydroquinolinone antipsychotic agent. Chemically, it is unrelated to phenothiazines, butyrophenones, or thienobenzodiazepines. Pharmacologically, it exhibits a novel mechanism of action, combining partial agonist activity at dopamine type 2 ( $D_2$ ), dopamine type 3 ( $D_3$ ), and serotonin type 1A ( $5-HT_{1A}$ ) receptors with antagonist activity at serotonin type 2A ( $5-HT_{2A}$ ) and  $D_2$  receptors ([Burris et al. 2002](#); [Jordan et al. 2002](#)). Aripiprazole represents a significant innovation, following the

introduction of typical (first-generation) and atypical antipsychotics, in the pharmacology of therapeutic agents for psychotic disorders.

Brexpiprazole has been developed with a goal for further stabilization of dopaminergic transmission, more specifically regarding an optimal level of D<sub>2</sub> intrinsic activity. The pharmacological profile of brexpiprazole is similar to that of aripiprazole, including combined partial agonist activity at D<sub>2</sub>, D<sub>3</sub>, and 5-HT<sub>1A</sub> receptors with antagonist activity at 5-HT<sub>2A</sub> and D<sub>2</sub> receptors. However, brexpiprazole has lower intrinsic activity at D<sub>2</sub> receptors, high-potency partial agonism at 5-HT<sub>1A</sub> receptors, and stronger antagonism at 5-HT<sub>2A</sub> receptors ([Maeda et al. 2014b](#)).

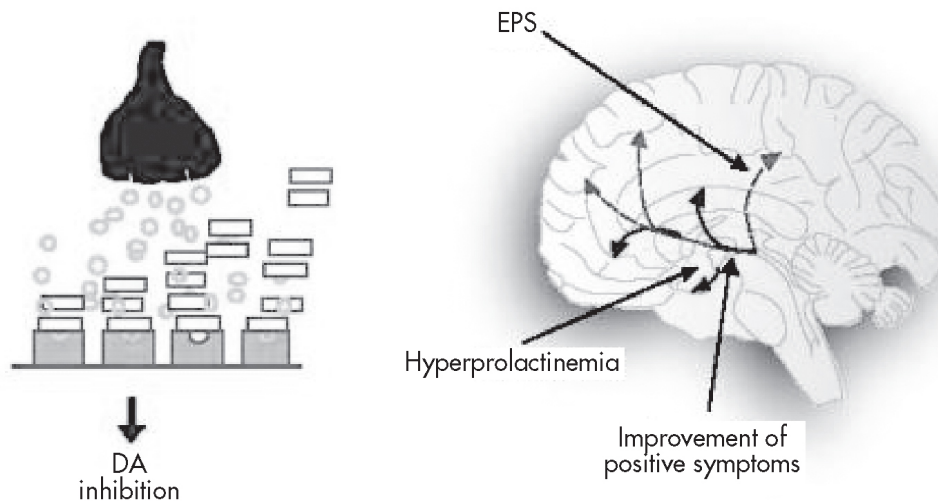
Although effective in alleviating psychotic symptoms and preventing their recurrence, the typical agents are ineffective in up to 40% of patients with schizophrenia, lack efficacy against the negative symptoms and cognitive deficits of schizophrenia, and are associated with a considerable burden of extrapyramidal side effects (EPS).

The atypical antipsychotics are partially effective against negative as well as positive symptoms and are associated with fewer EPS compared with the conventional antipsychotics. Nevertheless, individual atypical agents are associated with side effects such as weight gain and other metabolic abnormalities, hyperprolactinemia, QTc prolongation, and alterations in glucose and lipid levels ([Allison et al. 1999](#); [Glassman and Bigger 2001](#); [Koro et al. 2002a, 2002b](#); [McIntyre et al. 2001](#)).

The development of aripiprazole was guided by prevailing hypotheses of the etiology of schizophrenia. The dopamine hypothesis ([Seeman and Niznik 1990](#)) proposes that

abnormalities in dopaminergic neurotransmission in the brain cause the symptoms of schizophrenia and suggests that schizophrenia involves a biphasic disturbance in dopaminergic pathways (Davis et al. 1991; Pycock et al. 1980; Weinberger 1987). Underactivity of the mesocortical dopaminergic pathway leads to hypodopaminergic activity in the frontal cortex, whereas overactivity in the mesolimbic pathway causes increased dopaminergic neurotransmission. The latter is presumed to cause positive or psychotic symptoms, while the former is believed to underlie negative symptoms and cognitive impairment. Another influential hypothesis suggests that the activity of dopaminergic pathways is modulated by serotonergic neurons. In the striatum, serotonin (5-hydroxytryptamine; 5-HT) release inhibits dopamine, while in the frontal cortex it has a modulatory effect on pyramidal neurons and can affect glutamate release.

Most typical and atypical antipsychotic agents behave as full D<sub>2</sub> receptor antagonists. Their actions in the mesolimbic pathway would therefore be expected to benefit patients with schizophrenia by reducing positive symptoms. D<sub>2</sub> receptor antagonism in the other dopaminergic pathways, however, would be expected to cause unwanted side effects, including exacerbation of negative symptoms (mesocortical pathways), EPS and tardive dyskinesia (nigrostriatal tract), and hyperprolactinemia (tuberoinfundibular pathway) (Figure 29-1).

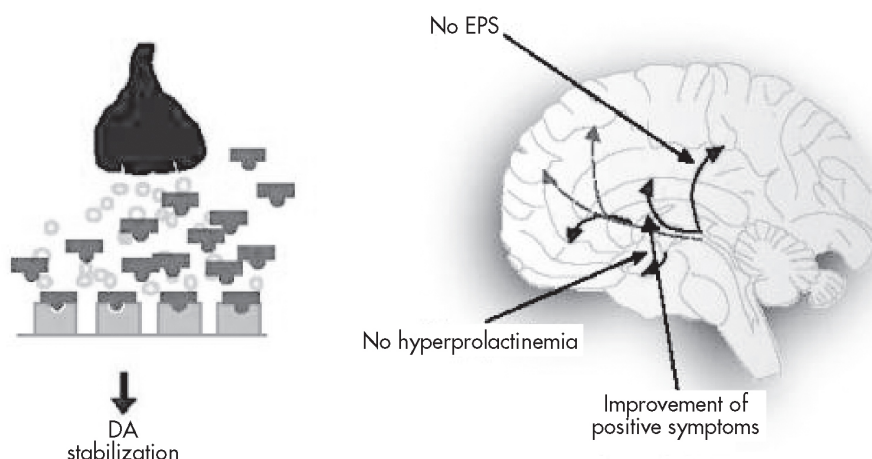


**FIGURE 29-1.** Conventional dopamine (DA) antagonist activity: effect on positive symptoms, extrapyramidal side effects (EPS), and prolactin levels.

The serotonin hypothesis may explain why the atypical agents, which have antagonist activity at 5-HT<sub>2A</sub> receptors, are associated with fewer EPS and do not exacerbate (and, in fact, partially alleviate) negative symptoms and cognitive impairment (Leysen et al. 1993; Millan 2000; Rao and Möller 1994; Richelson 1999).

On the basis of aripiprazole's pharmacodynamic profile—partial agonist activity (rather than full antagonist activity) at both dopaminergic (D<sub>2</sub>; Burris et al. 2002) and serotonergic (5-HT<sub>1A</sub>; Jordan et al. 2002) receptors, and full antagonist activity at 5-HT<sub>2A</sub> receptors (McQuade et al. 2002)—it was anticipated that aripiprazole treatment would be associated with a reduced burden of unwanted D<sub>2</sub> antagonist activity in the mesocortical, nigrostriatal, and tuberoinfundibular pathways—the activity associated with

some of the side effects of typical and atypical antipsychotic agents ([Figure 29-2](#)).



---

**FIGURE 29-2.** Dopamine (DA) partial agonist activity: effect on positive symptoms, extrapyramidal side effects (EPS), and prolactin levels.

Brexpiprazole's reduced intrinsic activity at  $D_2$  receptors and stronger antagonism at  $5-HT_{2A}$  receptors relative to aripiprazole suggest a lower potential to induce  $D_2$  partial agonist-mediated effects (i.e., akathisia, insomnia, nausea, and restlessness) and  $D_2$  antagonist effects (i.e., dystonias, tardive dyskinesia, and hyperprolactinemia) ([Fleischhacker 2005](#); [Maeda et al. 2014a](#)).

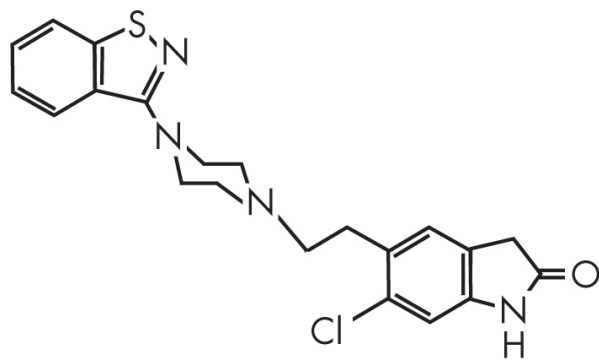
---

## Structure-Activity Relations and Pharmacological Profile

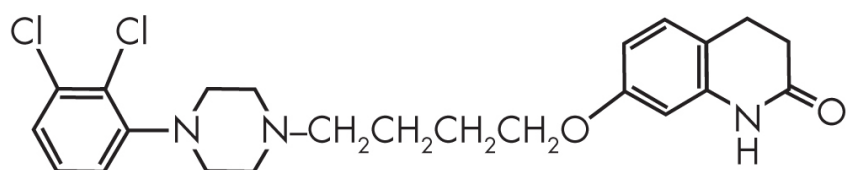
---

# Aripiprazole

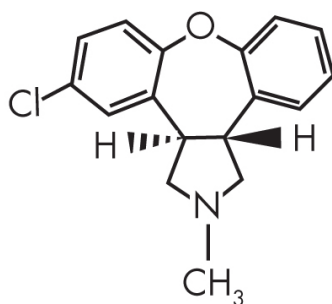
Aripiprazole—7-{ 4-(4-[2,3-dichlorophenyl]-1-piperazinyl)butoxy} -3,4-dihydrocarbostyryl, a dihydroquinolinone ([Figure 29-3](#))—exhibits potent partial agonist activity at D<sub>2</sub> ([Burris et al. 2002](#)) and 5-HT<sub>1A</sub> ([Jordan et al. 2002](#)) receptors, together with potent antagonist activity at 5-HT<sub>2A</sub> receptors. It also has high affinity for D<sub>3</sub> receptors; moderate affinity for dopamine<sub>4</sub> (D<sub>4</sub>), serotonin<sub>2C</sub> (5-HT<sub>2C</sub>), serotonin<sub>7</sub> (5-HT<sub>7</sub>), α<sub>1</sub>-adrenergic, and histamine<sub>1</sub> (H<sub>1</sub>) receptors and the serotonin transporter (SERT); and negligible affinity for cholinergic muscarinic receptors ([Table 29-1](#)). The active metabolite of aripiprazole, dehydroaripiprazole, exhibits a similar affinity at D<sub>2</sub> receptors and has not been shown to have a pharmacological profile that is clinically significantly different from that of the parent compound.



Ziprasidone



Aripiprazole



Asenapine

**FIGURE 29-3.** Chemical structure of aripiprazole.

**TABLE 29-1. Receptor-binding profile of aripiprazole**

Receptor type	K <sub>i</sub> (nM)
---------------	---------------------

Dopaminergic	
--------------	--



Receptor type	K <sub>i</sub> (nM)
D <sub>1</sub>	265
D <sub>2</sub> <sup>a</sup>	0.34
D <sub>3</sub>	0.8
D <sub>4</sub>	44
D <sub>5</sub>	95
<b>Serotonergic</b>	
5-HT <sub>1A</sub> <sup>b</sup>	1.7
5-HT <sub>2A</sub>	3.4
5-HT <sub>2C</sub>	15
5-HT <sub>6</sub>	214
5-HT <sub>7</sub>	39
SERT	98
<b>Histaminic</b>	
H <sub>1</sub>	61
<b>Adrenergic</b>	
α <sub>1</sub> <sup>c</sup>	57
<b>Muscarinic</b>	
M <sub>1</sub> <sup>c</sup>	IC <sub>50</sub> (nM) >1,000

**Receptor type****K<sub>i</sub> (nM)**

*Note.* SERT=serotonin transporter.

*Source.* Adapted from McQuade RD, Burris KD, Jordan S, et al.: “Aripiprazole: A Dopamine-Serotonin System Stabilizer.” *International Journal of Neuropsychopharmacology* 5 (Suppl 1):S176, 2002, with the following exceptions:

<sup>a</sup>Burris KD, Molski TF, Xu C, et al.: “Aripiprazole, A Novel Antipsychotic, Is a High Affinity Partial Agonist at Human Dopamine D<sub>2</sub> Receptors.” *Journal of Pharmacology and Experimental Therapeutics* 302:381–389, 2002.

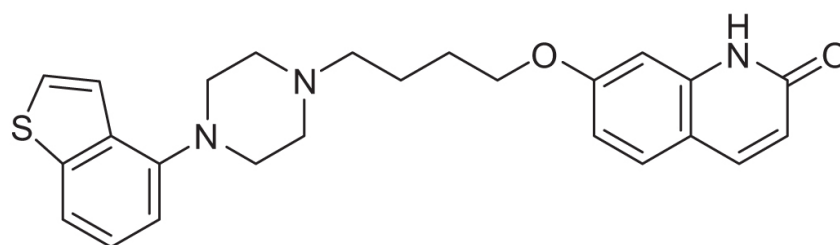
<sup>b</sup>Jordan S, Koprivica V, Chen R, et al.: “The Antipsychotic Aripiprazole Is a Potent, Partial Agonist at the Human 5-HT<sub>1A</sub> Receptor.” *European Journal of Pharmacology* 441:137–140, 2002.

<sup>c</sup>Abilify (Aripiprazole) Tablets: U.S. Full Prescribing Information. Tokyo, Japan, Otsuka Pharmaceutical Co., February 2012.

## Brexpiprazole

Brexpiprazole—7-{ 4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy} quinolin-2(1H)-one (Figure 29-4)—exhibits potent partial agonist properties at 5-HT<sub>1A</sub>, D<sub>2</sub>, and D<sub>3</sub> receptors. This is combined with potent antagonist activity at 5-HT<sub>2A</sub> receptors and α<sub>1B</sub>/α<sub>2C</sub> adrenoceptors. It also displays antagonistic properties at serotonin<sub>2B</sub> (5-HT<sub>2B</sub>) and serotonin<sub>7A</sub> (5-HT<sub>7A</sub>) receptors and moderate-potency antagonism at H<sub>1</sub> receptors. Brexpiprazole has negligible

affinity for cholinergic muscarinic receptors (Table 29-2) (Maeda et al. 2014a; Otsuka Pharmaceutical 2015).



**FIGURE 29-4.** Chemical structure of brexpiprazole.

**TABLE 29-2. Receptor-binding profile of brexpiprazole**

Receptor type	K <sub>i</sub> (nM)
<b>Dopaminergic</b>	
D <sub>2</sub>	0.30
D <sub>3</sub>	1.1
<b>Serotonergic</b>	
5-HT <sub>1A</sub>	0.12
5-HT <sub>2A</sub>	0.47
5-HT <sub>2B</sub>	1.9

*Source.* Adapted from Maeda K, Sugino H, Akazawa H, et al.: “Brexiprazole I: In Vitro and In Vivo Characterization of a Novel Serotonin-Dopamine Activity Modulator.” *J Pharmacol Exp Ther* 350:589–604, 2014, with the following exception:

<sup>a</sup>Rexulti (Brexiprazole) Tablets: U.S. Full Prescribing Information. Tokyo, Japan, Otsuka Pharmaceutical Co., August 2015.

Receptor type	K <sub>i</sub> (nM)
5-HT <sub>7</sub> <sup>a</sup>	3.7
<b>Histaminic</b>	
H <sub>1</sub>	19
<b>Adrenergic</b>	
α <sub>1A</sub> <sup>a</sup>	3.8
α <sub>1B</sub>	0.17
α <sub>1D</sub> <sup>a</sup>	2.6
α <sub>2C</sub>	0.59
<b>Muscarinic</b>	
M <sub>1</sub>	67% at 10 μM

*Source.* Adapted from Maeda K, Sugino H, Akazawa H, et al.: “Brexpiprazole I: In Vitro and In Vivo Characterization of a Novel Serotonin-Dopamine Activity Modulator.” *J Pharmacol Exp Ther* 350:589–604, 2014, with the following exception:

<sup>a</sup>Rexulti (Brexpiprazole) Tablets: U.S. Full Prescribing Information. Tokyo, Japan, Otsuka Pharmaceutical Co., August 2015.

---

## Pharmacokinetics and Disposition

---

### Aripiprazole

Aripiprazole is available for oral administration as tablets in strengths of 2, 5, 10, 15, 20, and 30 mg. The effective dosage range is 10–30 mg/day for schizophrenia patients and 15–30 mg/day for bipolar I disorder patients. For adjunctive treatment of major depressive disorder (MDD) and irritability associated with autism spectrum disorder, the recommended dosage range is 2–15 mg/day. For Tourette's disorder, body weight-based dosing of 2–10 mg/day for patients weighing less than 50 kg and 2–20 mg/day for patients weighing 50 kg or more is indicated. Aripiprazole is taken once daily with or without food and is well absorbed after oral administration, with peak plasma concentrations occurring within 3–5 hours. Absolute oral bioavailability is 87%. In plasma, aripiprazole and its major metabolite, dehydroaripiprazole, are both more than 99% bound to proteins, primarily albumin. Aripiprazole is extensively distributed outside the vascular system, and human studies demonstrating dose-dependent occupancy of D<sub>2</sub> receptors have confirmed that aripiprazole penetrates the brain. Elimination half-lives for aripiprazole and dehydroaripiprazole are 75 hours and 94 hours, respectively ([Otsuka Pharmaceutical 2016a](#)).

Of note, several aripiprazole formulations were withdrawn from the market by the manufacturer in 2015 for reasons unrelated to efficacy, safety, or tolerability. Discontinued formulations include the aripiprazole oral disintegrating tablet at 10-mg and 15-mg strengths, the oral solution, and the short-acting intramuscular injection.

In February 2013, the U.S. Food and Drug Administration (FDA) approved a long-acting injectable formulation of aripiprazole for the treatment of schizophrenia. The effective dosage range is 300–400 mg once monthly. It is recommended that oral aripiprazole supplementation (at

10–20 mg/day) or an alternative antipsychotic be continued for 2 weeks after the first administered injection of long-acting aripiprazole. The aripiprazole depot formulation consists of a lyophilized powder of unmodified aripiprazole. The depot formulation is reconstituted in water and injected into the gluteal muscle. The median peak plasma concentration is reached after 5–7 days. The mean terminal half-lives of the 300-mg and 400-mg doses are 29.9 and 46.5 days, respectively. Steady-state plasma concentration is attained after the fourth dose ([Otsuka Pharmaceutical 2016b](#)). The aripiprazole once-monthly dose of 400 mg with supplemental oral aripiprazole 10 mg/day for the first 2 weeks produces a pharmacokinetic profile consistent with multiple daily dosing of aripiprazole 10–30 mg, with a maximum plasma concentration comparable to the 30 mg/day dosage and a minimum plasma concentration comparable to the 10 mg/day dosage ([Mallikaarjun et al. 2013](#)).

In October 2015, the FDA approved aripiprazole lauroxil, a second long-acting injectable formulation of aripiprazole, for the treatment of schizophrenia. The effective dosages (441 mg, 662 mg, and 882 mg once monthly) correlate with oral aripiprazole dosages of 10 mg, 20 mg, and 30 mg/day, respectively. Aripiprazole lauroxil 882 mg may be administered at a dosing interval up to 6 weeks. The recommended period of oral aripiprazole supplementation is 3 weeks after the first administered injection.

Aripiprazole lauroxil, a prodrug of aripiprazole, initially undergoes enzyme-mediated hydrolysis to *N*-hydroxymethyl aripiprazole and then undergoes water-mediated hydrolysis to aripiprazole, the active form. After a single intramuscular injection, aripiprazole appears in systemic circulation within 5–6 days. Aripiprazole reaches steady state after

four consecutive monthly injections. Mean terminal half-life ranges from 29.2 to 34.9 days ([Alkermes 2015](#)).

Aripiprazole is metabolized primarily in the liver. Two hepatic cytochrome P450 (CYP) enzymes, 2D6 and 3A4, catalyze its dehydrogenation to dehydroaripiprazole. Therefore, coadministration of aripiprazole with inducers or inhibitors of these CYP enzymes may require dosage adjustment. The active metabolite accounts for 40% of drug exposure, but the predominant circulating moiety is the parent drug. Aripiprazole does not undergo direct glucuronidation and is not a substrate for the following CYP enzymes: 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2E1. Interactions with inhibitors or inducers of these enzymes, or with chemicals related to cigarette smoke, are therefore unlikely to occur.

## Brexpiprazole

Brexpiprazole is available for oral administration as tablets in strengths of 0.25, 0.5, 1, 2, and 3 mg. The effective dosage range is 2–4 mg/day for treatment of schizophrenia and 1–3 mg/day for adjunctive treatment of MDD. Brexpiprazole is taken once daily with or without food and is well absorbed after oral administration, with peak plasma concentrations occurring within 4 hours. Absolute oral bioavailability is 95%. Brexpiprazole is highly bound to serum albumin and  $\alpha_1$ -acid glycoprotein (>99%). Elimination half-lives for brexpiprazole and DM-3411, its major metabolite, are 91 hours and 86 hours, respectively ([Otsuka Pharmaceutical 2015](#)).

Brexpiprazole is metabolized primarily through the liver by CYP enzymes 2D6 and 3A4. Therefore, coadministration

of brexpiprazole with inducers or inhibitors of these CYP enzymes may require dosage adjustment. At steady state (which is reached in 10–12 days), the inactive metabolite DM-3411 represents 23%–48% of brexpiprazole AUC (area under the time–concentration curve) in plasma ([Otsuka Pharmaceutical 2015](#)).

---

## Mechanism of Action

---

Aripiprazole and brexpiprazole both have partial agonist activity at D<sub>2</sub> receptors. The activity of aripiprazole and brexpiprazole at D<sub>2</sub> receptors has been studied in animal models of schizophrenia ([Kikuchi et al. 1995](#); [Maeda et al. 2014b](#)). In the intact rat with repetitive stereotyped behavior (stereotypy) induced by apomorphine, aripiprazole and brexpiprazole inhibit stereotypy and locomotion ([Kikuchi et al. 1995](#); [Maeda et al. 2014a](#)). These agents may therefore be expected to inhibit hyperdopaminergic activity in the mesolimbic pathway of patients with schizophrenia, thereby (like other available agents) exerting antipsychotic action against the positive symptoms of schizophrenia. On the other hand, in animal models of hypodopaminergic activity, such as the reserpinized rat, aripiprazole and brexpiprazole have D<sub>2</sub> receptor agonist activity ([Maeda et al. 2014b](#)). Because aripiprazole and brexpiprazole may exert either D<sub>2</sub> antagonist activity under hyperdopaminergic conditions or D<sub>2</sub> agonist activity under hypodopaminergic conditions, they may be less likely than other antipsychotics to cause excessive D<sub>2</sub> receptor antagonism. In preclinical studies, brexpiprazole showed lower intrinsic activity at D<sub>2</sub>



receptors, which suggests a reduced propensity to cause D<sub>2</sub> agonist-associated side effects such as nausea, insomnia, and akathisia ([Maeda et al. 2014a, 2014b](#)). It is possible that this lower activity may diminish the effects of excess D<sub>2</sub> receptor antagonism, including EPS. No comparative clinical trials of aripiprazole and brexpiprazole have yet been conducted.

Both aripiprazole and brexpiprazole may offer further therapeutic benefits through modulation of central serotonergic pathways. Preclinical studies showed that aripiprazole and brexpiprazole have antagonist activity at 5-HT<sub>2A</sub> receptors ([Maeda et al. 2014b; McQuade et al. 2002](#)), a characteristic that has been associated with reductions in EPS ([Meltzer 1999](#)) and in negative symptoms. In vitro studies also have shown that both aripiprazole and brexpiprazole have partial agonist activity at 5-HT<sub>1A</sub> receptors ([Jordan et al. 2002; Maeda et al. 2014b](#)), a feature that has been associated with improvement in negative, cognitive, depressive, and anxiety symptoms ([Millan 2000](#)).

The side effects of nausea/vomiting may be explained by the dopamine agonist effects of aripiprazole and brexpiprazole, whereas orthostatic hypotension and mild sedation/weight gain are likely related to these agents' antagonist activity at  $\alpha_1$ -adrenergic and H<sub>1</sub> receptors, respectively.

Aripiprazole lauroxil is a prodrug of aripiprazole. It initially undergoes enzyme-mediated hydrolysis to *N*-hydroxymethyl aripiprazole and then undergoes water-mediated hydrolysis to aripiprazole, the active form ([Alkermes 2015](#)).

---

# Indications and Efficacy

---

## Aripiprazole

In the United States, aripiprazole is approved by the FDA for the following indications: treatment of schizophrenia in adults and in adolescents ages 13–17 years; acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in adults and pediatric patients ages 10–17 years; maintenance treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in adults; use as an adjunct to antidepressant treatment in adults with MDD who have had an inadequate response to antidepressant therapy; treatment of irritability associated with autism spectrum disorder in pediatric patients ages 6–17 years; and treatment of Tourette’s disorder in pediatric patients ages 6–18 years. Additionally, intramuscular aripiprazole injection is approved for the acute treatment of agitation associated with schizophrenia or bipolar disorder (manic or mixed) in adults, and currently is available in two formulations for long-acting injectable depot maintenance and relapse management of schizophrenia in adults. The previously available formulations Abilify Discmelt orally disintegrating tablet (10 mg and 15 mg), Abilify oral solution (1 mg/mL), and Abilify short-acting intramuscular injection (9.75 mg/1.3 mL) were voluntarily withdrawn from the U.S. market in 2015.

## Schizophrenia

The efficacy of aripiprazole in the treatment of an acute symptom relapse in schizophrenia was demonstrated in four short-term (4-week) double-blind, placebo-controlled studies. Among these was a pivotal Phase III parallel-group multicenter study with four treatment arms comparing aripiprazole (15 or 30 mg/day) with placebo ([Kane et al. 2002](#)). Aripiprazole at either dosage produced statistically significant improvements from baseline on standard psychometric scales by week 2. This trial suggested that at daily dosages of 15 mg and 30 mg, aripiprazole provides effective symptom control in patients experiencing an acute exacerbation of schizophrenia symptoms.

In another short-term multicenter Phase III study involving acute symptom relapse in schizophrenia or schizoaffective disorder ([Potkin et al. 2003](#)), patients were randomly assigned to receive aripiprazole 20 mg/day, aripiprazole 30 mg/day, risperidone 6 mg/day, or placebo for 4 weeks. Compared with placebo, aripiprazole (at both dosages) and risperidone produced statistically significant improvements in scores on standard scales designed to measure antipsychotic efficacy.

The antipsychotic efficacy of aripiprazole in acute symptom relapse in schizophrenia was also demonstrated in two Phase II dose-ranging studies. Patients were randomly assigned to receive aripiprazole 2 mg, 10 mg, or 30 mg/day or haloperidol 10 mg/day ([Daniel et al. 2000](#)). All three dosages of aripiprazole produced improvements from baseline on efficacy measures, and the 30-mg/day dosage produced statistically significant improvement compared with placebo on all illness scores. Similarly, in a Phase II dosage titration study, aripiprazole 5–30 mg/day was superior to placebo in improving Brief Psychiatric Rating Scale (BPRS) Total, BPRS Core, Clinical Global Impression–

Severity (CGI-S), and Positive and Negative Syndrome Scale (PANSS)-Total scores ([Petrie et al. 1997](#)).

Results from the three 4-week fixed-dosage studies discussed above were pooled for analysis with those from an additional 6-week placebo-controlled, fixed-dosage study of aripiprazole at 10 mg, 15 mg, or 20 mg/day ([Lieberman et al. 2002](#)). The pooled analysis, involving 898 patients randomly assigned to receive aripiprazole, showed that at all investigated dosages greater than 2 mg/day, aripiprazole exhibited antipsychotic efficacy superior to that of placebo. Onset of effect was rapid, with improvement on psychometric scores detectable within 1 week of starting treatment. These pooled efficacy results demonstrate that dosages of 10–30 mg/day represent an effective therapeutic range for aripiprazole treatment.

Two long-term double-blind, randomized controlled multicenter trials yielded further confirmation of aripiprazole's efficacy. A 26-week placebo-controlled study in patients with chronic stable schizophrenia investigated the efficacy of aripiprazole 15 mg/day in relapse prevention ([Pigott et al. 2003](#)). Aripiprazole treatment significantly increased the time to relapse and resulted in significantly fewer relapses at endpoint compared with placebo (34% vs. 57%). From week 6 of therapy, PANSS-Total and PANSS-Positive subscale scores were significantly more improved with aripiprazole than with placebo.

In a 52-week study ([Kasper et al. 2003](#)), patients with schizophrenia who were experiencing an acute symptom relapse were randomly assigned to receive aripiprazole 30 mg/day or haloperidol 10 mg/day. Significantly more aripiprazole-treated patients than haloperidol-treated patients were still taking the medication and responding to treatment at weeks 8, 26, and 52. Both treatments

produced sustained improvements from baseline on PANSS-Total and PANSS-Positive subscale scores. However, aripiprazole produced significantly greater improvements in negative and depressive symptoms at weeks 26 and 52 and was associated with significantly lower scores on all EPS assessments compared with haloperidol.

The efficacy of aripiprazole monotherapy in antipsychotic-resistant schizophrenia was evaluated in a 6-week double-blind, randomized trial in patients whose symptoms had not improved during a prospective 4- to 6-week open trial with either olanzapine or risperidone ([Kane et al. 2007](#)). Subjects were randomly assigned to receive aripiprazole (15–30 mg/day) or perphenazine (8–64 mg/day). After 6 weeks, there was no statistical difference between the two groups on efficacy measures. However, compared with aripiprazole, perphenazine was associated with higher rates of EPS and serum prolactin elevations.

The efficacy of aripiprazole in the treatment of schizophrenia in pediatric patients (ages 13–17 years) was evaluated in a 6-week placebo-controlled outpatient trial comparing two fixed daily dosages of aripiprazole (10 mg or 30 mg) with placebo ([Findling et al. 2008](#)). Both aripiprazole dosages demonstrated statistically significant differences from placebo in reductions in PANSS-Total score; the 30-mg/day dosage was not shown to be more efficacious than the 10-mg/day dosage. Adverse events occurring in more than 5% of either aripiprazole group and with a combined incidence at least twice the rate for placebo were EPS, somnolence, and tremor. Mean body weight changes were –0.8, 0.0, and +0.2 kg for placebo, aripiprazole 10 mg/day, and aripiprazole 30 mg/day, respectively.

Two studies have investigated the efficacy of aripiprazole long-acting depot injection in the prevention of relapse in schizophrenia. In the first investigation, a 52-week randomized, placebo-controlled, long-term multicenter maintenance study, subjects requiring chronic treatment with an antipsychotic entered an oral aripiprazole stabilization phase followed by an intramuscular depot conversion and stabilization phase. Those patients meeting stabilization criteria for 12 consecutive weeks were then randomly assigned to receive aripiprazole 400-mg long-acting depot or placebo depot for the 52-week double-blind maintenance phase of the study. The primary outcome measure was time to relapse, defined as meeting any or all of the following criteria at any time during the maintenance phase: 1) clinical worsening (defined as Clinical Global Impression-Improvement [CGI-I] score  $\geq 5$  plus increase in any core PANSS items), 2) hospitalization, 3) risk of suicide, or 4) violent behavior. The aripiprazole group showed a significantly lower rate of relapse compared with the placebo group (9.6% vs. 36.8%, respectively) ([Kane et al. 2012](#)). The second investigation was a 38-week double-blind noninferiority study that compared relapse rates for aripiprazole once-monthly 400-mg depot injection, oral aripiprazole (10–30 mg/day), and aripiprazole once-monthly 50-mg depot injection, using criteria similar to those used in the Kane et al. study discussed above. There was no significant difference in rate of relapse with the once-monthly 400-mg depot formulation (7.12%) versus the oral formulation (10–30 mg/day), and both were significantly superior to the 50-mg depot formulation (21.8%;  $P < 0.0001$ ) ([Fleischhacker et al. 2014](#)).

One 12-week randomized, double-blind, placebo-controlled Phase III multicenter trial evaluated the efficacy

of aripiprazole once-monthly injection for the management of acute exacerbations in chronic schizophrenia. Patients were randomly assigned to either the aripiprazole once-monthly 400-mg group with concomitant oral aripiprazole (mean daily dosage=12.8 mg) for 2 weeks ( $n=168$ ) or the placebo group ( $n=172$ ). The aripiprazole group showed sustained improvements in PANSS-Total scores, PANSS-Positive and -Negative subscale scores, and CGI-I scores, with improvements apparent within the first week of administration ([Kane et al. 2014](#)).

An open-label mirror-image multicenter study in a naturalistic community setting ([Kane et al. 2013](#)) compared total psychiatric hospitalization rates in 183 patients (18–65 years) who had previously been treated with oral antipsychotics (retrospective phase) and who were then switched to the aripiprazole once-monthly depot formulation for 6 months (prospective phase). The rate of hospitalization for the 6-month prospective phase (14.2%) was found to be lower than the rate for the 6-month retrospective oral antipsychotic period (41.5%;  $P<0.0001$ ). Additionally, the all-cause discontinuation rate for the prospective phase was high (44.8%), with 26 patients discontinuing because of adverse events including “psychiatric disorders” (e.g., worsening of psychoses, increased paranoia, agitation, anxiety, decreased self-care; 20 patients) and “nervous-system disorders” (akathisia; 2 patients). For all patients receiving at least one dose of aripiprazole once monthly ( $n=181$ ), the most common treatment-emergent adverse events (occurring in  $\geq 5\%$  of patients) were psychotic disorder (7.7%), akathisia (7.2%), and insomnia (7.2%) ([Kane et al. 2013](#)).

[Meltzer et al. \(2015\)](#) conducted a 12-week double-blind, placebo-controlled multicenter study comparing once-

monthly administration of aripiprazole lauroxil 441 mg or 882 mg versus placebo for 12 weeks. Statistically significant improvement was observed on the PANSS-Total score from baseline to day 85 in both medication groups, with placebo-adjusted differences of  $-10.9$  ( $P < 0.001$ ) and  $-11.9$  ( $P < 0.001$ ) for aripiprazole lauroxil 441 mg and 882 mg, respectively.

## **Bipolar Disorder**

The efficacy of aripiprazole in the treatment of acute manic episodes was established in two 3-week placebo-controlled trials in hospitalized patients whose symptoms met DSM-IV ([American Psychiatric Association 1994](#)) criteria for bipolar I disorder with manic or mixed episodes ([Keck et al. 2003](#); [Sachs et al. 2006](#)). Aripiprazole was superior to placebo in reducing the Young Mania Rating Scale (YMRS) Total score and the Clinical Global Impression-Bipolar (CGI-BP) Severity of Illness score. In a third large randomized, double-blind trial ([Vieta et al. 2005](#)), aripiprazole was compared with haloperidol in the treatment of acute bipolar mania over a 12-week period. Significantly more patients remained in treatment and were classified as responders ( $>50\%$  reduction in YMRS score from baseline) at week 12 in the aripiprazole group (49.7%) than in the haloperidol group (28.4%). EPS adverse events were more frequent with haloperidol than with aripiprazole (62.7% vs. 24.0%).

The efficacy of adjunctive aripiprazole with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week placebo-controlled study with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for bipolar I disorder ([Vieta et al. 2008](#)). Adjunctive aripiprazole starting at 15 mg/day with concomitant lithium or valproate



(in a therapeutic range of 0.6–1.0 mEq/L or 50–125 µg/mL, respectively) was found to be superior to lithium or valproate with adjunctive placebo on the basis of reductions in YMRS Total scores and CGI-BP Severity of Illness scores.

Aripiprazole monotherapy was evaluated in the treatment of nonpsychotic depressive episodes associated with bipolar I disorder. The results of two identically designed 8-week randomized, double-blind, placebo-controlled multicenter studies were reported by [Thase et al. \(2008\)](#). The primary outcome measure was mean change from baseline to week 8 (last observation carried forward [LOCF]) in the Montgomery-Åsberg Depression Rating Scale (MADRS) Total score. Although statistically significant differences were observed during weeks 1–6, there were no statistically significant differences in change in MADRS Total score between aripiprazole and placebo at week 8 in either study.

To evaluate the long-term effectiveness of aripiprazole in delaying relapse in bipolar I disorder, a trial was conducted in patients whose symptoms met DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode ([Keck et al. 2006](#)). Patients whose condition had been stabilized while taking open-label aripiprazole and who had maintained a clinical response for at least 6 weeks were randomly assigned to receive aripiprazole or placebo for the 26-week, double-blind phase. Aripiprazole-treated patients had significantly fewer relapses than placebo-treated patients (25% vs. 43%). Aripiprazole was superior to placebo in delaying the time to manic relapse but did not differ from placebo in delaying time to depressive relapse. Significant weight gain ( $\geq 7\%$  increase from baseline) was seen in 13% of the aripiprazole patients and none of the placebo patients.

The efficacy of aripiprazole in the treatment of bipolar I disorder in pediatric patients (ages 10–17 years) was evaluated in two studies. The first study was a 4-week double-blind, placebo-controlled trial of outpatients whose symptoms met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features. The trial compared two fixed daily dosages of aripiprazole (10 mg or 30 mg). Both dosages of aripiprazole were superior to placebo as measured by change from baseline to week 4 on the YMRS Total score ([Otsuka Pharmaceutical 2016a](#)). The second study was a 30-week randomized, placebo-controlled study comparing fixed daily dosages of aripiprazole (10 mg and 30 mg) with placebo in the treatment of adolescent bipolar disorder ([Findling et al. 2013](#)). Two hundred ten youths (ages 10–17 years) with bipolar I disorder (manic or mixed) with or without psychotic features were randomly assigned to receive oral aripiprazole 10 mg/day, oral aripiprazole 30 mg/day, or placebo. Both dosages of aripiprazole were superior to placebo; at week 30, aripiprazole-treated patients demonstrated significantly greater improvement on YMRS Total scores compared with placebo-treated patients.

## **Acute Agitation**

The efficacy of the injectable formulation of aripiprazole in controlling acute agitation was evaluated in three short-term (24-hour) randomized, double-blind, placebo-controlled studies in patients with schizophrenia ([Andrezina et al. 2006](#); [Tran-Johnson et al. 2007](#)) and patients with bipolar disorder (manic or mixed) ([Zimbroff et al. 2007](#)). Aripiprazole injection was statistically superior to placebo ( $P<0.05$ ) in all three studies, as measured by PANSS-Excited Component (PANSS-EC) scores. In the two studies

in agitated patients with schizophrenia, injectable aripiprazole and intramuscular haloperidol were both superior to placebo. In the study in agitated patients with bipolar I disorder, aripiprazole injection and lorazepam injection were both superior to placebo.

## **Adjunctive Treatment of Major Depressive Disorder**

The efficacy of aripiprazole in the adjunctive treatment of MDD was demonstrated in three short-term (6-week) placebo-controlled trials ([Berman et al. 2007, 2009](#); [Marcus et al. 2008](#)). During prospective antidepressant treatment, patients received one of several antidepressants (escitalopram, fluoxetine, paroxetine controlled release, sertraline, or venlafaxine extended release), each with single-blind adjunctive placebo. Patients with incomplete response continued taking the antidepressant and were randomly assigned to receive double-blind adjunctive placebo or adjunctive aripiprazole (2–15 mg/day with the potent CYP2D6 inhibitor fluoxetine or paroxetine; 2–20 mg/day with all other antidepressants). In all three trials, the mean change in MADRS Total score was significantly greater with adjunctive aripiprazole than with adjunctive placebo. Akathisia and restlessness were significantly more frequent with adjunctive aripiprazole than with adjunctive placebo.

[Fava et al. \(2012\)](#) evaluated the efficacy of low-dosage aripiprazole added to antidepressant therapy in patients with MDD who had experienced an inadequate response to prior antidepressant treatment. Two hundred twenty-five patients were randomly assigned to receive adjunctive treatment with aripiprazole 2 mg/day or placebo. The

pooled, weighted response difference between aripiprazole 2 mg/day and placebo was 5.6% ( $P=0.18$ ; not significant [NS]); the difference on the MADRS was  $-1.51$  ( $P=0.065$ ; NS). Of note, there was no difference in rates of akathisia with low-dosage aripiprazole compared with placebo. Thus, a reasonable initial therapeutic approach may be to try a low-dosage (2 mg/day) augmentation of aripiprazole, in view of its better tolerability, and to increase the dosage to 5 mg/day, and if necessary to 10 or 15 mg/day, in the face of continued nonresponse, given that the efficacy of the higher dosage range was supported by robust evidence in three previous positive studies ([Fava et al. 2012](#)).

## **Irritability in Autism Spectrum Disorder**

The efficacy of aripiprazole in the treatment of irritability associated with DSM-IV autistic disorder was established in two 8-week placebo-controlled trials in children and adolescents (ages 6–17 years). Efficacy was evaluated with two assessment scales: the Aberrant Behavior Checklist (ABC) and the CGI-I scale. In the first trial ([Owen et al. 2009](#)), pediatric patients with DSM-IV autistic disorder received aripiprazole (2–15 mg/day, based on clinical response) or placebo. Patients who received aripiprazole (at a mean daily dosage of 8.6 mg at the end of the 8-week treatment) demonstrated significantly improved scores on the ABC-Irritability (ABC-I) subscale and on the CGI-I scale compared with patients who received placebo. In the other trial ([Marcus et al. 2009](#)), three fixed dosages of aripiprazole (5, 10, or 15 mg/day) were compared with placebo. All three dosages of aripiprazole were associated with significantly improved scores on the ABC-I subscale compared with placebo.

The efficacy and safety of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with DSM-IV autistic disorder were evaluated in a double-blind, randomized, placebo-controlled multicenter study in patients ages 6–17 years. After an initial phase in which single-blind aripiprazole was flexibly dosed (2–15 mg/day; average dosage of 9.0 mg/day) for 13–26 weeks to establish a stable response (defined as a  $\geq 25\%$  decrease on the ABC-I subscale and a rating of “much improved” or “very much improved” on the CGI-I scale), patients were randomly assigned to receive either aripiprazole ( $n=41$ , 2–15 mg/day) or placebo ( $n=44$ ) for 16 weeks or until relapse. The primary outcome measure was time from randomization to relapse. No statistically significant differences in time to relapse were seen between the drug and the placebo group ( $P=0.97$ , hazard ratio=0.57, number needed to treat=6) ([Findling et al. 2014](#)).

## **Tourette’s Disorder**

The efficacy of aripiprazole in children and adolescents with Tourette’s disorder was established in two short-term trials. In the first study, a double-blind, randomized, placebo-controlled, flexible-dose multicenter trial, patients with Tourette’s disorder ( $n=61$ ) ages 6–18 years were randomly assigned to receive either placebo or aripiprazole (2–20 mg/day) for 10 weeks. Aripiprazole-treated patients demonstrated significant reductions on Yale Global Tic Severity Scale scores compared with patients receiving placebo ( $-15.0$  [8.4] and  $-9.6$  [8.8], respectively;  $P=0.0196$ ) ([Yoo et al. 2013](#)). The mean change in phonic tic scores favored the aripiprazole group, but there was no difference in motor tic scores. Treatment-emergent adverse events were not statistically significantly different. The

mean dosage range was 11.0 mg/day ([Yoo et al. 2013](#)). In the second study, a Phase III randomized, double-blind, placebo-controlled multicenter trial in patients with a diagnosis of Tourette's disorder (ages 7–17 years), patients first underwent a 3- to 42-day washout period ([Sallee et al. 2014](#)). A total of 133 patients were then randomly assigned to receive low-dosage aripiprazole (5 mg/day if < 50 kg, 10 mg/day if ≥50 kg), high-dosage aripiprazole (10 mg/day if <50 kg, 20 mg/day if ≥50 kg), or placebo for 8 weeks. Both the low-dosage and high-dosage aripiprazole groups showed significant improvement in Yale Global Tic Severity Scale and CGI-Tourette's Syndrome Scale scores compared with the placebo group ([Sallee et al. 2014](#)).

## Off-Label Use

[De Deyn et al. \(2005\)](#) compared the efficacy, safety, and tolerability of aripiprazole versus placebo in patients with psychosis associated with Alzheimer's disease in a 10-week double-blind multicenter study. The initial aripiprazole dosage of 2 mg/day was titrated upward (to 5, 10, or 15 mg/day) according to efficacy and tolerability, and evaluations included the Neuropsychiatric Inventory (NPI) Psychosis subscale and the BPRS. Aripiprazole-treated patients showed significantly greater improvements from baseline in BPRS-Psychosis subscale and BPRS-Core subscale scores at endpoint compared with patients receiving placebo.

In another double-blind multicenter study ([Mintzer et al. 2007](#)), patients with psychosis associated with Alzheimer's disease were randomly assigned to receive either placebo or aripiprazole 2, 5, or 10 mg/day. The primary efficacy measure was mean change from baseline to week 10 on the Neuropsychiatric Inventory-Nursing Home (NPI-NH)

Psychosis subscale score. Aripiprazole 10 mg/day showed significantly greater improvements than placebo on all efficacy measures (NPI-NH Psychosis subscale, CGI-S, BPRS Total and Core, and Cohen-Mansfield Agitation Inventory [CMAI] scores). Aripiprazole 5 mg/day showed significant improvements versus placebo on BPRS and CMAI scores. Aripiprazole 2 mg/day was not efficacious. No antipsychotic is currently approved in the United States for treating the behavioral and psychotic symptoms that frequently accompany dementia, and all carry a bolded warning based on increased mortality observed in patients with dementia-related psychosis treated with these agents.

[Nickel et al. \(2006\)](#) conducted a double-blind, placebo-controlled study in individuals whose clinical presentation met DSM-III-R ([American Psychiatric Association 1987](#)) criteria for borderline personality disorder. Subjects were randomly assigned in a 1:1 ratio to receive either aripiprazole (15 mg/day) or placebo for 8 weeks. At endpoint, significant changes in scores on most scales of the Symptom Checklist-90—Revised (SCL-90-R), on the Hamilton Rating Scale for Depression (Ham-D), on the Hamilton Anxiety Scale (Ham-A), and on all subscales of the State-Trait Anger Expression Inventory were observed in subjects who received aripiprazole. The improvements observed at 8 weeks were maintained at 18-month follow-up ([Nickel et al. 2007](#)).

[Tiihonen et al. \(2007\)](#) conducted a study in which individuals whose symptoms met DSM-IV criteria for intravenous amphetamine dependence were randomly assigned to receive aripiprazole (15 mg/day), slow-release methylphenidate (54 mg/day), or placebo for 20 weeks. The study was terminated prematurely because of unexpected results in the interim analysis. Contrary to the hypothesized



result, patients who received aripiprazole treatment had significantly more amphetamine-positive urine samples than did patients in the placebo group, and patients who received methylphenidate had significantly fewer amphetamine-positive urine samples than patients who received placebo. Studies in subjects with cocaine use disorder are ongoing.

In a 12-week double-blind, placebo-controlled multicenter trial ([Anton et al. 2008](#)) evaluating the efficacy of aripiprazole in patients with DSM-IV alcohol dependence, aripiprazole did not differ from placebo on the study's primary efficacy measure, mean percentage of days abstinent.

## Brexpiprazole

Brexpiprazole is currently approved in the United States for schizophrenia and for use as an adjunct to antidepressant treatment in adults with MDD who have had an inadequate response to antidepressant therapy ([Otsuka Pharmaceutical 2015](#)).

### Schizophrenia

The efficacy of brexpiprazole in the treatment of acute symptom exacerbations in schizophrenia has been evaluated in two 6-week double-blind, placebo-controlled multicenter studies. In the first study, a Phase III multicenter trial (BEACON study), patients with acute schizophrenia were randomly assigned to receive aripiprazole (1 mg, 2 mg, or 4 mg/day) or placebo. Brexpiprazole 4 mg/day produced statistically significant reductions (treatment difference  $-6.47$ ;  $P=0.0022$ ) versus



placebo on the PANSS-Total score. Brexpiprazole dosages of 1 mg/day and 2 mg/day also produced numerical improvements versus placebo, although the degree of improvement was not statistically significant ( $P>0.05$ ) ([Kane et al. 2015](#)).

In another 6-week multicenter double-blind, placebo-controlled Phase III trial (VECTOR study), patients experiencing an acute schizophrenia relapse were randomly assigned to receive aripiprazole (0.25 mg, 2 mg, or 4 mg/day) or placebo. At 6 weeks, both the 2-mg/day and the 4-mg/day dosages of brexpiprazole had produced statistically significantly greater reductions on PANSS-Total scores compared with placebo (treatment difference  $-8.72$  [ $P<0.0001$ ] and  $-7.64$  [ $P=0.0006$ ] for 2 mg/day and 4 mg/day, respectively) ([Correll et al. 2015](#)).

## **Adjunctive Treatment of Major Depressive Disorder**

The efficacy of brexpiprazole in the adjunctive treatment of MDD has been demonstrated in two short-term randomized, double-blind Phase III studies. In the first study ([Thase et al. 2015b](#)), patients who had not responded to three prior trials with antidepressants entered an 8-week prospective period of open-label treatment with an antidepressant. Patients who showed inadequate response (defined as a score of  $\geq 14$  on the 17-item Ham-D [Ham-D-17];  $<50\%$  reduction from baseline on the Ham-D-17 and the MADRS Total score; and a CGI-I score of  $\geq 3$ ) were randomly assigned to receive double-blind antidepressant plus brexpiprazole (2 mg/day) or antidepressant plus placebo. Adjunctive brexpiprazole 2 mg/day produced statistically significant reductions on MADRS Total scores

versus adjunctive placebo (i.e., antidepressant monotherapy) per final protocol ( $-8.36$  vs.  $-5.15$ , respectively;  $P=0.0002$ ) ([Thase et al. 2015b](#)).

The second study ([Thase et al. 2015a](#)) also evaluated the efficacy and safety of brexpiprazole (1 mg and 3 mg/day) versus placebo in the adjunctive treatment of antidepressant-resistant MDD. The study's design also included an 8-week single-blind prospective treatment phase in which patients received one antidepressant. Patients who had an inadequate response (defined as a Ham-D-17 score  $\geq 14$ ;  $<50\%$  reduction from baseline on the Ham-D-17 Total score and the MADRS Total score; and a CGI score  $\geq 3$ ) were randomly assigned to receive double-blind antidepressant plus brexpiprazole (1 mg/day or 3 mg/day) or antidepressant plus placebo. The brexpiprazole 3 mg/day treatment group showed statistically significant improvement (assessed by mean reduction from baseline in MADRS Total score) versus the placebo group ( $-8.29$  vs.  $-6.33$ , respectively;  $P=0.0079$ ), whereas the numerical improvement in MADRS Total score was not statistically significant for brexpiprazole 1 mg/day versus placebo ( $-7.64$ ;  $P=0.0079$ ) ([Thase et al. 2015a](#)).

---

## Side Effects and Toxicology

---

### Aripiprazole

A pooled analysis of safety and tolerability data from the five short-term studies ([Marder et al. 2003](#); [Stock et al. 2002](#)) showed that aripiprazole treatment was well tolerated. The most commonly reported adverse events

with aripiprazole were headache, insomnia, agitation, and anxiety. The incidence of adverse events was similar in the aripiprazole and placebo groups. The adverse-event profile of aripiprazole did not vary according to patient characteristics of age, sex, and race/ethnicity, and no deaths were reported during the short-term studies. Data from the four fixed-dosage studies showed that somnolence was the only adverse event seen with aripiprazole that was possibly dose related. Objective rating scale assessments were used to measure changes in parkinsonian symptoms (Simpson-Angus Scale [SAS]), dyskinesias (Abnormal Involuntary Movement Scale [AIMS]), and akathisia (Barnes Akathisia Rating Scale [BARS]). SAS scores with aripiprazole did not differ significantly from those with placebo, whereas AIMS scores improved significantly from baseline with aripiprazole compared with placebo. Aripiprazole did not produce consistent dose-dependent changes in BARS scores. The rate of discontinuation due to adverse events was 7.3% ([Otsuka Pharmaceutical 2016a](#)). According to the product labeling for aripiprazole in the United States, treatment-emergent adverse events most commonly reported with aripiprazole (occurring in  $\geq 10\%$  of patients with an incidence greater than that with placebo) in short-term trials of patients with schizophrenia (up to 6 weeks) or bipolar disorder (up to 3 weeks), respectively, included headache (aripiprazole 30% vs. placebo 25%), anxiety (20% vs. 17%), insomnia (19% vs. 14%), nausea (16% vs. 12%), vomiting (12% vs. 6%), dizziness (11% vs. 8%), constipation (11% vs. 7%), dyspepsia (10% vs. 8%), and akathisia (10% vs. 4%). A 26-week trial in schizophrenia reported a similar adverse-event profile except for a higher incidence of tremor (aripiprazole 8% vs. placebo 2%).

The most frequently reported adverse events with aripiprazole injection were headache (aripiprazole 12% vs. placebo 7%), nausea (9% vs. 3%), dizziness (8% vs. 5%), and somnolence (7% vs. 4%). In the three aripiprazole injection trials, the drug's safety profile was comparable to that of placebo regarding the incidence of EPS, akathisia, or dystonia. The incidence of akathisia-related adverse events with aripiprazole injection was 2% (vs. 0% for placebo), while the incidence of dystonia with aripiprazole injection was less than 1% (vs. 0% for placebo). In addition, the incidence of QTc prolongation was also comparable between aripiprazole injection and placebo.

The most common adverse events reported for the aripiprazole long-acting injectable formulation in the [Kane et al. \(2012\)](#) 52-week trial were insomnia (aripiprazole 10% vs. placebo 9%), tremor (5.9% vs. 1.5%), headache (5.9% vs. 5.2%), and akathisia (5.6% vs. 6%). In the [Kane et al. \(2014\)](#) 12-week acute management of schizophrenia study, the most common adverse events were increased weight (aripiprazole 16.8% vs. placebo 7%), headache (14.4% vs. 16.3%), and akathisia (11.4% vs. 3.5%). There was no significant difference in rates of EPS other than akathisia between the 400-mg aripiprazole group and the placebo group. In a 24-week open-label parallel-arm study conducted by [Mallikaarjun et al. \(2013\)](#), the tolerability and safety of aripiprazole once monthly in schizophrenia were comparatively evaluated for dosages of 200 mg, 300 mg, and 400 mg. The most common adverse events were injection-site pain (aripiprazole 400 mg, 28.6%), tremor (aripiprazole 400 mg, 21.4%; aripiprazole 300 mg, 6.7%), and vomiting (aripiprazole 300 mg, 13.3%; aripiprazole 400 mg, 14.3%).

The most common adverse events in a 12-week Phase III trial of aripiprazole lauroxil in the treatment of acute exacerbations of schizophrenia were akathisia, headache, insomnia, and injection-site pain (occurring in >5% of patients). Akathisia occurred at twice the rate of placebo for aripiprazole lauroxil 882 mg and 441 mg (4.3%, 11.6%, and 11.5%, respectively) ([Meltzer et al. 2015](#)). The majority (>75%) of akathisia episodes occurred within 3 weeks of receiving the first injection.

Minimal changes in mean body weight were observed with aripiprazole treatment in short-term studies (pooled data +0.71 kg) ([Marder et al. 2003](#)) and in long-term studies (26-week: -1.26 kg; 52-week: +1.05 kg) ([Kasper et al. 2003](#); [Pigott et al. 2003](#)).

Olanzapine and aripiprazole were compared on their propensity to cause weight gain and other metabolic disturbances in a 26-week randomized, double-blind multicenter trial ([McQuade et al. 2004](#)). Statistically significant differences in mean weight change were observed between treatments beginning at week 1 and were sustained throughout the study. At week 26, there was a mean weight loss of 1.37 kg (3.04 lb) with aripiprazole compared with a mean weight gain of 4.23 kg (9.40 lb) with olanzapine among patients who continued with therapy ( $P<0.001$ ). Changes in fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were significantly different in the two treatment groups, with worsening of the lipid profile among patients treated with olanzapine.

Aripiprazole treatment was not associated with increases in prolactin levels during either short- or long-term studies. (In fact, prolactin levels were shown to be slightly decreased by aripiprazole.)

Overall, aripiprazole treatment is associated with a low incidence of EPS (other than akathisia) and EPS-related symptoms and with minimal or no effects on weight gain, QTc interval, or circulating levels of cholesterol, glucose, and prolactin. Treatment with aripiprazole may reduce the burden of antipsychotic-associated side effects, thereby leading to improved patient adherence and decreased risks of acute relapse.

## Brexpiprazole

Overall, brexpiprazole has been well tolerated in the four short-term clinical trials conducted thus far, with lower rates of discontinuation due to adverse events compared with placebo. In pooled analyses for two trials of brexpiprazole in the adjunctive treatment of MDD, the rate of discontinuation due to adverse reactions for all dosages of brexpiprazole was 3%, compared with 1% for placebo ([Otsuka Pharmaceutical 2015](#)). In the two Phase III trials for brexpiprazole in acute schizophrenia, the overall rates of discontinuation due to adverse event were lower than those for placebo ([Correll et al. 2015](#); [Kane et al. 2015](#)).

The most common side effects varied per available studies. In one Phase III trial in acute schizophrenia, the most common adverse events for brexpiprazole were headache, agitation, and insomnia, with rates of akathisia lower than those with placebo but with a dose-dependent increase for brexpiprazole ([Correll et al. 2015](#)). Comparatively, the most common adverse event in another Phase III trial was akathisia for brexpiprazole 2 mg (4.4%) and 4 mg (7.2%) versus placebo (2.2%), with akathisia most commonly occurring within the first 3 weeks of treatment.

In two short-term trials for adjunctive use in MDD, pooled analysis showed that the most common adverse event was akathisia (8.6%) ([Citrome 2015](#)).

Pooled data from two short-term Phase III schizophrenia trials showed that 10% of brexpiprazole-treated patients had weight gains of 7% or greater from baseline during a 6-week trial, compared with 4.1% of patients receiving placebo. Similarly, the pooled data from both short-term MDD trials showed weight gain in the brexpiprazole group to be higher than that in the placebo group (6.7% vs. 1.9%), with the greatest increase being 1.6 kg for brexpiprazole 3 mg/day at 6 weeks ([Citrome 2015](#); [Otsuka Pharmaceutical 2015](#)).

Change in prolactin level was studied in all treatment trials. In one Phase III trial of brexpiprazole in schizophrenia, there was no statistically significant change in prolactin level ([Correll et al. 2015](#)). In a second Phase III short-term trial of brexpiprazole in schizophrenia, the incidence of potentially clinically relevant prolactin values (one to two times the upper limit of normal) was highest in the brexpiprazole 4-mg/day group (19.1%) versus the placebo group (13.9%) ([Kane et al. 2015](#)). In a short-term Phase III trial of brexpiprazole in the adjunctive treatment of MDD, 0.4% of patients receiving brexpiprazole 3 mg/day, compared with 1.4% of patients receiving placebo, had a prolactin level greater than three times the upper limit of normal ([Thase et al. 2015b](#)).

The incidence of EPS was evaluated in all four short-term treatment trials by means of the BARS and the SAS. The percentage of patients treated with brexpiprazole plus an antidepressant who showed a shift from normal to abnormal was greater versus placebo for both the BARS (4% vs. 0.6%) and the SAS (4% vs. 3%). Similarly, the

brexpiprazole group showed a greater shift from normal to abnormal versus placebo in both the BARS (2% vs. 1%) and the SAS (7% vs. 5%) in pooled data from both schizophrenia trials ([Otsuka Pharmaceutical 2015](#)).

With an overall minimal incidence of EPS beyond akathisia and minimal observed changes in QTc, lipid panel, and glucose panel values compared with placebo, brexpiprazole is another antipsychotic with a tolerable side-effect profile that may improve adherence long term ([Correll et al. 2015](#); [Kane et al. 2015](#); [Thase et al. 2015a, 2015b](#)).

---

## Drug-Drug Interactions

---

### Aripiprazole

Because aripiprazole is metabolized primarily by the hepatic CYP enzymes 2D6 and 3A4, it has the potential to interact with other substrates for these enzymes. Inducers of these enzymes may increase clearance and thereby reduce blood levels of aripiprazole, whereas inhibitors of CYP3A4 or CYP2D6 may inhibit elimination and thereby increase blood levels of aripiprazole. In vivo studies showed decreased levels of aripiprazole and dehydroaripiprazole in the plasma when aripiprazole was coadministered with carbamazepine, a CYP3A4 inducer. The aripiprazole dose should therefore be increased when the drug is administered concomitantly with carbamazepine. In vivo studies coadministering aripiprazole and ketoconazole (a CYP3A4 inhibitor) or quinidine (a CYP2D6 inhibitor) suggest that the aripiprazole dose should be reduced when



aripiprazole is administered with strong 3A4 or 2D6 inhibitors. Aripiprazole exhibits  $\alpha_1$ -adrenergic receptor antagonist activity and therefore may enhance the effects of certain antihypertensive agents.

## Brexpiprazole

Brexpiprazole is metabolized primarily by hepatic CYP enzymes 2D6 and 3A4; therefore, coadministration with inducers or inhibitors of these CYP enzymes requires dosage adjustments for brexpiprazole. In vivo studies showed increased levels of brexpiprazole when it was coadministered with ketoconazole (a CYP3A4 inhibitor) or quinidine (a CYP2D6 inhibitor), and it is therefore recommended that brexpiprazole dosages be reduced when brexpiprazole is coadministered with known CYP2D6 and CYP3A4 inhibitors. Plasma levels of brexpiprazole were decreased when the drug was coadministered with rifampin (a CYP3A4 inducer) during in vivo studies, and it is therefore recommended that brexpiprazole dosages be reduced when brexpiprazole is coadministered with known CYP3A4 inducers. Brexpiprazole has limited induction or inhibition of other CYP enzymes per multiple in vivo studies ([Otsuka Pharmaceutical 2015](#)).

---

## Conclusion

---

Aripiprazole was the first agent that was not a full D<sub>2</sub> receptor antagonist to show rapid and sustained antipsychotic activity, and it may be considered the first partial dopamine agonist combined with 5-HT-stabilizing

properties. Short-term and long-term clinical trials in adult and pediatric patients with schizophrenia and bipolar I disorder have demonstrated that aripiprazole combines sustained antipsychotic and mood-stabilizing efficacy with an excellent safety and tolerability profile. Additional augmentation trials have confirmed the utility of aripiprazole in alleviating depressive symptomatology in patients with MDD who have not achieved adequate symptom relief with antidepressants alone. The efficacy and safety of aripiprazole have also been established in child and adolescent populations for the management of irritability in autism spectrum disorders and Tourette's disorder. Aripiprazole is now also available in two different long-term depot injectable formulations for the management of schizophrenia in adults.

Brexpiprazole shares multiple similarities with aripiprazole, including partial dopamine agonism and 5-HT-stabilizing properties. However, brexpiprazole has lower intrinsic dopaminergic activity than does aripiprazole, which may indicate an even more favorable side-effect profile relative to the well-tolerated older drug. Several short-term clinical trials in adult patients with acute schizophrenia or with a lack of response to previous therapy for MDD have confirmed the efficacy and tolerability of this newly established atypical antipsychotic. A variety of clinical trials with brexpiprazole targeting different treatment populations, including head-to-head trials with other antipsychotics to further establish clinical efficacy, have been initiated or are ongoing.

In general, both aripiprazole and brexpiprazole are associated with low liability for EPS, QTc interval prolongation, prolactin elevation, weight gain, and disturbance of glucose or lipid metabolism. The

combination of efficacy, safety, and tolerability suggests that both aripiprazole and brexpiprazole represent important options for the acute treatment of schizophrenia as well as for the adjunctive treatment of MDD. Aripiprazole additionally represents an important treatment option for bipolar I disorder, irritability in autism spectrum disorder, and Tourette's disorder, and for long-term management of schizophrenia.

---

## References

---

- Alkermes: Aristada: Prescribing information. Waltham, MA, Alkermes, Inc., October 2015. Available at: <https://www.aristada.com/downloadables/ARISTADA-PI.pdf>. Accessed May 24, 2016.
- Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156(11):1686-1696, 1999 10553730
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Andrezina R, Josiassen RC, Marcus RN, et al: Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology (Berl)* 188(3):281-292, 2006 16953381
- Anton RF, Kranzler H, Breder C, et al: A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment

of alcohol dependence. *J Clin Psychopharmacol* 28(1):5-12, 2008 18204334

Berman RM, Marcus RN, Swanink R, et al: The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 68(6):843-853, 2007 17592907

Berman RM, Fava M, Thase ME, et al: Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr* 14(4):197-206, 2009 19407731

Burris KD, Molski TF, Xu C, et al: Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D<sub>2</sub> receptors. *J Pharmacol Exp Ther* 302(1):381-389, 2002 12065741

Citrome L: Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antipsychotic—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 69(9):978-997, 2015 26250067

Correll CU, Skuban A, Ouyang J, et al: Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 172(9):870-880, 2015 25882325

Daniel DG, Saha AR, Ingenito G, et al: Aripiprazole, a novel antipsychotic: overview of a phase II study result (abstract). *Int J Neuropsychopharmacol* 3 (suppl 1):S157, 2000

Davis KL, Kahn RS, Ko G, et al: Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry* 148(11):1474-1486, 1991 1681750

De Deyn P, Jeste DV, Swanink R, et al: Aripiprazole for the treatment of psychosis in patients with Alzheimer's

- disease: a randomized, placebo-controlled study. *J Clin Psychopharmacol* 25(5):463-467, 2005 16160622
- Fava M, Mischoulon D, Iosifescu D, et al: A double-blind, placebo-controlled study of aripiprazole adjunctive to antidepressant therapy among depressed outpatients with inadequate response to prior antidepressant therapy (ADAPT-A Study). *Psychother Psychosom* 81(2):87-97, 2012 22286203
- Findling RL, Robb A, Nyilas M, et al: A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *Am J Psychiatry* 165(11): 1432-1441, 2008 18765484
- Findling RL, Correll CU, Nyilas M, et al: Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. *Bipolar Disord* 15(2):138-149, 2013 23437959
- Findling RL, Mankoski R, Timko K, et al: A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry* 75(1):22-30, 2014 24502859
- Fleischhacker WW: Aripiprazole. *Expert Opin Pharmacother* 6(12):2091-2101, 2005 16197361
- Fleischhacker WW, Sanchez R, Perry PP, et al: Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. *Br J Psychiatry* 205(2):135-144, 2014 24925984
- Glassman AH, Bigger JT Jr: Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 158(11):1774-1782, 2001 11691681
- Jordan S, Koprivica V, Chen R, et al: The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT<sub>1A</sub> receptor. *Eur J Pharmacol* 441(3):137-140, 2002 12063084

- Kane JM, Carson WH, Saha AR, et al: Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 63(9):763-771, 2002 12363115
- Kane JM, Meltzer HY, Carson WH Jr, et al; Aripiprazole Study Group: Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. *J Clin Psychiatry* 68(2):213-223, 2007 17335319
- Kane JM, Sanchez R, Perry PP, et al: Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 73(5):617-624, 2012 22697189
- Kane JM, Sanchez R, Zhao J, et al: Hospitalisation rates in patients switched from oral anti-psychotics to aripiprazole once-monthly for the management of schizophrenia. *J Med Econ* 16(7):917-925, 2013 23663091
- Kane JM, Peters-Strickland T, Baker RA, et al: Aripiprazole once-monthly in the acute treatment of schizophrenia: findings from a 12-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 75(11):1254-1260, 2014 25188501
- Kane JM, Skuban A, Ouyang J, et al: A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res* 164(1-3):127-135, 2015 25682550
- Kasper S, Lerman MN, McQuade RD, et al: Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. *Int J Neuropsychopharmacol* 6(4):325-337, 2003 14609439
- Keck PE Jr, Marcus R, Tourkodimitris S, et al; Aripiprazole Study Group: A placebo-controlled, double-blind study of

the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry* 160(9):1651–1658, 2003 12944341

Keck PE Jr, Calabrese JR, McQuade RD, et al; Aripiprazole Study Group: A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry* 67(4):626–637, 2006 16669728

Kikuchi T, Tottori K, Uwahodo Y, et al: 7-(4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D2 receptor antagonistic activity. *J Pharmacol Exp Ther* 274(1):329–336, 1995 7616416

Koro CE, Fedder DO, L'Italien GJ, et al: An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry* 59(11):1021–1026, 2002a 12418935

Koro CE, Fedder DO, L'Italien GJ, et al: Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 325(7358):243, 2002b 12153919

Leysen JE, Janssen PMF, Schotte A, et al: Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of 5HT<sub>2</sub> receptors. *Psychopharmacology (Berl)* 112 (1 suppl):S40–S54, 1993 7530377

Lieberman J, Carson WH, Saha AR, et al: Meta-analysis of the efficacy of aripiprazole in schizophrenia (abstract P.4.E.031). *Int J Neuropsychopharmacol* 5 (suppl 1): S186, 2002

- Maeda K, Lerdrup L, Sugino H, et al: Brexpiprazole II: Antipsychotic-like and precognitive effects of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther* 350(3):605-614, 2014a 24947464
- Maeda K, Sugino H, Akazawa H, et al: Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther* 350(3):589-604, 2014b 24947465
- Mallikaarjun S, Kane JM, Bricmont P, et al: Pharmacokinetics, tolerability and safety of aripiprazole once-monthly in adult schizophrenia: an open-label, parallel-arm, multiple-dose study. *Schizophr Res* 150(1):281-288, 2013 23890595
- Marcus RN, McQuade RD, Carson WH, et al: The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 28(2):156-165, 2008 18344725
- Marcus RN, Owen R, Kamen L, et al: A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry* 48(11):1110-1119, 2009 19797985
- Marder SR, McQuade RD, Stock E, et al: Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res* 61(2-3):123-136, 2003 12729864
- McIntyre RS, McCann SM, Kennedy SH: Antipsychotic metabolic effects: weight gain, diabetes mellitus, and lipid abnormalities. *Can J Psychiatry* 46(3):273-281, 2001 11320682
- McQuade RD, Burris KD, Jordan S, et al: Aripiprazole: a dopamine-serotonin system stabilizer (abstract). *Int J Neuropsychopharmacol* 5 (suppl 1):S176, 2002
- McQuade RD, Stock E, Marcus R, et al: A comparison of weight change during treatment with olanzapine or



aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 65 (suppl 18):47–56, 2004 15600384

Meltzer HY: The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology* 21 (2 suppl):106S–115S, 1999 10432496

Meltzer HY, Risinger R, Nasrallah HA, et al: A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry* 76(8):1085–1090, 2015 26114240

Millan MJ: Improving the treatment of schizophrenia: focus on serotonin (5-HT)<sub>(1A)</sub> receptors. *J Pharmacol Exp Ther* 295(3): 853–861, 2000 11082417

Mintzer JE, Tune LE, Breder CD, et al: Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. *Am J Geriatr Psychiatry* 15(11):918–931, 2007 17974864

Nickel MK, Muehlbacher M, Nickel C, et al: Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* 163(5):833–838, 2006 16648324

Nickel MK, Loew TH, Pedrosa Gil F: Aripiprazole in treatment of borderline patients, part II: an 18-month follow-up. *Psychopharmacology (Berl)* 191(4):1023–1026, 2007 17318503

Otsuka Pharmaceutical: Rexulti: Prescribing information. Tokyo, Japan, Otsuka Pharmaceutical Co, 2015. Available at: [https://www.otsuka-us.com/media/images/RexultiPI\\_544.pdf](https://www.otsuka-us.com/media/images/RexultiPI_544.pdf). Accessed May 24, 2016.

Otsuka Pharmaceutical: Abilify: Prescribing information. Tokyo, Japan, Otsuka Pharmaceutical Co, 2016a. Available at: <https://www.otsuka->

[us.com/media/images/AbilifyPI\\_538.pdf](https://www.otsuka-us.com/media/images/AbilifyPI_538.pdf). Accessed May 24, 2016.

Otsuka Pharmaceutical: Abilify Maintenna: Prescribing information. Tokyo, Japan, Otsuka Pharmaceutical Co, 2016b. Available at: [https://www.otsuka-us.com/media/images/AbilifyMPI\\_539.pdf](https://www.otsuka-us.com/media/images/AbilifyMPI_539.pdf). Accessed May 24, 2016.

Owen R, Sikich L, Marcus RN, et al: Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics* 124(6):1533-1540, 2009 19948625

Petrie JL, Saha AR, McEvoy JP: Aripiprazole, a new novel atypical antipsychotic: phase II clinical trial result (abstract). *Eur Neuropsychopharmacol* 7 (suppl 2):S227, 1997

Pigott TA, Carson WH, Saha AR, et al; Aripiprazole Study Group: Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry* 64(9):1048-1056, 2003 14628980

Potkin SG, Saha AR, Kujawa MJ, et al: Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 60(7):681-690, 2003 12860772

Pycock CJ, Kerwin RW, Carter CJ: Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. *Nature* 286(5768):74-76, 1980 7393327

Rao ML, Möller HJ: Biochemical findings of negative symptoms in schizophrenia and their putative relevance to pharmacologic treatment. A review. *Neuropsychobiology* 30(4):160-172, 1994 7862264

Richelson E: Receptor pharmacology of neuroleptics: relation to clinical effects. *J Clin Psychiatry* 60 (suppl 10):5-14, 1999 10340682

- Sachs G, Sanchez R, Marcus R, et al; Aripiprazole Study Group: Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol* 20(4):536-546, 2006 16401666
- Sallee FR, Kohegyi E, Zhao J, et al: Children and adolescents with tourette's disorder: a randomized, double-blind, placebo-controlled trial (abstract). *Neuropsychopharmacology* 39 (suppl 1): s378-s379, 2014
- Seeman P, Niznik HB: Dopamine receptors and transporters in Parkinson's disease and schizophrenia. *FASEB J* 4(10):2737-2744, 1990 2197154
- Stock E, Marder SR, Saha AR, et al: Safety and tolerability meta-analysis of aripiprazole in schizophrenia (abstract). *Int J Neuropsychopharmacol* 5 (suppl 1):S185, 2002
- Thase ME, Jonas A, Khan A, et al: Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol* 28(1):13-20, 2008 18204335
- Thase ME, Youakim JM, Skuban A, et al: Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry* 76(9):1232-1240, 2015a 26301771
- Thase ME, Youakim JM, Skuban A, et al: Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *J Clin Psychiatry* 76(9):1224-1231, 2015b 26301701
- Tiihonen J, Kuoppasalmi K, Föhr J, et al: A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry* 164(1):160-162, 2007 17202560

- Tran-Johnson TK, Sack DA, Marcus RN, et al: Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 68(1):111-119, 2007 17284138
- Vieta E, Bourin M, Sanchez R, et al; Aripiprazole Study Group: Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry* 187:235-242, 2005 16135860
- Vieta E, T'joen C, McQuade RD, et al: Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *Am J Psychiatry* 165(10):1316-1325, 2008 18381903
- Weinberger DR: Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44(7):660-669, 1987 3606332
- Yoo HK, Joung YS, Lee JS, et al: A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry* 74(8):e772-e780, 2013 24021518
- Zimbroff DL, Marcus RN, Manos G, et al: Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole. *J Clin Psychopharmacol* 27(2):171-176, 2007 17414241

---

This chapter is an update and revision of Sharif ZA, Cole YI, Lieberman JA: "Aripiprazole," in *Essentials of Clinical Psychopharmacology*, Third Edition. Edited by Schatzberg

AF, Nemeroff CB. Arlington, VA, American Psychiatric Publishing, 2013, pp 291-303.

# CHAPTER 30

## Ziprasidone

John W. Newcomer, M.D.

Elise Fallucco, M.D.

Martin T. Strassnig, M.D.

---

### History and Discovery

---

Ziprasidone (CP-88059) is an atypical, or *second-generation*, antipsychotic agent that has activity for treating positive, negative, cognitive, and affective symptoms of schizophrenia and schizoaffective disorder and for treating mania and mixed states in bipolar disorder, with limited adverse extrapyramidal, sedative, anticholinergic, and cardiometabolic effects. First approved in 2001, this antipsychotic was initially part of a new drug application for the treatment of psychotic disorders submitted to the U.S Food and Drug Administration (FDA) in 1997. Because of concerns regarding an increase in the mean duration of the QT interval, an electrocardiographic measure of the ventricular depolarization and repolarization phases of

cardiac conduction, the application was not initially approved. Further studies, designed in collaboration with the FDA, quantified the limited extent of the QTc interval lengthening effect seen with ziprasidone compared with that seen with other agents in wide use; these studies established the safety of ziprasidone with respect to cardiac conduction and a benchmark for the approach to evaluating drug effects on the QT interval that has subsequently been applied to other agents evaluated by the FDA. Ziprasidone has received regulatory approval and is available in more than 92 countries.

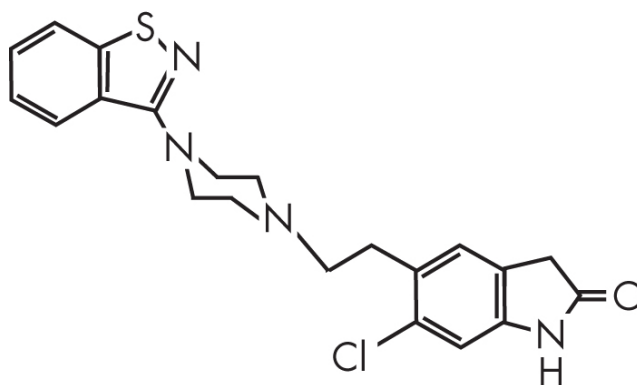
---

## Pharmacological Profile

---

### Neuropharmacology and Receptor-Binding Profile

Ziprasidone, or 5-{2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-1,3-dihydro-2H-indol-2-one, is a novel benzisothiazolylpiperazine antipsychotic ([Figure 30-1](#)).



---

**FIGURE 30-1.** Chemical structure of ziprasidone.

## **Dopamine Type 2 and Serotonin Type 2A Receptor Activity**

Ziprasidone is a potent antagonist at dopamine type 2 ( $D_2$ ) receptors with inverse agonist activity at serotonin (5-hydroxytryptamine) type 2A ( $5-HT_{2A}$ ) receptors.  $D_2$  receptor antagonism is thought to be a key mechanism explaining efficacy for the treatment of psychotic symptoms ([Kapur and Remington 2001](#)); positron emission tomography (PET) studies have shown that clinical antipsychotic response to ziprasidone is predicted by occupancy of at least 60% of striatal  $D_2$  receptors.  $D_2$  receptor antagonism is also associated with potential liability for extrapyramidal side effects (EPS). However, ziprasidone also has inverse agonist activity at  $5-HT_{2A}$  receptors, an effect that can disinhibit dopamine neurotransmission in the nigrostriatal, mesocortical, and tuberoinfundibular pathways ([Kapur and Remington 1996](#); [Schmidt et al. 2001](#)). This effect suggests a mechanism for reduced liability for EPS compared with antipsychotics with unopposed  $D_2$  receptor antagonism and may contribute to therapeutic effects. Increased dopamine activity in the prefrontal cortex is linked to efficacy in improving the negative and cognitive symptoms of schizophrenia ([Stahl and Shayegan 2003](#)). Enhanced dopaminergic transmission in the tuberoinfundibular pathway minimizes the potential effect of  $D_2$  receptor antagonism on prolactin secretion. Ziprasidone's relatively high in vitro  $5-HT_{2A}/D_2$  receptor affinity ratio, compared with that of other second-generation antipsychotics (SGAs), predicts a low liability for



EPS and potential therapeutic benefits for negative symptoms ([Altar et al. 1986](#)).

## **Serotonin Type 1A, 1D, and 2C Receptor Activity**

Ziprasidone exhibits antagonist activity at serotonin type 1D (5-HT<sub>1D</sub>) and type 2C (5-HT<sub>2C</sub>) receptors and unusual (among SGAs) agonist activity at serotonin type 1A (5-HT<sub>1A</sub>) receptors ([DeLeon et al. 2004](#); [Schmidt et al. 2001](#)). The 5-HT<sub>1A</sub> affinity is comparable to that of buspirone, an agent with antidepressant and anxiolytic properties ([Mazei et al. 2002](#)), suggesting a mechanism that may contribute to beneficial effects on affective, cognitive, and negative symptoms in schizophrenia and schizoaffective disorder ([Díaz-Mataix et al. 2005](#); [Ichikawa et al. 2001](#); [Millan 2000](#); [Rollema et al. 2000](#); [Sumiyoshi et al. 2003](#); [Tauscher et al. 2002](#)). Potent antagonism at 5-HT<sub>1D</sub> receptors has been proposed to potentially mediate antidepressant and anxiolytic effects ([Briley and Moret 1993](#); [Zorn et al. 1998](#)). Blockade of 5-HT<sub>2C</sub> receptors disinhibits both dopamine and norepinephrine neurons in the cortex, an effect that could contribute to improvements in cognitive and affective abnormalities ([Bremner et al. 2003](#); [Bymaster et al. 2002](#); [Mazei et al. 2002](#); [Stahl 2003](#)).

Although 5-HT<sub>2C</sub> receptor antagonist activity might predict weight gain liability, based largely on a 5-HT<sub>2C</sub> knockout mouse model of obesity ([Tecott et al. 1995](#)), clinically significant predictive effects of 5-HT<sub>2C</sub> receptor antagonist activity on the relative weight gain risk associated with antipsychotic drugs have not been reliably detected ([Kroeze et al. 2003](#)), and the weight gain risk

associated with ziprasidone is among the lowest of currently available antipsychotics ([Allison et al. 1999b](#)).

## **Serotonin and Norepinephrine Transporter Activity**

Another important feature of ziprasidone is its relatively high affinity for serotonin and norepinephrine transporters ([Seeger et al. 1995](#); [Tatsumi et al. 1999](#)). In vitro, ziprasidone demonstrates dose-dependent reuptake inhibition of serotonin and norepinephrine transport, with effects ranging up to those of imipramine and amitriptyline ([Schmidt et al. 2001](#)), suggesting potential antidepressant activity. In vivo, the clinical significance of ziprasidone's monoaminergic reuptake inhibition may be limited by plasma protein binding or may be clinically relevant only at daily dosages higher than those currently approved. Monoaminergic reuptake inhibition is associated with hippocampal neurogenesis, suggesting potential value in countering the neuronal cell loss observed in both affective illness and schizophrenia ([Arango et al. 2001](#); [Duman 2004](#); [Thome et al. 1998](#)). Relevant to this activity, treatment with ziprasidone or risperidone is associated with an increase in cortical gray matter volume ([Garver et al. 2005](#)).

Ziprasidone has a low affinity for histaminergic type 1 ( $H_1$ ), muscarinic type 1 ( $M_1$ ), and  $\alpha_1$ -noradrenergic receptors. Among the biogenic amine receptors,  $H_1$  receptor antagonist activity is the largest predictor of weight gain liability ([Kroeze et al. 2003](#)).  $H_1$  antagonist activity also predicts sedative effects, which are potentially undesirable for patients aiming to maximize cognitive performance and social, occupational, and community engagement. Low affinity for  $\alpha_1$ -adrenergic receptors

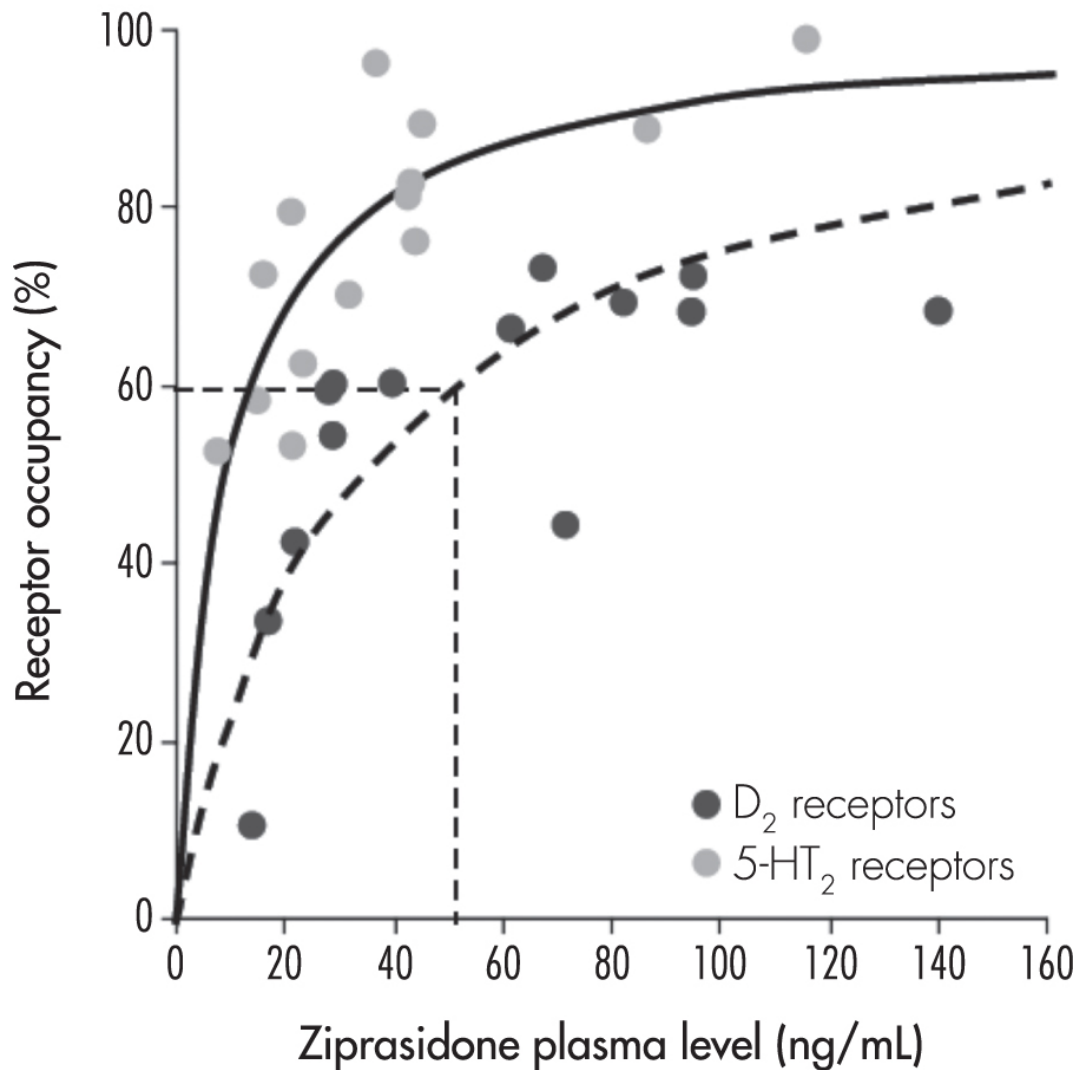
predicts a lower likelihood of orthostatic hypotension and sedation with ziprasidone than with commonly used antipsychotics with potent  $\alpha_1$ -adrenergic receptor antagonist activity. Low affinity for  $M_1$  receptors predicts a low risk for anticholinergic side effects such as dry mouth, blurry vision, urinary retention, constipation, confusion, and memory impairment.

Ziprasidone's complex neuropharmacology provides explanatory support for observed treatment effects on psychotic and affective symptoms of schizophrenia, schizoaffective disorder, and bipolar disorder and for the observed favorable tolerability profile with minimal EPS and minimal metabolic side effects ([Stahl and Shayegan 2003](#)).

## Positron Emission Tomography Studies

An in vivo PET study ([Mamo et al. 2004](#)) examining the affinity of ziprasidone for  $D_2$  and  $5-HT_2$  receptors observed that optimal  $D_2$  receptor occupancy occurs at the high end of ziprasidone's initially recommended dosage range. In this study, the ziprasidone plasma concentration associated with 50% of maximal  $D_2$  receptor occupancy was more than twice the plasma concentration associated with 50% of maximal  $5-HT_2$  receptor occupancy. Using an imaging protocol where 60% or greater dopamine  $D_2$  receptor occupancy is generally predictive of antipsychotic activity, approximately 60%  $D_2$  occupancy was observed in relation to plasma concentrations equivalent to those attained with a dosage at or above 120 mg/day. These results, consistent

with clinical trial results discussed later in this chapter (see “Indications and Efficacy”), suggest that antipsychotic activity with ziprasidone is most commonly associated with dosages of 120 mg/day or greater ([Figure 30-2](#)).



**FIGURE 30-2.** Relationship between dopamine<sub>2</sub> ( $D_2$ ) and serotonin<sub>2</sub> ( $5-HT_2$ ) receptor occupancy and ziprasidone plasma levels in 16 patients with schizophrenia or schizoaffective disorder receiving therapeutic dosages of ziprasidone.

*Dotted straight lines* represent the minimum D<sub>2</sub> receptor occupancy and plasma concentration that would be expected to be associated with a clinical antipsychotic response, corresponding to a ziprasidone dosage of approximately 120 mg/day.

*Source.* Adapted from [Mamo et al. 2004](#).

## Dosing Recommendations

In addition to the PET data just described, evidence from clinical trials suggests that ziprasidone target dosages should be higher than those originally recommended. In the United States, it was initially recommended that ziprasidone treatment in patients with schizophrenia be initiated at a dosage of 20 mg twice daily, with the dosage then titrated at intervals of no less than 2 days to a maximum of 80 mg twice daily ([Pfizer Inc. 2008](#)). In contrast, subsequent FDA approval of ziprasidone for the treatment of bipolar mania included a recommendation that treatment be initiated at 40 mg twice daily with a more rapid titration; on the second day of treatment, the dosage might be increased to 60 or 80 mg twice daily, with subsequent adjustment based on tolerability and efficacy within a 40- to 80-mg twice-daily range.

Ziprasidone dosages of 120–160 mg/day are observed to be more effective than lower dosages in the treatment of acute schizophrenia ([Kane 2003b](#)) and bipolar disorders ([Citrome et al. 2009b](#)) in adults and also are associated with lower rates of medication discontinuation ([Citrome et al. 2009c](#)). A 6-month prospective, observational, naturalistic, uncontrolled study in Spain observed that dosages greater than 120 mg/day were associated with a lower risk of discontinuation for any cause ([Arango et al. 2007](#)). In an

analysis of commercial and Medicare prescription databases, [Citrome et al. \(2009a\)](#) observed significantly lower discontinuation rates among schizophrenia and bipolar disorder patients receiving ziprasidone at dosages of 120–160 mg/day compared with those receiving ziprasidone at lower dosages. Similarly, a European observational multicenter trial found that initial and overall underdosing of ziprasidone were associated with high discontinuation rates ([Kudla et al. 2007](#)), and a pooled analysis of both flexible-dose and fixed-dose studies ( $N=2,174$ ) observed greater efficacy in patients who received an initial dosage of 80 mg/day compared with patients who received an initial dosage of 40 mg/day ([Murray et al. 2004](#)). Finally, two large observational database analyses suggested that higher dosages of ziprasidone are associated with better treatment outcomes than lower dosages ([Joyce et al. 2006](#); [Mullins et al. 2006](#)). Both studies used prescription refills as an indicator of prescription adherence. [Joyce et al. \(2006\)](#) examined records from more than 1,000 commercially insured patients with schizophrenia or schizoaffective disorder and concluded that an initial daily dosage of 120–160 mg was associated with a significantly lower risk of medication discontinuation at 6 months than an initial daily dosage of 60–80 mg. [Mullins et al. \(2006\)](#) evaluated more than 1,000 Medicaid recipients with schizophrenia and similarly concluded that patients receiving an initial dosage of 120–160 mg/day had lower rates of medication discontinuation than patients receiving 20–60 mg/day. Reported clinical experience with ziprasidone has also suggested the need for dosages greater than 160 mg/day in selected patients ([Citrome et al. 2009a](#); [Harvey and Bowie 2005](#); [Nemeroff et al. 2005](#)). A dosage of 320 mg/day, twice the maximum

recommended dosage of 160 mg/day, did not lead to any additional symptom improvement in a small 8-week placebo-controlled trial as compared with a dosage of 160 mg/day, and plasma drug levels were similar between the two dosages at the end of the study period. There was a trend toward increasing diastolic blood pressure, more prominent negative symptoms, and greater QTc prolongation ([Goff et al. 2013](#)) with the 320 mg/day dosage.

Taken together, results from receptor occupancy studies, clinical trials, and pharmacoepidemiological analyses support the conclusion that initiation and treatment with ziprasidone at dosages greater than 120 mg/day, with rapid titration, are more likely to be effective than lower dosages in the treatment of schizophrenia, schizoaffective disorder, and bipolar disorder, while excessive dosages may incur additional side effects rather than additional efficacy.

---

## Pharmacokinetics and Disposition

---

### Absorption and Distribution

On the basis of evidence of enhanced absorption of ziprasidone in the presence of food, it is recommended that oral ziprasidone be taken with meals of at least 500 kcal to avoid substantial reduction in drug absorption ([Gandelman et al. 2009](#)) that cannot be effectively compensated for by increasing the dosage ([Citrome 2009](#)). Administration with food increases absorption by more than 50%, giving ziprasidone an oral bioavailability of approximately 60%

(Pfizer Inc. 2008). Maximal plasma concentration ( $C_{\max}$ ) is achieved within 3.7–4.7 hours and reaches 45–139  $\mu\text{g/L}$  in healthy volunteers receiving 20–60 mg twice daily, and steady-state serum concentrations occur within 1–3 days of twice-daily dosing (Hamelin et al. 1998; Miceli et al. 2000c). In contrast to oral administration, intramuscular administration of ziprasidone results in 100% bioavailability. A therapeutic plasma level is reached within 10 minutes, and  $C_{\max}$  is achieved within 30 minutes of administration of a 20-mg dose (Pfizer Inc. 2008).

The mean apparent volume of distribution of ziprasidone is 1.5 L/kg (Pfizer Inc. 2008), which is lower than that of many other antipsychotic drugs. Given the wider potential for unwanted interactions with various intracellular targets that has been observed with lipophilic drugs having a high volume of distribution (Dwyer et al. 1999), this may be a favorable attribute for ziprasidone and other similar compounds. Ziprasidone is more than 99% bound to plasma proteins.

## Metabolism and Elimination

Ziprasidone is extensively metabolized, with a mean terminal elimination half-life of approximately 7 hours after oral administration within the recommended clinical dosage range (Pfizer Inc. 2008). The elimination half-life of intramuscular ziprasidone is less than 3 hours with a single dose (Brook et al. 2000). Ziprasidone is cleared primarily via three metabolic pathways to yield four major circulating metabolites. Elimination occurs primarily through hepatic metabolism, with less than one-third of metabolic clearance mediated via cytochrome P450 (CYP)-catalyzed oxidation



and approximately two-thirds via reduction of the parent compound by aldehyde oxidase to dihydroziprasidone, which then undergoes *S*-methylation. The literature reports no commonly encountered clinically significant pharmacological inhibitors of aldehyde oxidase, suggesting limited real-world potential for drug-drug interactions that would alter the clinical activity of ziprasidone (Obach et al. 2004).

Additional secondary metabolic pathways include *N*-dealkylation (via CYP enzymes 3A4 and 1A2) and direct *S*-oxidation (via CYP3A4) (Beedham et al. 2003; Prakash et al. 2000). *S*-Methyl-dihydroziprasidone is the only active metabolite, with lower D<sub>2</sub> receptor affinity and no significant binding to H<sub>1</sub>, M<sub>1</sub>, or  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors. A small amount of the parent compound is excreted unchanged in the urine (<1%) and feces (<4%).

There are no clinically significant age- or sex-related differences in the pharmacokinetics of oral ziprasidone (Pfizer Inc. 2008). Hepatic impairment might be expected to increase the area under the time-concentration curve (AUC). A multiple-dose study (Everson et al. 2000) comparing subjects with clinically significant (Child-Pugh Class A and B) cirrhosis versus healthy control subjects indicated that 12 hours after administration of ziprasidone, the AUC was 13% and 34% greater in subjects with Child-Pugh Class A and B cirrhosis, respectively, than in matched control subjects, suggesting that dose adjustments are generally not mandatory for patients with hepatic impairment. Impairment in renal function is unlikely to significantly alter the pharmacokinetics of oral ziprasidone, suggesting that ziprasidone would not be removed by hemodialysis (Pfizer Inc. 2008). Intramuscular ziprasidone has not been systematically evaluated in the elderly or in

patients with hepatic or renal impairment. Intramuscular ziprasidone contains a cyclodextrin excipient that is cleared by renal filtration; thus, it should be administered with caution to patients with impaired renal function ([Pfizer Inc. 2008](#)).

## Impact of Food on Pharmacokinetics

Pharmacokinetic studies have examined ziprasidone bioavailability under fasting conditions and after eating food with varying caloric and fat composition to better understand effects of food intake on drug availability ([Gandelman et al. 2009](#); [Lombardo et al. 2007](#)). In an open-label, nonrandomized six-way crossover study, healthy adults received single doses of ziprasidone under fasting conditions and then under fed conditions with a standard meal of 800–1,000 calories. Dose-proportional increases in ziprasidone AUC and  $C_{\max}$  were observed under fed but not fasting conditions.  $C_{\max}$  was significantly higher in fed states than in fasting states at doses of 40 mg (63% higher) and 80 mg (97% higher). Results from two additional open-label crossover studies further clarified the factors regulating drug bioavailability ([Gandelman et al. 2009](#); [Lombardo et al. 2007](#)) and indicated that 1) medium-calorie meals (500 calories) are associated with ziprasidone exposure close to the exposure that can be achieved with high-calorie meals (1,000 calories) and nearly twice the exposure observed under fasting conditions, and 2) absorption is not significantly influenced by the fat content of the meal. These studies suggest that the administration of ziprasidone with even a low-fat meal of at least 500 calories provides linear pharmacokinetics and optimal

absorption. In addition, the results suggest that larger meal bulk, sufficient to slow gastric and duodenal transit time (e.g., a bowl of oatmeal), rather than fat content or specific calorie counts, may be an important contributor to reliable dose-dependent drug absorption with meals.

---

## Indications and Efficacy

---

### Schizophrenia and Schizoaffective Disorder

#### Acute Treatment

Ziprasidone is indicated for the acute treatment of schizophrenia and schizoaffective disorder. Its efficacy in the treatment of hospitalized patients with acute schizophrenia or schizoaffective disorder has been demonstrated in a series of double-blind, placebo-controlled trials of 4–6 weeks' duration ([Daniel et al. 1999](#); [Kane 2003b](#); [Keck et al. 1998, 2001](#)). Additional short-term (4- to 8-week) randomized, double-blind treatment studies using active antipsychotic comparator agents have indicated that ziprasidone has efficacy comparable to that of haloperidol, risperidone, and olanzapine for the treatment of positive symptoms and overall psychopathology ([Addington et al. 2004](#); [Goff et al. 1998](#); [Simpson et al. 2004a](#)). In a pooled analysis of four short-term placebo-controlled trials and three active-comparator trials, [Murray et al. \(2004\)](#) demonstrated that ziprasidone dosages of at least 120 mg/day, in comparison with lower dosages, are associated

with a more rapid and favorable response in overall psychopathology as well as a lower discontinuation rate due to inadequate clinical response, suggesting the importance of rapid titration to at least 120 mg/day ([Kane 2003b](#); [McCue et al. 2006](#)).

Suboptimal dosing, inadequate titration regimens, and failure to administer ziprasidone with food may have negatively affected its performance in some clinical trials. Some clinical trials included efficacy analyses on dosages that would now be considered suboptimal (i.e., <120 mg/day), whereas other studies used prolonged titration of ziprasidone, with a therapeutic dosage not reached until 1 week or more into the study. Clinical trials conducted before the release of pharmacokinetic data by [Lombardo et al. \(2007\)](#) may not have been designed to ensure that ziprasidone was administered with food for optimal oral absorption.

Ziprasidone has also been studied in the treatment of early psychosis and schizophrenia. In a study by [Johnsen et al. \(2010\)](#), patients admitted to the emergency ward with early psychosis were consecutively randomly assigned to receive one of several different SGAs: ziprasidone, olanzapine, quetiapine, or risperidone. No clinically significant differences in effectiveness of the tested antipsychotics emerged after a 2-year follow-up period. [Crespo-Facorro et al. \(2013, 2014\)](#), in a 12-week prospective open-label, randomized trial followed by a year-long extension period comparing quetiapine, aripiprazole, and ziprasidone for the treatment of first-episode psychosis, found significantly greater discontinuation rates with quetiapine than with aripiprazole or ziprasidone, owing to “insufficient” efficacy of quetiapine and comparable efficacy of the other two tested agents.

A series of meta-analyses found no consistent differences among the SGAs, either when comparing agents within the same class or when comparing SGAs with first-generation antipsychotics (FGAs) ([Bagnall et al. 2003](#); [Geddes et al. 2000](#); [Leucht et al. 1999](#); [Srisurapanont and Maneeton 1999](#); [Tandon and Fleischhacker 2005](#)). One meta-analysis of randomized controlled trials (RCTs) by [Davis et al. \(2003\)](#) suggested that although some SGAs (i.e., clozapine, risperidone, olanzapine, and amisulpride) were significantly more efficacious than FGAs, ziprasidone was not. It is important to note that this meta-analysis excluded data relating to low dosages of other antipsychotics (olanzapine <11 mg/day and risperidone <4 mg/day) but included data on ziprasidone dosages as low as 80 mg/day. In addition, the Davis et al. meta-analysis included relatively few studies of ziprasidone (4 studies as compared with 31 studies of clozapine, 22 studies of risperidone, and 14 studies of olanzapine), leaving significance testing for this agent more vulnerable to issues associated with individual studies. [Leucht et al. \(2013\)](#) used a novel approach, a Bayesian-framework, multiple-treatment meta-analysis of available RCT data, comparing 15 antipsychotic drugs and placebo in the acute treatment of schizophrenia, and concluded that antipsychotics differed substantially in side effects and that, while all antipsychotics were better than placebo, small but robust differences exist in efficacy, with clozapine representing the most effective—but not necessarily the best tolerated—antipsychotic.

Using Medicaid claims data, [Olfson et al. \(2012\)](#) compared the effectiveness (as measured by rates of medication discontinuation and hospital admission) of commonly prescribed SGA medications in child and adolescent outpatients (ages 6–17 years) with

schizophrenia or related disorders. Most youth with early psychosis (defined as onset before age 18 years) treated with quetiapine (70.7%), ziprasidone (73.3%), olanzapine (73.1%), risperidone (74.4%), or aripiprazole (76.5%) discontinued the medication within the first 180 days following medication initiation. Studies like these underscore both the comparable effectiveness among SGA agents and the high discontinuation rates associated with available treatments, the latter in part related to unwanted medication-induced adverse events. The favorable side-effect profile of ziprasidone recommends it as an important first-line option in the treatment of early psychosis.

---

## Maintenance Therapy

---

The maintenance efficacy of ziprasidone in treating schizophrenia and schizoaffective disorder has been studied in a series of double-blind and open-label extension trials ([Arato et al. 2002](#); [Hirsch et al. 2002](#); [Kane 2003a](#); [Schooler 2003](#); [Simpson et al. 2002, 2004b](#)). These studies indicate that long-term therapy with ziprasidone maintains clinical response and is effective in preventing relapse.

**Maintenance of effect.** In two maintenance-of-effect studies, patients with schizophrenia or schizoaffective disorder who had previously demonstrated acute response to treatment (defined as a  $\geq 20\%$  decrease in Positive and Negative Syndrome Scale [PANSS]-Total score and a Clinical Global Impression [CGI] scale score of  $\leq 2$ ) were randomly assigned to receive either ziprasidone or a comparator antipsychotic agent for at least 26 weeks ([Addington et al. 2009](#); [Schooler 2003](#); [Simpson et al. 2002](#),

2005). In both of these studies, the ziprasidone treatment groups demonstrated significant improvements from baseline in overall psychopathology, as measured by mean changes in symptom ratings using PANSS-Total, PANSS-Negative subscale, Brief Psychiatric Rating Scale-Depression Factor (BPRSd), and CGI-Severity (CGI-S) scores. These improvements were comparable to those seen in the olanzapine (Simpson et al. 2005) and risperidone (Addington et al. 2009) treatment groups.

**Relapse prevention.** To evaluate the efficacy of ziprasidone for relapse prevention, the Ziprasidone Extended Use in Schizophrenia (ZEUS) study enrolled stable inpatients with chronic schizophrenia and randomly assigned participants to 1 year of treatment with ziprasidone 40 mg/day ( $n=72$ ), 80 mg/day ( $n=68$ ), or 160 mg/day ( $n=67$ ) or placebo ( $n=71$ ), with a planned primary Kaplan-Meier analysis of time to relapse (Arato et al. 2002). In this study, all three dosages of ziprasidone were superior to placebo in the prevention of relapse. In addition, a penultimate-observation-carried-forward analysis (in which the last visit prior to relapse is excluded) was performed to filter out clinical worsening associated with relapse that might otherwise obscure symptom response trends during the rest of maintenance therapy (O'Connor and Schooler 2003). This analysis indicated that nonrelapsing patients treated with ziprasidone experienced modest symptomatic improvement during maintenance treatment. This study, like a number of other studies of other antipsychotic agents in schizophrenia patients, was limited by the relatively high level of attrition observed in all groups over the year of treatment.

## **Long-term response to treatment in symptomatic patients.**

A number of long-term double-blind trials designed to examine the efficacy of ziprasidone in symptomatic patients with schizophrenia have been performed ([Breier et al. 2005](#); [Hirsch et al. 2002](#); [Kinon et al. 2006](#); [Simpson et al. 2004a, 2005](#)). [Hirsch et al. \(2002\)](#) compared the efficacy of ziprasidone ( $n=148$ ) and haloperidol ( $n=153$ ) in a 28-week double-blind trial of stable outpatients with schizophrenia with prominent negative symptoms. In this study, ziprasidone and haloperidol were similarly efficacious in reducing overall psychopathology, with an advantage for ziprasidone in the percentage of patients classified as negative symptom responders. [Breier et al. \(2005\)](#) conducted a 28-week study of ziprasidone and olanzapine in outpatients as well as inpatients ( $N=548$ ) with active symptoms. In this study, olanzapine treatment was associated with greater improvement from baseline in total psychopathology scores (PANSS-Total, the primary efficacy measure) compared with ziprasidone and a higher rate of criterion-level response to treatment. [Simpson et al. \(2004a\)](#) conducted a 6-week double-blind, parallel-design flexible-dose comparison ( $N=269$ ) of ziprasidone ( $n=136$ ) and olanzapine ( $n=133$ ) in which patients who showed at least minimal response (CGI-Improvement [CGI-I] score  $\leq 2$  or  $\geq 20\%$  reduction in PANSS-Total score) were enrolled in a 6-month double-blind continuation trial ([Simpson et al. 2005](#)). In both the 6-week and the 6-month analyses, no differences between the treatment groups were detected on any primary (e.g., Brief Psychiatric Rating Scale [BPRS] total score, CGI-S) or secondary (e.g., PANSS-Total, CGI-I) measures.



[Potkin et al. \(2009\)](#) compared the effects of ziprasidone and haloperidol in a 196-week double-blind study using the Andreasen criteria for remission ([Andreasen et al. 2005](#)) by longitudinal analysis. During the initial 40-week study, no differences in PANSS or Global Assessment of Functioning Scale (GAF) score changes between the two antipsychotics compared emerged. In a subsequent 3-year extension study, ziprasidone-treated subjects were more likely to achieve remission (51%) compared with haloperidol-treated subjects (40%). The PANSS-Total and GAF score trajectories favored the higher 80–160 mg/day ziprasidone dosage as opposed to lower dosages, and the superior outcome for ziprasidone versus haloperidol may have been due in part to tolerability and adherence advantages.

**Clinical effectiveness.** There have been a number of effectiveness trials involving ziprasidone and using various definitions for *effectiveness*. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies, funded by the National Institute of Mental Health (NIMH), included a long-term, double-blind, randomized study of patients with schizophrenia ( $N=1,493$ ; [Lieberman et al. 2005](#)). Phase 1 of the CATIE schizophrenia study compared ziprasidone, olanzapine, quetiapine, risperidone, and perphenazine on a primary endpoint of time to discontinuation for lack of efficacy or for any cause. Because of the timing of its FDA approval, ziprasidone was added to the study after enrollment had begun for all other treatment arms; this resulted in a smaller sample size for the ziprasidone treatment arm and some limitations regarding conclusions about ziprasidone in phase 1 of the study.

The primary analysis for the phase 1 study detected significant differences in time to discontinuation across the treatment groups overall. The longest time to discontinuation was in the olanzapine group. In the total study sample, no significant differences were seen in the time to discontinuation between the ziprasidone and olanzapine treatment groups, or between the ziprasidone group and other antipsychotic treatment groups.

Several considerations in this complex study are worth mentioning. Very few patients who entered the CATIE schizophrenia study were currently (i.e., prior to study entry) taking the relatively newly available medication, ziprasidone, compared with the number of patients taking the other antipsychotic medications in the trial. This resulted in a larger proportion of patients assigned to the ziprasidone treatment arm who were just starting to take a new medication and discontinuing their prior treatment. For example, 23% of subjects randomly assigned to receive olanzapine treatment were already receiving olanzapine monotherapy as their ongoing treatment, requiring no medication discontinuation or new drug initiation. Supplemental analysis of phase 1 CATIE data by [Essock et al. \(2006\)](#) indicated the overall importance, in terms of subsequent discontinuation rates, of whether randomized subjects were switching medications or whether the study randomization allowed them to continue receiving their prior treatment. A significantly higher rate of subsequent discontinuation was observed in patients who actually made a medication switch compared with those who were randomly assigned to stay with the same medication they had been taking prior to the trial. This effect of switching medications therefore favored treatment arms with a larger percentage of “nonswitchers” (i.e., olanzapine and

risperidone recipients in the CATIE phase 1 study). In a reanalysis of phase 1 CATIE data that excluded those patients randomly assigned to continue taking the antipsychotic that they were already taking at baseline, [Essock et al. \(2006\)](#) found that differences between rates of discontinuation in the ziprasidone group and rates in the other antipsychotic groups were attenuated, and no statistically significant differences in the primary outcome measure were observed for any agent.

The Ziprasidone Experience in Schizophrenia in Germany/Austria (ZEISIG) study investigated the effectiveness of ziprasidone as measured by discontinuation rates and mean changes on the BPRS Total score in moderately ill and reasonably stable patients ( $N=276$ ) with schizophrenia or schizoaffective disorder ([Kudla et al. 2007](#)). Approximately 60% of subjects discontinued ziprasidone prematurely, most within the first 4 weeks of study treatment. Among study completers, ziprasidone was associated with significant improvements in BPRS total score. The relatively high rate of discontinuation may be explained in part by the planned dosing strategy. In this study, ziprasidone use was initiated at a low dosage of 40 mg/day, which is now known to be associated with higher discontinuation rates and shorter durations of therapy compared with higher dosages ([Joyce et al. 2006](#); [Mullins et al. 2006](#)). The maximal dosage allowed was 160 mg/day, which may be insufficient for some patients ([Harvey and Bowie 2005](#); [Nemeroff et al. 2005](#)).

[Arango et al. \(2007\)](#), of the Ziprasidone in Spain Study Group, examined the effectiveness of ziprasidone ( $N=1,022$  in the primary analysis sample) as measured by response rate (defined as a  $\geq 30\%$  reduction in the PANSS-Total score). Nearly half of the patients experienced the defined

level of clinical response, and patients overall had significant and clinically relevant mean reductions in both the PANSS-Total score and the Positive, Negative, and General Psychopathology subscale scores (effect sizes were 1.60, 1.83, 0.62, and 1.40, respectively). Compared with lower dosages, ziprasidone dosages greater than 120 mg/day were associated with a lower risk of discontinuation for any cause.

[Díaz-Marsá et al. \(2009\)](#) conducted a prospective, uncontrolled, naturalistic study to evaluate the effectiveness and tolerability of oral ziprasidone in psychiatric inpatients with an acute exacerbation of schizophrenia or schizoaffective disorder. Among the 196 patients enrolled, the mean dosage of ziprasidone at discharge was  $186.3 \pm 67.7$  mg/day. Progressive and statistically significant improvements in BPRS- and CGI-measured symptom severity were observed from the first week through discharge (after  $23.4 \pm 34.2$  days). Changes from baseline to study endpoint were deemed clinically relevant, with reported effect sizes greater than  $d=0.8$ , indicating that the results are of notable clinical—not just statistical—significance.

The European First Episode Schizophrenia Trial (EUFEST; [Kahn et al. 2008](#)) included 49 sites in Europe and Israel and assessed 498 first-episode patients ages 18–40 years who had experienced psychosis for less than 2 years, had been exposed to antipsychotic drugs for less than 2 weeks during the preceding year, and had less than 6 weeks of total lifetime exposure to antipsychotic drugs. Participants were randomly assigned to receive haloperidol (which served as the FGA comparator) 1–4 mg/day, amisulpride 200–800 mg/day, olanzapine 5–20 mg/day, quetiapine 200–750 mg/day, or ziprasidone 40–160 mg/day

and were followed up for 1 year. Analysis of all-cause treatment discontinuation revealed rates of 40% for haloperidol, 40% for amisulpride, 33% for olanzapine, 53% for quetiapine, and 45% for ziprasidone. Symptom reductions were similar in all groups (approximately 60%). In addition to efficacy considerations, tolerability differences—whether due to different pharmacological profiles or to patient preferences—should guide the clinician in choosing an appropriate first-line treatment.

## **Efficacy by Symptom Type**

**Efficacy for cognitive symptoms of schizophrenia.** The effect of ziprasidone on cognitive function in schizophrenia patients was evaluated by a battery of cognitive tests included in a double-blind olanzapine comparator study that evaluated changes at 6 weeks and 6 months ([Harvey et al. 2004, 2006a](#)). Antipsychotic treatment with ziprasidone and with olanzapine both resulted in significant cognitive improvements from baseline in attention memory, working memory, motor speed, and executive functions, with olanzapine also associated with improvement in verbal fluency. Further improvements in both treatment groups were observed from the end of 6 weeks to the 6-month assessment time point on verbal learning, executive functioning, and verbal fluency, with no differences between treatment groups. It should be noted that despite these improvements, a substantial proportion of patients studied continued to experience clinically significant cognitive impairment posttreatment. Neuropsychological improvements in general are not related to clinical changes ([Harvey et al. 2006b](#)).

Data from the CATIE schizophrenia study indicate that treatment with all of the antipsychotics tested (i.e., ziprasidone, perphenazine, olanzapine, risperidone, and quetiapine) was associated with a small but significant improvement in cognition after 2 months of treatment, with no significant difference between ziprasidone and the other antipsychotics ([Keefe et al. 2007](#)). Cognitive improvement predicted a longer time to treatment discontinuation, independent of symptom improvement, in patients treated with quetiapine or ziprasidone.

**Efficacy for affective symptoms.** Ziprasidone has been hypothesized to be a promising treatment for mood disorders, based on its unique in vitro potency as a serotonin and norepinephrine reuptake inhibitor comparable to that of known antidepressants (see “Neuropharmacology and Receptor-Binding Profile” section earlier in this chapter). Addressing the question of ziprasidone’s potential antidepressant efficacy in schizophrenia patients with comorbid affective symptoms, data can be examined from randomized, double-blind, placebo-controlled clinical trials ([Daniel et al. 1999](#); [Keck et al. 1998, 2001](#)) and from double-blind head-to-head trials comparing ziprasidone with risperidone or olanzapine ([Kane 2003b](#)). The results of placebo-controlled studies ([Daniel et al. 1999](#); [Keck et al. 1998](#)) suggest that treatment of schizophrenia and schizoaffective disorder with ziprasidone is associated with significant improvement in comorbid depressive symptoms, based on intent-to-treat analyses, but sometimes only in the subset of patients with higher levels of baseline depression. The baseline severity of depressive symptoms in these studies tends to be relatively mild, so subgroups of patients with more

pronounced comorbid depressive symptoms at baseline were also analyzed; the antidepressant effect of ziprasidone was larger than that of placebo in these analyses. In the two active-comparator studies, improvement in depression and anxiety symptoms in patients receiving ziprasidone was comparable to the improvement in olanzapine recipients but greater than the improvement in risperidone recipients. A smaller study ([Kinon et al. 2006](#)) compared the efficacy of olanzapine and ziprasidone over 24 weeks in the treatment of schizophrenia or schizoaffective disorder patients with prominent depressive symptoms. Both treatment groups had significant improvements in depressive symptoms for the first 8 weeks, with olanzapine-treated patients showing significantly greater improvements in depressive symptoms at study endpoint. However, interpretation of the findings from this study is limited by that fact that a substantial number of patients (52.8% of  $N=394$  at study entry) received concurrent treatment with nonstandardized antidepressants. These overall results provide preliminary evidence suggesting that ziprasidone, like some other antipsychotic agents, may be effective in treating comorbid depressive symptoms in patients with schizophrenia and schizoaffective disorder.

**Efficacy for social deficits and improvement in quality of life.** The NIMH CATIE study is the largest trial to date to have examined the effect of ziprasidone and other antipsychotics on psychosocial functioning in patients with schizophrenia ([Swartz et al. 2007](#)). This study employed the Quality of Life Scale, a widely used clinician-rated measurement ([Heinrichs et al. 1984](#)), to assess changes in social functioning, interpersonal relationships, vocational functioning, and psychological well-being. One-



third of the patients in the phase 1 study antipsychotic treatment groups made modest improvements on the Quality of Life Scale from baseline to the 12-month endpoint (average effect size, 0.19 standard deviation units), with no significant differences between the agents.

The effect of ziprasidone on social functioning has also been evaluated using the Prosocial subscale of the PANSS, including items related to active and passive social avoidance, emotional withdrawal, stereotypical thinking, and suspiciousness ([Purnine et al. 2000](#)). In three separate but related studies from one group, stable patients taking FGAs, olanzapine, or risperidone were switched to ziprasidone and followed for 6 weeks with ratings of safety, efficacy, and effectiveness ([Weiden et al. 2003b](#)). Six weeks of treatment with ziprasidone in all three prior-treatment groups resulted in significant improvement on the PANSS Prosocial subscale ([Loebel et al. 2004](#)). The interpretation of results as being specific to ziprasidone use, rather than being simply an effect of extended, closely monitored treatment, is complicated by the absence of a control other than pretreatment baseline ratings.

[Harvey et al. \(2009\)](#) examined quality-of-life changes in community-dwelling patients with schizophrenia randomly assigned to receive either haloperidol ( $n=47$ ) or ziprasidone ( $n=139$ ) over a follow-up interval of up to 196 weeks. Long-term treatment with ziprasidone was associated with greater functional gains than treatment with haloperidol. Both treatment retention and functional gains favored ziprasidone in this long-term study, suggesting superior efficacy and tolerability, which may reflect back favorably on adherence rates. Post hoc analysis revealed the most significant quality-of-life improvements in the high-dosage ziprasidone group (80–160 mg/day) ([Stahl](#)



[et al. 2010b](#)), concordant with recent recommendations that higher dosages of ziprasidone may be more effective than lower dosages.

## **Treatment-Resistant Schizophrenia**

Several studies have evaluated ziprasidone use in refractory schizophrenia, albeit using different criteria for “refractory.” A 12-week double-blind comparison of ziprasidone and chlorpromazine ( $N=306$  patients) defined treatment-resistant status as inability to achieve criterion-level response after 6 weeks of prospective treatment with haloperidol ([Kane et al. 2006](#)). The mean daily dose of ziprasidone at study endpoint was approximately 154 mg, compared with a mean daily chlorpromazine dose of approximately 744 mg. Treatment with ziprasidone produced significantly greater improvement at endpoint in PANSS–Negative subscale scores compared with chlorpromazine. In addition, ziprasidone treatment was associated with a 1.3-fold higher likelihood of achieving a 50% reduction in BPRS total score compared with chlorpromazine treatment. The Monitoring Oral Ziprasidone As Rescue Therapy (MOZART) study in antipsychotic-resistant/intolerant patients ([Sacchetti et al. 2009](#)), an 18-week randomized, flexible-dose, double-blind trial, evaluated ziprasidone as an alternative to clozapine in treatment-refractory schizophrenia. Patients had a history of nonresponse and/or intolerance to at least three acute cycles of different antipsychotic medications given at therapeutic doses, with persistent PANSS–Total scores of at least 80. Patients were randomly assigned to receive ziprasidone 80–160 mg/day or clozapine 250–600 mg/day. A progressive and significant reduction from baseline in PANSS–Total score was observed from day 11 in both study

arms, without between-drug differences and with similar rates of early discontinuation due to adverse events. Ziprasidone had a more tolerable metabolic profile in the short-term treatment.

A small amount of literature suggests that the addition of a second antipsychotic medication to clozapine in patients who do not respond to or cannot tolerate standard dosages of clozapine may provide additional benefits. In the context of safety concerns and increasing health care costs, there is currently limited empirical evidence for the efficacy and safety of such antipsychotic combinations ([Kreyenbuhl et al. 2007](#)). However, adjunctive treatment with ziprasidone or risperidone, for example, was found helpful in patients with refractory schizophrenia that was incompletely responsive to clozapine ([Zink et al. 2009](#)). Both adjunctive antipsychotics produced additional reductions on PANSS-Positive and -Negative symptom subscale scores after 6 weeks of treatment, and the intervention was well tolerated. Further investigations are needed before definitive recommendations can be made, and treatment resistance should be operationalized uniformly so as to facilitate comparative research.

## **Switching From Other Antipsychotics**

The efficacy of ziprasidone has been found to be comparable to that of other SGAs and FGAs during both acute and maintenance treatment of schizophrenia and schizoaffective disorder. Evidence also points to the safety—particularly the cardiometabolic safety—of ziprasidone compared with other antipsychotics (see “Side Effects and Toxicology” section later in this chapter). These results support interest in switching from antipsychotic treatment with other agents to treatment with ziprasidone.

Several open-label medication-switching studies evaluated strategies for switching from other antipsychotics to ziprasidone on measures of efficacy, safety, and tolerability, including the effect of different titration schedules on the outcome ([Weiden et al. 2003b](#)). In each study, patients were randomly assigned to one of three switching strategies to be completed in 1 week: 1) immediately discontinuing the previous antipsychotic and immediately starting ziprasidone the next day; 2) lowering the dose of the previous antipsychotic by half while simultaneously starting ziprasidone; or 3) overlapping the start of ziprasidone with the full dosage of the prior antipsychotic and then gradually reducing the prior antipsychotic dosage after 4 days of ziprasidone therapy.

For these switching strategies, the starting dosage of ziprasidone was 80 mg/day (40 mg twice daily), with subsequent dosage adjustments based on clinical judgment. In one study, patients taking high-potency FGAs such as haloperidol ( $N=108$ ) were switched to ziprasidone. In the second study, patients ( $N=58$ ) were switched from risperidone to ziprasidone. In the third study, patients ( $N=104$ ) were switched from olanzapine to ziprasidone. Discontinuation rates were low in all three studies, ranging from 2%–6% for lack of efficacy to 6%–9% for adverse events. Among study completers, statistically significant improvements were observed in PANSS-Total, PANSS-Positive, and PANSS-Negative subscale scores and BPRS total scores. Different switching strategies were not associated with a different likelihood of trial completion or different magnitude of clinical response.

[Rossi et al. \(2011\)](#) examined pooled data from 10 previously completed “switch” studies involving a total of 1,395 patients who were switched to ziprasidone. Switching

from FGAs or other SGAs generally resulted in maintenance or improvement of efficacy across all studied symptom domains, including improvements in tolerability and acute and long-term benefits regarding cardiometabolic parameters. The recommended titration schedule was a “plateau cross-titration strategy,” which the authors described as rapid uptitration of ziprasidone to a dosage range of 60–80 mg administered twice daily with food. To facilitate the crossover and minimize patient discomfort, temporary coadministration of benzodiazepines, anticholinergics, or beta-blockers was recommended for management of potential rebound effects due to differences in pharmacological profiles of the pre-switch medications and ziprasidone.

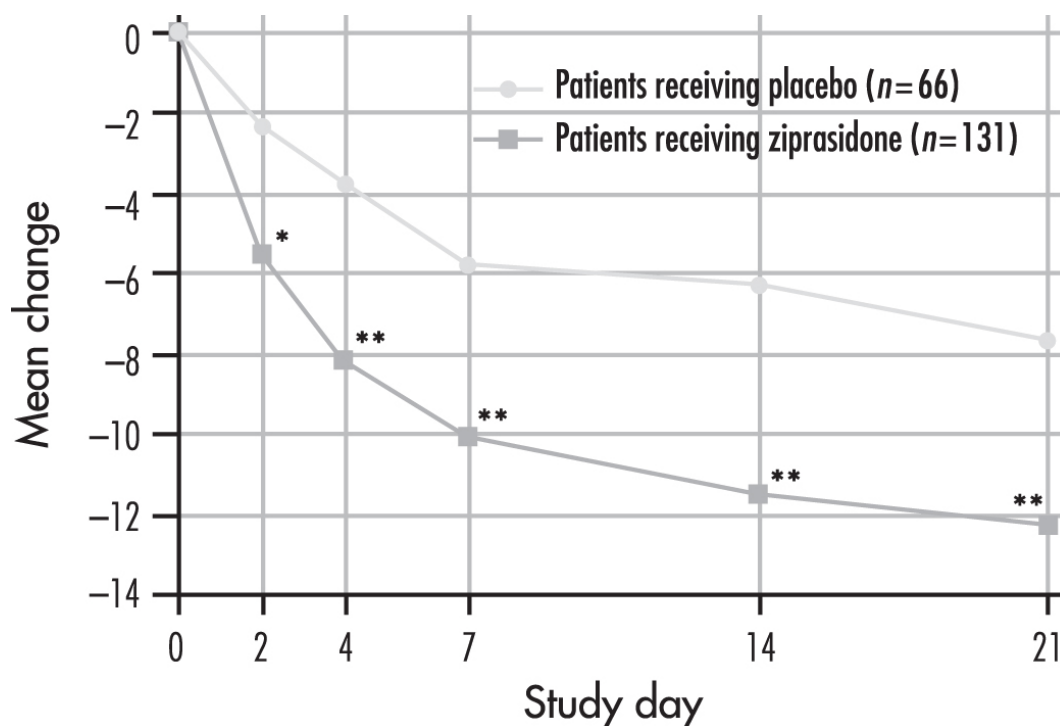
The balance of the evidence from studies examining strategies for switching to ziprasidone favors rapid uptitration of ziprasidone to a comparatively higher dosage (up to 160 mg/day) combined with rapid discontinuation of the previous agent, including management of specific rebound effects combined with close clinical monitoring during the switch. Predictable changes in tolerability (e.g., weight loss when switched from olanzapine, reduction in EPS when switched from haloperidol) are observed along with maintenance of efficacy.

## Bipolar Disorder

### **Acute Mania**

Ziprasidone has received regulatory approval (e.g., by the FDA) for the acute treatment of bipolar mania, with efficacy for acute mania demonstrated in two double-blind, placebo-controlled trials, each 3 weeks in duration, in patients with

bipolar I disorder (Keck et al. 2003b; Potkin et al. 2005). In both studies, onset of action was rapid (within 48 hours) and sustained through 3 weeks of treatment in patients with bipolar mania or bipolar mixed states, with or without psychotic symptoms. (The results of the study by Keck et al. [2003b] are shown in Figure 30-3.) At endpoint, approximately half of the treated patients from both studies met response criteria for mania ( $\geq 50\%$  reduction in Mania Rating Scale [MRS] scores).



**FIGURE 30-3.** Effect of ziprasidone on mania: rating scale scores in patients with bipolar disorder receiving 21-day randomized treatment with ziprasidone or placebo.

\* $P < 0.003$  (F test), placebo-treated patients versus ziprasidone-treated patients.

\*\* $P < 0.001$  (F test), placebo-treated patients and ziprasidone-treated patients.

*Source.* Adapted from [Keck et al. 2003b](#).

A number of placebo-controlled trials evaluating the efficacy of short-term monotherapy with various antipsychotics, including haloperidol, ziprasidone, olanzapine, risperidone, quetiapine, and aripiprazole, have demonstrated comparable improvement in symptoms of mania ([Bowden et al. 2005](#); [Hirschfeld et al. 2004](#); [Keck et al. 2003a, 2003b](#); [Khanna et al. 2005](#); [McIntyre et al. 2005](#); [McQuade et al. 2003](#); [Potkin et al. 2005](#); [Sachs et al. 2006](#); [Smulevich et al. 2005](#); [Tohen et al. 1999, 2000](#); [Vieta et al. 2010](#); [Weisler et al. 2003](#)). Two large meta-analyses of randomized, placebo-controlled trials have examined the relative efficacy of various SGAs for the adjunctive treatment of mania ([Perlis et al. 2006](#); [Scherk et al. 2007](#)). Although the statistical results of the two meta-analyses are similar, the authors of each study interpreted the results somewhat differently. [Perlis et al. \(2006\)](#) concluded that add-on therapy with SGAs (ziprasidone, olanzapine, quetiapine, and risperidone) conferred an additional benefit over monotherapy with a traditional mood stabilizer in reducing manic symptoms, with no difference in efficacy among the drugs. [Scherk et al. \(2007\)](#) also concluded that SGAs as a group were significantly superior to placebo as adjunctive treatment for mania but that ziprasidone and other individual agents may not be significantly superior to placebo in the adjunctive treatment of manic symptoms. This conclusion is in contrast with results reported by [Vieta et al. \(2010\)](#) from a 12-week double-blind two-part study in 438 adults with bipolar-associated acute mania. In the first part, a 3-week period in which ziprasidone (80–160 mg/day) and placebo were compared with haloperidol (8–30 mg/day) as a reference standard, changes from baseline

MRS scores for ziprasidone and haloperidol were superior to those for placebo beginning with day 2 of treatment until week 3. At week 3, response rates were 36.9%, 54.7%, and 20.5%, respectively, for ziprasidone, haloperidol, and placebo. In the 9-week extension phase to examine tolerability, during which ziprasidone replaced placebo, improvements were maintained for 96.3% of patients receiving haloperidol and 88.1% of those receiving ziprasidone, with ziprasidone demonstrating superior tolerability.

Finally, regulatory approvals for the individual agents have supported the efficacy and safety of a number of individual antipsychotics for the acute treatment of mania, including ziprasidone (which is also approved for the acute treatment of mixed states). Prospective head-to-head comparator trials like that of [Vieta et al. \(2010\)](#) may further clarify whether differences in efficacy suggested by some meta-analyses are clinically informative or merely related to limitations in study design or methodology (e.g., underdosing of ziprasidone or dosing without food).

## **Bipolar Depression**

Preliminary results indicate that ziprasidone may be a viable treatment option in bipolar depression. For example, an 8-week open-label study investigating ziprasidone monotherapy for depressive symptoms in bipolar II patients ( $n=30$  completers) demonstrated effective attenuation of depression with a relatively low mean dosage of 58 mg/day ([Liebowitz et al. 2009](#)). The authors concluded that larger and controlled trials are required to confirm their findings.

## **Dysphoric Mania**

Dysphoric mania is a common and often difficult-to-treat subset of bipolar mania that is associated with significant depressive symptoms. Data from a post hoc analysis of two similarly designed 3-week placebo-controlled trials ([Stahl et al. 2010a](#)) in acute bipolar mania that were pooled and analyzed indicated that ziprasidone significantly improved both depressive and manic mood symptoms in patients with dysphoric mania. A meta-analysis by [Muralidharan et al. \(2013\)](#) suggested that SGAs, including ziprasidone, are effective for the treatment of mixed states of bipolar disorder with predominant manic symptoms. A number of trials could not be included because data for mixed episodes were not presented separately. Similar to the preliminary results obtained in bipolar depression, definitive conclusions await further prospective controlled trials.

## **Maintenance Treatment**

Two 52-week open-label extension studies support the safety, tolerability, and sustained efficacy of ziprasidone as maintenance treatment for bipolar disorder (P.E. [Keck et al. 2004, 2009](#); [Weisler et al. 2004](#)). P.E. [Keck et al. \(2004\)](#) reported that treatment with ziprasidone ( $n=127$ ; mean dosage, 123 mg/day) was associated with significantly lower MRS and CGI-S scores compared with baseline, beginning as early as the first week. Overall, improvements in manic symptoms achieved during acute treatment continued to consolidate during maintenance treatment with ziprasidone. During 52 weeks of treatment, only 6% of patients discontinued ziprasidone use because of relapse of mania. Similarly, only 4% of patients discontinued because of a clinical switch into depression. An important caveat regarding these results is the high rate of attrition



observed by the end of 1 year, which is consistent with long-term studies involving other SGAs but still limits the full interpretation of results. Comparable results were observed in a separate extension study of adjunctive ziprasidone therapy (mean dosage, 92.6 mg/day) by [Weisler et al. \(2004\)](#); this study reported a mean improvement from baseline in MRS scores at all points throughout the study ([Patel and Keck 2006](#)). Finally, subjects with DSM-IV bipolar I disorder achieving 8 or more consecutive weeks of stability with open-label ziprasidone (80–160 mg/day) and lithium or valproate were randomly assigned in a 6-month double-blind maintenance period to receive ziprasidone plus mood stabilizer or placebo plus mood stabilizer. The time to intervention for a mood episode and the time to discontinuation for any reason were significantly longer for ziprasidone compared with placebo ([Bowden et al. 2010](#)), indicating that ziprasidone may be useful in combination with a classic mood stabilizer for maintenance of euthymia in bipolar disorder.

## Treatment-Resistant Depression

A randomized, double-blind, placebo-controlled study, as well as a series of uncontrolled studies, has sparked interest in the efficacy of ziprasidone for depression, especially treatment-resistant depression ([Barbee et al. 2004](#); [Jarema 2007](#); [Papakostas et al. 2004, 2015](#)).

[Papakostas et al. \(2004\)](#) reported the results of a small study of 20 patients with major depression resistant to treatment with selective serotonin reuptake inhibitors (SSRIs). Open-label treatment with ziprasidone for 6 weeks, adjunctive to ongoing SSRI treatment, was evaluated with

an intent-to-treat analysis that identified 10 treatment responders (defined as having a  $\geq 50\%$  decrease in depressive symptoms as measured by the 17-item version of the Hamilton Rating Scale for Depression (Ham-D-17). In order to further evaluate these effects, a randomized, double-blind, placebo-controlled trial was conducted to compare adjunctive ziprasidone with adjunctive placebo among 139 adult outpatients with major depressive disorder (MDD) that had not responded to an 8-week open-label trial of escitalopram alone ([Papakostas et al. 2015](#)). Compared with the patients randomly assigned to receive adjunctive placebo, those assigned to receive adjunctive ziprasidone (mean dosage, 98 mg/day; SD=40) with escitalopram demonstrated significantly greater rates of clinical response as well as significantly greater improvement on the Ham-D-17 Total score and the Hamilton Rating Scale for Anxiety score. Ziprasidone has also been tested in non-treatment-resistant depression. A 12-week randomized, double-blind, placebo-controlled sequential parallel comparison trial of ziprasidone as monotherapy for MDD in 120 outpatients with depression conducted by [Papakostas et al. \(2012\)](#) showed no significant efficacy for ziprasidone compared with placebo. The authors suggested that a larger trial may be required to detect significant differences.

## Agitation

The efficacy of intramuscular ziprasidone for the treatment of agitated psychosis has been demonstrated in two randomized double-blind trials (2 mg intramuscular vs. 10 mg or 20 mg intramuscular, respectively, with up to three

more doses allowed as needed at 4-hour or 2-hour intervals, respectively), leading to regulatory approval by the FDA ([Daniel et al. 2001](#); [Lesem et al. 2001](#)). Treatment with single 10- or 20-mg doses leads to rapid reductions in symptom severity, with most patients having remission of agitation within 1 hour of dosing. Treatment with intramuscular ziprasidone is associated with a relatively low rate of concomitant benzodiazepine use (<20%) and may be better tolerated than haloperidol ([Zhang et al. 2013](#)). Sequential use of intramuscular ziprasidone followed by oral ziprasidone for the treatment of acute psychotic agitation has demonstrated superior efficacy, compared with sequential use of intramuscular and oral haloperidol, in two 7-day randomized open-label trials ([Brook et al. 2000](#); [Swift et al. 1998](#)) as well as in a 6-week randomized, single-blind, flexible-dose study ([Brook et al. 2005](#)). Clinical improvement occurred more rapidly than with haloperidol in one study and as quickly as 30 minutes after the first intramuscular administration of ziprasidone ([Swift et al. 1998](#)). Cumulative data from these studies indicate that intramuscular ziprasidone can rapidly control agitation and psychotic symptoms and provide greater mean improvements in acute agitation than seen with intramuscular haloperidol (e.g., greater mean improvements in BPRS total score, agitation, and CGI-S score) ([Brook 2003](#)).

## Pediatric Use

Ziprasidone is not approved in the United States by the FDA for use in pediatric patients. Its use has been evaluated in children and adolescents (ages 10–17 years)

experiencing manic or mixed episodes associated with bipolar disorder ([Kuehn 2009](#)). In the European Union it has been approved for the treatment of bipolar disorder (mania) in pediatric patients. Results from RCTs of ziprasidone in children and adolescents (ages 10–17 years) with bipolar disorder ([Versavel et al. 2005](#)) and with bipolar disorder, schizophrenia, or schizoaffective disorder ([DelBello et al. 2008](#)) have been reported. In the former study, treatment with ziprasidone was associated with improvement in mania and overall psychopathology ([Versavel et al. 2005](#)). The latter study focused on safety and did not report any unexpected tolerability findings in this age population, using a starting dosage of 20 mg/day titrated to between 80 and 160 mg/day over 1–2 weeks for clinically determined optimal dosing ([DelBello et al. 2008](#)). Finally, a 4-week acute randomized, placebo-controlled multicenter trial, followed by a 26-week open-label extension study, in pediatric patients with bipolar disorder (ages 10–17 years) showed benefits of ziprasidone and a benign short-term side-effect profile ([Findling et al. 2013a](#)). In pediatric schizophrenia, in a study using a 6-week randomized (2:1), double-blind, placebo-controlled design, ziprasidone did not separate from placebo ([Findling et al. 2013b](#)).

---

## Side Effects and Toxicology

---

### Tolerability Profile in Clinical Trials

Ziprasidone has a favorable tolerability profile based on both short- and long-term clinical trials ([Daniel 2003](#); [Pfizer](#)

[Inc. 2004](#)). The four most common treatment-related adverse events associated with oral ziprasidone in short-term premarketing placebo-controlled trials for schizophrenia were somnolence (14%), EPS (14%), nausea (10%), and constipation (9%) ([Pfizer Inc. 2008](#)). In subsequent clinical trials, treatment with ziprasidone was associated with a low occurrence of adverse events, most of which were considered mild to moderate in severity ([Arango et al. 2007](#); [Arato et al. 2002](#); [Lieberman 2007](#); [Nemeroff et al. 2005](#); [Weiden et al. 2002, 2003b](#)). In addition to the comprehensive listing of potential adverse events available in the full U.S. prescribing information (USPI) ([Pfizer Inc. 2008](#)), published case reports offer accounts of various rare adverse events that may be associated with the use of ziprasidone ([Akkaya et al. 2006](#); [Kaufman et al. 2006](#); [Miodownik et al. 2005](#); [Murty et al. 2002](#); [Villanueva et al. 2006](#)).

Intramuscular ziprasidone shows a favorable tolerability profile similar to that of oral ziprasidone. In premarketing trials of intramuscular ziprasidone, the most common side effects (those with an incidence of >5% and an incidence greater than that seen in placebo recipients) were somnolence (20%), headache (13%), and nausea (12%) ([Pfizer Inc. 2008](#)). Pooled data from clinical trials of intramuscular ziprasidone indicate that most treatment-related adverse events were mild to moderate in severity, with the most common side effects being headache, nausea, dizziness, insomnia, anxiety, and pain at the injection site ([Daniel 2003](#); [Zimbroff et al. 2002](#)).

## Safety in Pregnancy

Ziprasidone is considered a Category C drug in pregnancy. Although some specific developmental effects have been noted in animal studies at dosages ranging from 0.5 to 8.0 times the maximal recommended human dosage ([Pfizer Inc. 2008](#)), there are as yet no similar reports of such effects in humans. The reader is advised to consult the current USPI for a detailed listing of potential adverse drug effects identified in the regulatory approval process and postmarketing surveillance.

## Increased Mortality Risk in Elderly Patients With Dementia-Related Psychosis

In 2005, the FDA mandated the addition of a black box warning in the USPI regarding an increased risk of mortality associated with the use of both SGAs and FGAs in elderly patients with dementia-related psychosis. Observed causes of death have been varied, and the mechanism of any drug effect in schizophrenia remains uncertain ([Pfizer Inc. 2008](#)). In particular, it remains unclear to what extent these uncontrolled observations of increased mortality are due to specific drug effects or to the advanced medical risk characteristics of patients with dementia or delirium who tend to receive these medications ([Farber et al. 2000](#); [Rochon et al. 2008](#)). A recent retrospective cohort study among antipsychotic-exposed older adults did not find increased mortality associated with ziprasidone, in contrast with haloperidol, olanzapine, and risperidone ([Gerhard et al. 2014](#)).

Retrospective analysis of intramuscular use of ziprasidone, olanzapine, or haloperidol in large matched cohorts of hospitalized patients did not indicate significant differences in mortality rates among the three cohorts ([Holdridge et al. 2010](#)).

## Activation Effects

Clinical experience with ziprasidone in the years following initial U.S. approval has suggested that a small subgroup of patients may experience insomnia, or what has been characterized as *activation* or *akathisia*, soon after initiation of treatment ([Nemeroff et al. 2005](#)). These presentations have been described as transient manifestations of anxiety, restlessness, insomnia, increased energy, or hypomania-like symptoms, occurring most commonly at what is now considered the lower end of the dosage range. Anecdotal reports suggest that starting dosages of 120 mg/day or greater and more rapid dose titration can substantially reduce the incidence of these clinical presentations ([Weiden et al. 2002](#)). These anecdotal clinical observations are consistent with controlled experimental evidence indicating that a significantly lower rate of discontinuation occurs in patients who begin ziprasidone therapy at higher dosages (120–160 mg/day) than in patients who receive initial dosages of 80 mg/day or less ([Joyce et al. 2006](#)). Several mechanisms may explain these observations. First, ziprasidone is less intrinsically sedating than many other antipsychotics in current use (e.g., due to less H<sub>1</sub> receptor antagonism), so that patients initiating ziprasidone treatment after months or years of receiving a more sedating therapy may experience initial

difficulties adjusting to the new level of drug-related sedation. Second, as discussed earlier in this chapter (see “Pharmacological Profile” and “Indications and Efficacy” sections), many patients have been treated with ziprasidone at dosages that were insufficient to achieve optimal D<sub>2</sub> receptor blocking, leading to undertreatment of the underlying illness compared with what might have been achieved with an appropriately dosed prior therapy.

Furthermore, ziprasidone underdosing with respect to D<sub>2</sub> receptor binding can produce a well-understood but unwanted pharmacodynamic situation with respect to the differential balance of 5-HT<sub>2C</sub> receptor antagonism relative to D<sub>2</sub> receptor antagonism. As was illustrated in [Figure 30-2](#), use of ziprasidone dosages at the lower end of the clinical dosage range can allow 5-HT<sub>2</sub> receptors to reach 50% or greater maximal receptor occupancy well before clinically significant levels of D<sub>2</sub> receptor occupancy are achieved ([Mamo et al. 2004](#)). 5-HT<sub>2C</sub> receptor antagonist activity at this level disinhibits cortical monoaminergic neurotransmission (e.g., dopamine release), which, in the absence of sufficient D<sub>2</sub> receptor blockade, may lead to clinically relevant excess monoaminergic neurotransmission ([Bonaccorso et al. 2002](#); [Pozzi et al. 2002](#)). Clinicians commonly address these potential issues through appropriate dosing and through the transient targeted use of concomitant medication strategies (e.g., adjunctive benzodiazepine treatment) for relevant patients starting new treatment in the acute inpatient setting or for stable outpatients needing a smooth transition to new therapy.

## DRESS Syndrome



In 2014, the FDA issued a warning that ziprasidone is one of more than 50 medications associated with a rare condition called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. This potentially life-threatening hypersensitivity reaction presents as a skin rash with fever, eosinophilia, lymphadenopathy, and multiorgan inflammation. Patients who develop this constellation of symptoms during treatment with ziprasidone should be evaluated for possible DRESS syndrome, and if that syndrome is suspected, their medication should be discontinued ([Cacoub et al. 2011](#)).

## Extrapyramidal, Metabolic, and Cardiac Adverse Effects

### Extrapyramidal Side Effects

Short-term trials indicate that treatment with ziprasidone is associated with a larger incidence of EPS compared with treatment with placebo ([Pfizer Inc. 2008](#); [Potkin et al. 2005](#)). In contrast, data from a 52-week trial ([Arato et al. 2002](#)) indicate that the incidence of abnormal movement disorders during treatment with ziprasidone is comparable to the incidence during placebo treatment. Other long-term studies suggest a low (<6%) incidence of treatment-related EPS ([Arango et al. 2007](#); [Kudla et al. 2007](#)). Both active-comparator studies and medication-switching studies suggest that ziprasidone is associated with fewer EPS than risperidone ([Addington et al. 2003, 2009](#); [Weiden et al. 2003a, 2003b](#)) or FGAs ([Hirsch et al. 2002](#); [Weiden et al. 2003a, 2003b](#)). A direct comparison study of ziprasidone and olanzapine, a drug with intrinsic antimuscarinic activity

as well as 5-HT<sub>2</sub> receptor antagonist activity, reported that treatment with olanzapine was associated with fewer EPS ([Kinon et al. 2006](#)), whereas two other direct comparison studies ([Breier et al. 2005](#); [Simpson et al. 2002](#)) and one medication-switching study ([Weiden et al. 2003b](#)) reported that the two drugs exhibited similar liability for EPS. With respect to akathisia, one comparison study indicated that less akathisia occurs with olanzapine use ([Breier et al. 2005](#)), whereas another study noted no difference in akathisia rates with olanzapine versus ziprasidone ([Kinon et al. 2006](#)). Results from phase 1 and phase 2 of the large-scale CATIE study suggested no significant differences among ziprasidone, perphenazine, olanzapine, quetiapine, and risperidone in the incidence of EPS and akathisia ([Lieberman 2007](#); [Lieberman et al. 2005](#); [Stroup et al. 2006](#)). However, the perphenazine arm in the CATIE study was restricted to patients who did not already have tardive dyskinesia, suggesting a possible selection bias toward patients less likely to experience EPS. Despite this advantage, the perphenazine group still had the highest rate of dropouts due to EPS. Investigating SGAs only, a recent meta-analysis ([Rummel-Kluge et al. 2012](#)) of 54 comparative clinical trials analyzed the use of antiparkinsonian medication as an indicator of treatment-related EPS. The authors reported that risperidone was associated with greater use of antiparkinsonian medication compared with clozapine, olanzapine, quetiapine, or ziprasidone. Ziprasidone was associated with more use of antiparkinsonian medication than olanzapine or quetiapine; however, the authors concluded that overall differences were small. EUFEST data ([Rybakowski et al. 2014](#)) suggest that in first-episode schizophrenia patients during the first year of antipsychotic treatment (including quetiapine), EPS

were present at low and manageable levels. More recently, SGAs in patients never exposed to FGAs have been examined for their tardive movement disorder liability ([Ryu et al. 2015](#)). Although the incidence of movement disorder symptoms was low, the authors found that the median interval between the first exposure to the antipsychotic and movement syndrome onset was 15 months for tardive dyskinesia and 43 months for tardive dystonia.

Intramuscular ziprasidone has been tolerated at dosages of up to 80 mg/day with a low liability for EPS ([Daniel 2003](#); [Daniel et al. 2001](#); [Lesem et al. 2001](#)). Both intramuscular ziprasidone use and sequential intramuscular/oral ziprasidone use are associated with a lower incidence of treatment-related movement disorders than intramuscular haloperidol use ([Swift et al. 1998](#); [Zimbroff et al. 2002](#)) and sequential intramuscular/oral haloperidol use ([Brook et al. 2000](#), [2005](#)). Although the results of controlled experimental studies indicate a generally low risk of EPS with ziprasidone, there have been uncontrolled observational reports of EPS-related adverse events co-occurring with ziprasidone treatment and, in many cases, concomitant treatment with other agents ([Dew and Hughes 2004](#); [Duggal 2007](#); [Keck et al. 2004](#); [Mason et al. 2005](#); [Papapetropoulos et al. 2005](#); [Ramos et al. 2003](#); [Rosenfield et al. 2007](#); [Weinstein et al. 2006](#); [Yumru et al. 2006](#); [Ziegenbein et al. 2003](#)).

## **Metabolic Adverse Effects**

Adverse medication effects on modifiable risk factors for cardiovascular disease and type 2 diabetes mellitus have become an important topic of clinical, research, and regulatory concern, based in part on the increased prevalence of these conditions and associated premature

mortality in patients with major mental disorders ([Brown 1997](#); [Brown et al. 2000](#); [Colton and Manderscheid 2006](#); [Harris and Barraclough 1998](#); [Hennekens et al. 2005](#); [Joukamaa et al. 2001](#); [Osby et al. 2000, 2001](#)). Modifiable cardiometabolic risk factors include obesity, hyperglycemia, dyslipidemia, hypertension, and smoking—all prevalent conditions in patients with major mental disorders, with substantial evidence that primary and secondary prevention approaches are underutilized in these patients ([Allison et al. 1999a](#); [Brown et al. 2000](#); [Druss and Rosenheck 1998](#); [Druss et al. 2000, 2001](#); [Frayne et al. 2005](#); [Hippisley-Cox et al. 2007](#); [McEvoy et al. 2005](#); [Nasrallah et al. 2006](#); [Newcomer and Hennekens 2007](#)). In particular, use of recommended monitoring of changes in weight and in plasma glucose and lipid levels during antipsychotic treatment has heightened interest in cardiometabolic risk effects that may go undetected during the course of treatment ([American Diabetes Association 2004](#); [Morrato et al. 2008](#)). All currently available antipsychotic medications are associated with a risk of weight gain, as well as potential adverse effects on plasma glucose and lipid levels, although there is substantial variability in the magnitude of these effects across individual agents ([Casey et al. 2004](#); [Eli Lilly 2008](#); [Newcomer 2005](#); [Schizophrenia.com 2007](#)). Potential adverse treatment effects on body weight can increase the risk for cardiovascular disease and type 2 diabetes, commonly via adiposity-related increases in insulin resistance, dyslipidemia, and hyperglycemia ([Fontaine et al. 2001](#); [Haupt et al. 2007](#); [Koro et al. 2002a, 2002b](#)).

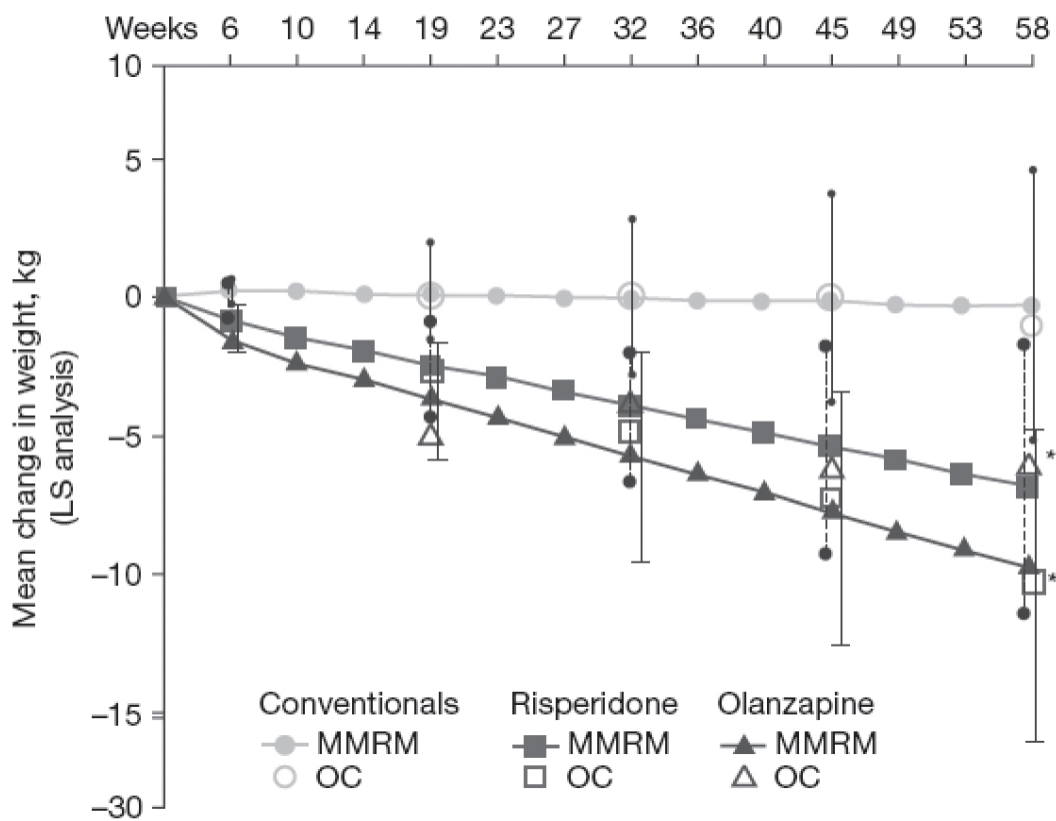
Treatment with ziprasidone is associated with a relatively low risk of clinically significant increases in body weight. An analysis of available studies with this agent and other

antipsychotics, both FGAs and SGAs ([Allison et al. 1999b](#)), estimated a mean 0.04-kg weight gain over a 10-week treatment period with ziprasidone, identifying ziprasidone as having one of the lowest estimated effects on body weight of those analyzed. In a 6-week RCT in patients with acute exacerbations of schizophrenia or schizoaffective disorder, treatment with ziprasidone 80 mg/day produced a median increase in body weight of 1 kg, compared with no change in median weight with ziprasidone 160 mg/day or placebo ([Daniel et al. 1999](#)). In a 28-week study of outpatients with schizophrenia, mean changes in body weight from baseline to endpoint were similar during treatment with ziprasidone (+0.31 kg) and haloperidol (+0.22 kg) ([Hirsch et al. 2002](#)). In a 28-week study comparing the effects of ziprasidone and olanzapine, ziprasidone-treated patients experienced a small decrease in mean body weight (−1.12 kg) compared with a statistically and clinically different 3.06-kg mean increase in body weight observed with olanzapine treatment ([Hardy et al. 2003](#); [Kinon et al. 2006](#)). Reductions in body weight were also associated with ziprasidone treatment in the 1-year ZEUS study of patients with chronic, stable schizophrenia ([Arato et al. 2002](#)); this study reported mean decreases from baseline of 2.7 kg, 3.2 kg, and 2.9 kg with 40 mg/day, 80 mg/day, and 160 mg/day dosages of ziprasidone, respectively, compared with a 3.6-kg decrease observed with placebo treatment. Results from the phase 1 and phase 2 CATIE studies provide further confirmation that treatment with ziprasidone has a low intrinsic risk for producing clinically significant weight gain, with 6%–7% of ziprasidone recipients demonstrating a 7% or greater increase from baseline body weight compared with, for example, 27%–30% of olanzapine recipients ([Lieberman](#)

2007; Stroup et al. 2006). In the phase 1 CATIE study, ziprasidone treatment was associated with a mean reduction in body weight of 0.14 kg (0.3 lb) per month of treatment, compared with a mean increase of 0.91, 0.23, and 0.18 kg per month (2.0, 0.5, and 0.4 lb per month, respectively) during treatment with olanzapine, quetiapine, and risperidone, respectively, the other SGAs tested (Lieberman et al. 2005). A recent meta-analysis of pooled data from nine placebo-controlled RCTs suggested no significant differences in weight gain between patients treated with ziprasidone versus those receiving placebo (Gao et al. 2013).

It is important to note that initial courses of treatment can clearly be associated with greater weight gain than subsequent courses of treatment (McEvoy et al. 2007). In addition, chronically treated patients switching treatment from a medication with greater weight gain liability to a medication with less weight gain liability are likely to lose body weight in relation to that medication change, an effect that likely underlies the mean reductions in weight noted in some of the trials with ziprasidone discussed above. The magnitude of change in body weight during treatment with ziprasidone varies as a function of the weight gain liability of the prior treatment: the greatest potential for weight loss is associated with switching from previous treatments with the greatest weight gain liability (Weiden et al. 2008). For example, 6 weeks of ziprasidone therapy was associated with statistically significant decreases in mean body weight from baseline in patients switched from olanzapine (−1.8 kg) and from risperidone (−0.9 kg), whereas patients switched from high-potency FGAs such as haloperidol experienced a small increase in weight (+0.3 kg) (Weiden et al. 2008). The 1-year extension of this medication-

switching study indicated that weight loss was progressive and persistent throughout the 1-year period for patients who switched from olanzapine (−9.8 kg, or 10.3% of baseline body weight) and from risperidone (−6.9 kg, or 7.8% of baseline) (Figure 30-4; Weiden et al. 2008). Another study found significant decreases in weight in patients treated for 6 months with ziprasidone who were switched from olanzapine (−7.0 kg) and from risperidone (−2.2 kg) (Montes et al. 2007).



**FIGURE 30-4.** Time course of weight change over 58 weeks after switching to ziprasidone.

Previous treatments were conventional antipsychotics (line with circles;  $n=71$ ), risperidone (line with squares;  $n=43$ ), or olanzapine (line with triangles;  $n=71$ ). Individual observed cases within each treatment group are also shown (circle=conventional agent:



baseline weight, 198 lbs [90 kg]; square=risperidone: baseline weight, 194.9 lbs [88.6 kg]; triangle=olanzapine: baseline weight, 210.3 lbs [95.6 kg]). LS=least-squares analysis; MMRM=mixed-model repeated-measures analysis; OC=observed case analysis.

\* $P < 0.01$  versus baseline (MMRM and OC).

*Source.* Adapted from [Weiden et al. 2008](#), Figure 1 (p. 988).

Ziprasidone's effects on plasma glucose and lipid levels are best understood as being a function of treatment-related changes in adiposity. Whereas some antipsychotics, such as clozapine and olanzapine, have been reported to produce adiposity-independent effects on insulin sensitivity and related changes in glucose and lipid metabolism, ziprasidone has demonstrated no similar adiposity-independent effects in this same experimental paradigm ([Houseknecht et al. 2007](#)). In general, increases in adiposity are associated with decreases in insulin sensitivity in individuals taking or not taking antipsychotic medications, with reduced insulin sensitivity leading to increased risk for hyperglycemia, dyslipidemia, and other adverse changes in cardiometabolic risk indicators ([Haupt et al. 2007](#); [Newcomer and Haupt 2006](#); [Strassnig et al. 2015](#)).

Both short- and long-term studies have shown minimal adverse effects of ziprasidone on glucose levels, plasma insulin levels, insulin resistance, or fasting and nonfasting lipid levels ([Daniel et al. 1999](#); [Glick et al. 2001](#); [Rettenbacher et al. 2006](#); [Simpson et al. 2004a, 2005](#)), in contrast to the degree of adverse effects detected with some active comparators. For example, olanzapine treatment can produce statistically significant increases in fasting glucose and insulin levels ([Glick et al. 2001](#); [Hardy et al. 2003](#); [Simpson et al. 2002, 2005](#)). In the CATIE phase 1 study, ziprasidone treatment was associated with minimal



drug exposure-adjusted mean increases in blood glucose ( $+2.9 \pm 3.4$  mg/dL) and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) ( $+0.11 \pm 0.09\%$ ) and decreases in plasma triglycerides ( $-16.5 \pm 12.2$  mg/dL) and total cholesterol ( $-8.2 \pm 3.2$  mg/dL) ([Lieberman 2007](#)). In the CATIE phase 2 study, ziprasidone-treated patients showed minimal drug exposure-adjusted mean increases in blood glucose ( $+0.8 \pm 5.6$  mg/dL) and HbA<sub>1c</sub> ( $+0.46 \pm 0.3\%$ ) and decreases in triglycerides ( $-3.5 \pm 20.9$  mg/dL) and total cholesterol ( $-10.7 \pm 5.1$  mg/dL) ([Stroup et al. 2006](#)).

Similar to the effect of prior treatment conditions on changes in weight during treatment with ziprasidone, improvements in plasma lipid levels observed during ziprasidone treatment in the CATIE study can best be understood as the effect of switching from a previous treatment that is associated with larger adverse effects on lipid metabolism to a treatment with minimal adverse effects. [Weiden et al. \(2003a\)](#) noted that ziprasidone treatment was associated with significant decreases from baseline in both median nonfasting triglyceride levels and median nonfasting total cholesterol levels at the end of the 6-week treatment period in patients whose prior medication was olanzapine or risperidone, with minimal change following prior treatment with high-potency FGAs like haloperidol. Notably, the reductions in lipids observed during this study occurred within the first 6 weeks of initiating treatment with ziprasidone, with substantial reductions in total cholesterol ( $>20$  mg/dL) and plasma triglycerides (78 mg/dL) in the patients previously treated with olanzapine. In the 12-month extension of this study, the reductions achieved in the initial weeks following the switch from prior treatment were sustained during continued treatment with ziprasidone ([Weiden et al. 2008](#)).

## Cardiac Effects and Risks

Some medications, including psychotropic medications, can increase the duration of the QTc interval (i.e., the QT interval corrected for heart rate). Basic research suggests plausible mechanisms by which an increase in the QTc interval could increase the risk of sudden cardiac death, and clinical investigations suggest that certain small subgroups of the general population may have an increased risk of sudden cardiac death—for example, those with a family history of congenital long-QT syndrome (>500 msec) and those who concomitantly use drugs that markedly increase the QTc interval (e.g., by >60 msec) via either pharmacokinetic or pharmacodynamic interactions ([Montanez et al. 2004](#)). These potential risks have understandably led to regulatory interest in drug effects on the QTc interval. It should be noted that epidemiological studies in the general population suggest that modest prolongations of the QTc interval are not a risk factor for cardiovascular mortality or sudden death, so any risk in the general population of modest QTc prolongations is likely to be small and difficult to detect reliably ([Montanez et al. 2004](#)). When considered alongside risks such as obesity, hypercholesterolemia, diabetes, hypertension, physical inactivity, or cigarette smoking, each with well-characterized effects in the general population, modest QTc prolongations do not represent a comparable risk factor for cardiovascular mortality or sudden death in the general population.

With this background, thioridazine, following decades of use, was required to add to its prescribing information a black box warning related to its QTc interval-prolonging effects. Other FGAs, including haloperidol, are also

associated with some risk of QTc interval prolongation (Gury et al. 2000; O'Brien et al. 1999). The rate of occurrence of torsades de pointes with FGAs has been estimated as "10–15 such events in 10,000 person-years of observation" (Glassman and Bigger 2001, p. 1774). Ziprasidone, in common with certain other antipsychotic agents, can induce orthostatic hypotension, particularly early in treatment exposure, which can lead to transient tachycardia, dizziness, or syncope (Swainston Harrison and Scott 2006). However, tachycardia has been observed to be infrequent and to be as common in patients treated with placebo as in those treated with ziprasidone (Swainston Harrison and Scott 2006). Tachycardia and syncope related to hypotension are to be distinguished from ventricular arrhythmias that in rare cases can occur in relation to QTc interval prolongation.

Ziprasidone treatment has been demonstrated to result in a modestly increased risk of QTc interval prolongation (Pfizer Inc. 2008). This QTc interval prolongation at  $C_{max}$  (mean increase, >15 msec) is 9–14 msec greater than that seen with risperidone, olanzapine, quetiapine, or haloperidol but approximately 14 msec less than that seen with thioridazine. Unlike the case with thioridazine, the modest effect of ziprasidone on the QTc interval is not worsened by the presence of commonly encountered inhibitors of drug metabolism. In clinical trials of ziprasidone monotherapy that reported QTc interval changes, in studies of high-dosage intramuscular administration (Miceli et al. 2010), and in case reports of ziprasidone overdose, there was no evidence of any significant clinical sequelae such as torsades de pointes or sudden death (Arato et al. 2002; Arbuck 2005; Daniel 2003; Gómez-Criado et al. 2005; Harrigan et al. 2004; Insa

Gómez and Gutiérrez Casares 2005; Levy et al. 2004; Lieberman 2007; Miceli et al. 2004; Montanez et al. 2004; Nemeroff et al. 2005; Tan et al. 2009; Taylor 2003; Weiden et al. 2002, 2003a). These findings are consistent with analyses of large population samples, which have failed to demonstrate any association between QTc interval duration and either cardiovascular or all-cause mortality (Goldberg et al. 1991).

The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) was a large (>18,000 participants) international randomized trial designed to examine the risks of nonsuicide mortality and hospitalization associated with ziprasidone's use in routine medical practice settings (Strom et al. 2011). The main objective of ZODIAC was to evaluate nonsuicide mortality in the year following treatment initiation, which limited the study's ability to provide data on drug efficacy. Nevertheless, findings did not show an elevated risk of nonsuicide mortality for ziprasidone relative to olanzapine, and the study excluded a relative risk larger than 1.39 with a high probability. A total of 205 deaths occurred in the overall study population (N=18,154). It should be noted that ZODIAC was not designed to measure electrocardiographic parameters or to examine the risk of rare cardiac events associated with lengthening of the QTc interval. A recent meta-analysis evaluating the cardiac safety of antipsychotics in pediatric patients (Jensen et al. 2015) found a mean increase in QTc interval of 8.74 ms with ziprasidone. Compared with placebo, none of the tested antipsychotics caused a significant increase in the incidence of QTc prolongation, although there was significant reporting bias. The authors concluded that individual risk factors need to be taken into

account when evaluating medication-related QTc interval changes.

Rare cases of torsades de pointes have been reported with a number of different medications, including ziprasidone, but the incidence of these events appears to be below the known prevalence of torsades de pointes in community-based population samples ([Heinrich et al. 2006](#)). The USPI suggests that clinicians should nonetheless be cognizant of this potential risk and be aware of circumstances that may increase the risk of torsades de pointes and/or sudden death in association with the use of any drugs that can prolong the QTc interval. Such circumstances include bradycardia, hypokalemia, or hypomagnesemia; concomitant use of other medications known to cause clinically significant QT prolongation (although an additive effect with ziprasidone has not been established); and presence of congenital long-QT syndrome. The USPI further states that ziprasidone should not be used in patients who have significant cardiovascular conditions, such as uncompensated heart failure or a cardiac arrhythmia, or in those who have had a recent acute myocardial infarction or persistent QTc interval measurements of greater than 500 msec, and the prudent clinician might consider employing the same caution with many other antipsychotic and psychotropic medications currently in use. A comprehensive review of the cardiac safety of antipsychotics ([Hasnain and Vieweg 2014](#)) reached a similar conclusion—that little evidence exists that antipsychotic drug-associated QTc interval prolongation is in itself sufficient to cause torsades de pointes in the absence of other factors that facilitate or attenuate progression of drug-associated QTc interval prolongation to torsades de pointes.

---

## Drug-Drug Interactions

---

A study of in vitro enzyme inhibition ([Pfizer Inc. 2008](#)) indicated that ziprasidone has very little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and is thus unlikely to interfere with the metabolism of other medications relying on these enzymes for clearance. In vivo studies indicated that ziprasidone has no effect on the pharmacokinetics of lithium, estrogen, progesterone, or dextromethorphan ([Pfizer Inc. 2008](#)). As noted earlier (in the “Metabolism and Elimination” subsection), less than one-third of ziprasidone clearance is mediated by CYP-catalyzed oxidation, and because of this, one would not anticipate a substantial change in ziprasidone AUC during coadministration with CYP3A4 inhibitors or inducers. Aldehyde oxidase-mediated reduction constitutes the primary metabolic pathway for ziprasidone. As also noted above, currently no clinically significant pharmacological inhibitors of aldehyde oxidase are commonly encountered ([Obach et al. 2004](#)).

Consistent with this prediction, coadministration of ziprasidone with ketoconazole, a potent CYP3A4 inhibitor, results in only a modest increase in ziprasidone AUC (33%) and  $C_{\max}$  (34%) ([Miceli et al. 2000b](#)), whereas coadministration with carbamazepine, an inducer of 3A4, results in modest reductions in ziprasidone AUC (44%) and  $C_{\max}$  (39%) ([Miceli et al. 2000a](#)). Coadministration with CYP2D6 inhibitors has no effect on ziprasidone plasma levels. Coadministration of ziprasidone with lithium results in no significant change in steady-state lithium levels ([Apseloff et al. 2000](#)), and commonly used antacids and

cimetidine do not significantly alter ziprasidone pharmacokinetics ([Pfizer Inc. 2008](#)).

---

## Conclusion

---

Ziprasidone was the fourth atypical antipsychotic following clozapine to become available in the United States. This agent has a unique pharmacological profile, with the highest 5-HT<sub>2A</sub>/D<sub>2</sub> affinity ratio among currently available agents, potent serotonin and norepinephrine reuptake inhibition activity, agonist activity at 5-HT<sub>1A</sub> receptors, and clinically relevant antagonist activity at various 5-HT<sub>2</sub> receptor subtypes. Ziprasidone has demonstrated rapid-onset and sustained efficacy for the treatment of schizophrenia, schizoaffective disorder, and bipolar mania, with promising evidence of favorable mood, cognitive, and prosocial effects. It is also available in an intramuscular formulation for the treatment of acute agitated psychoses, and it was approved for the use of bipolar mania in children and adolescents 10–17 years of age.

Ziprasidone has highly favorable safety and tolerability profiles with limited potential for drug–drug and drug–disease interactions—critical issues for a patient population that generally has a high burden of medical comorbidity and is commonly exposed to complex polypharmacy. The adverse-effect profile of ziprasidone is particularly noteworthy in areas that are key to safety and tolerability in patients with major mental disorders such as schizophrenia and bipolar disorder, including low drug-related risk for acute EPS and minimal effects on cardiometabolic risk factors such as obesity and dyslipidemia.

---

# References

---

- Addington D, Pantelis C, Dineen M, et al: Ziprasidone vs risperidone in schizophrenia: 52 weeks' comparison. Poster presented at the annual meeting of the American Psychiatric Association, San Francisco, CA, May 17-22, 2003
- Addington DE, Pantelis C, Dineen M, et al: Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry* 65(12):1624-1633, 2004 15641867
- Addington DE, Labelle A, Kulkarni J, et al: A comparison of ziprasidone and risperidone in the long-term treatment of schizophrenia: a 44-week, double-blind, continuation study. *Can J Psychiatry* 54(1):46-54, 2009 19175979
- Akkaya C, Sarandol A, Sivrioglu EY, et al: A patient using ziprasidone with polydipsia, seizure, hyponatremia and rhabdomyolysis. *Prog Neuropsychopharmacol Biol Psychiatry* 30(8):1535-1538, 2006 16820256
- Allison DB, Fontaine KR, Heo M, et al: The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry* 60(4):215-220, 1999a 10221280
- Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156(11):1686-1696, 1999b 10553730
- Altar CA, Wasley AM, Neale RF, et al: Typical and atypical antipsychotic occupancy of D2 and S2 receptors: an autoradiographic analysis in rat brain. *Brain Res Bull* 16(4):517-525, 1986 2872945
- American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the



Study of Obesity: Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 27(2):596-601, 2004 14747245

Andreasen NC, Carpenter WT Jr, Kane JM, et al: Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry* 162(3):441-449, 2005 15741458

Apseloff G, Mullet D, Wilner KD, et al: The effects of ziprasidone on steady-state lithium levels and renal clearance of lithium. *Br J Clin Pharmacol* 49 (suppl 1): 61S-64S, 2000 10771456

Arango C, Kirkpatrick B, Koenig J: At issue: stress, hippocampal neuronal turnover, and neuropsychiatric disorders. *Schizophr Bull* 27(3):477-480, 2001 11596848

Arango C, Gómez-Beneyto M, Brenlla J, et al; ZIS Study Group: A 6-month prospective, observational, naturalistic, uncontrolled study to evaluate the effectiveness and tolerability of oral ziprasidone in patients with schizophrenia. *Eur Neuropsychopharmacol* 17(6-7):456-463, 2007 17234389

Arato M, O'Connor R, Meltzer HY; ZEUS Study Group: A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol* 17(5):207-215, 2002 12177583

Arbuck DM: 12,800-mg ziprasidone overdose without significant ECG changes. *Gen Hosp Psychiatry* 27(3):222-223, 2005 15882771

Bagnall AM, Jones L, Ginnelly L, et al: A systematic review of atypical antipsychotic drugs in schizophrenia. *Health Technol Assess* 7(13):1-193, 2003 12925268

Barbee JG, Conrad EJ, Jamhour NJ: The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major

- depressive disorder. *J Clin Psychiatry* 65(7):975-981, 2004 15291687
- Beedham C, Miceli JJ, Obach RS: Ziprasidone metabolism, aldehyde oxidase, and clinical implications. *J Clin Psychopharmacol* 23(3):229-232, 2003 12826984
- Bonaccorso S, Meltzer HY, Li Z, et al: SR46349-B, a 5-HT(2A/2C) receptor antagonist, potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens. *Neuropsychopharmacology* 27(3): 430-441, 2002 12225700
- Bowden CL, Grunze H, Mullen J, et al: A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 66(1):111-121, 2005 15669897
- Bowden CL, Vieta E, Ice KS, et al: Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 71(2):130-137, 2010 20122373
- Breier A, Berg PH, Thakore JH, et al: Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *Am J Psychiatry* 162(10): 1879-1887, 2005 16199834
- Bremner JD, Vythilingam M, Ng CK, et al: Regional brain metabolic correlates of alpha-methylparatyrosine-induced depressive symptoms: implications for the neural circuitry of depression. *JAMA* 289(23):3125-3134, 2003 12813118
- Briley M, Moret C: Neurobiological mechanisms involved in antidepressant therapies. *Clin Neuropharmacol* 16(5):387-400, 1993 8221701
- Brook S: Intramuscular ziprasidone: moving beyond the conventional in the treatment of acute agitation in schizophrenia. *J Clin Psychiatry* 64 (suppl 19):13-18, 2003 14728085

- Brook S, Lucey JV, Gunn KP; Ziprasidone I.M. Study Group: Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 61(12):933-941, 2000 11206599
- Brook S, Walden J, Benattia I, et al: Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology (Berl)* 178(4):514-523, 2005 15650846
- Brown S: Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 171:502-508, 1997 9519087
- Brown S, Inskip H, Barraclough B: Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 177:212-217, 2000 11040880
- Bymaster FP, Katner JS, Nelson DL, et al: Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 27(5):699-711, 2002 12431845
- Cacoub P, Muzette P, Descamps V, et al: The DRESS syndrome: a literature review. *Am J Med* 124(7):588-597, 2011 21592453
- Casey DE, Haupt DW, Newcomer JW, et al: Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry* 65 (suppl 7):4-18, quiz 19-20, 2004 15151456
- Citrome L: Using oral ziprasidone effectively: the food effect and dose-response. *Adv Ther* 26(8):739-748, 2009 19669631
- Citrome L, Jaffe A, Levine J: How dosing of ziprasidone in a state hospital system differs from product labeling. *J Clin Psychiatry* 70(7):975-982, 2009a 19653974

- Citrome L, Reist C, Palmer L, et al: Impact of real-world ziprasidone dosing on treatment discontinuation rates in patients with schizophrenia or bipolar disorder. *Schizophr Res* 115(2-3):115-120, 2009b 19864113
- Citrome L, Yang R, Glue P, et al: Effect of ziprasidone dose on all-cause discontinuation rates in acute schizophrenia and schizoaffective disorder: a post-hoc analysis of 4 fixed-dose randomized clinical trials. *Schizophr Res* 111(1-3):39-45, 2009c 19375893
- Colton CW, Manderscheid RW: Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* 3(2):A42, 2006 16539783
- Crespo-Facorro B, Ortiz-García de la Foz V, Mata I, et al: Aripiprazole, Ziprasidone and Quetiapine in the treatment of first-episode nonaffective psychosis: a 12-week randomized, flexible-dose, open-label trial. *Schizophr Res* 147(2-3):375-382, 2013 23643328
- Crespo-Facorro B, de la Foz VO, Mata I, et al: Treatment of first-episode non-affective psychosis: a randomized comparison of aripiprazole, quetiapine and ziprasidone over 1 year. *Psychopharmacology (Berl)* 231(2):357-366, 2014 23958945
- Daniel DG: Tolerability of ziprasidone: an expanding perspective. *J Clin Psychiatry* 64 (suppl 19):40-49, 2003 14728089
- Daniel DG, Zimbroff DL, Potkin SG, et al; Ziprasidone Study Group: Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology* 20(5):491-505, 1999 10192829
- Daniel DG, Potkin SG, Reeves KR, et al: Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind,

- randomized trial. *Psychopharmacology* (Berl) 155(2):128-134, 2001 11401000
- Davis JM, Chen N, Glick ID: A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 60(6): 553-564, 2003 12796218
- DelBello MP, Versavel M, Ice K, et al: Tolerability of oral ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. *J Child Adolesc Psychopharmacol* 18(5):491-499, 2008 18928413
- DeLeon A, Patel NC, Crismon ML: Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin Ther* 26(5):649-666, 2004 15220010
- Dew RE, Hughes D: Acute dystonic reaction with moderate-dose ziprasidone. *J Clin Psychopharmacol* 24(5):563-564, 2004 15349021
- Díaz-Marsá M, Sánchez S, Rico-Villademoros F; ZIP-IIG-79 Study Group: Effectiveness and tolerability of oral ziprasidone in psychiatric inpatients with an acute exacerbation of schizophrenia or schizoaffective disorder: a multicenter, prospective, and naturalistic study. *J Clin Psychiatry* 70(4):509-517, 2009 19358789
- Díaz-Mataix L, Scorza MC, Bortolozzi A, et al: Involvement of 5-HT<sub>1A</sub> receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. *J Neurosci* 25(47):10831-10843, 2005 16306396
- Druss BG, Rosenheck RA: Mental disorders and access to medical care in the United States. *Am J Psychiatry* 155(12):1775-1777, 1998 9842793
- Druss BG, Bradford DW, Rosenheck RA, et al: Mental disorders and use of cardiovascular procedures after myocardial infarction. *JAMA* 283(4):506-511, 2000 10659877

- Druss BG, Bradford WD, Rosenheck RA, et al: Quality of medical care and excess mortality in older patients with mental disorders. *Arch Gen Psychiatry* 58(6):565-572, 2001 11386985
- Duggal HS: Ziprasidone-induced acute laryngeal dystonia. *Prog Neuropsychopharmacol Biol Psychiatry* 31(4):970; author reply 971, 2007 17343967
- Duman RS: Depression: a case of neuronal life and death? *Biol Psychiatry* 56(3):140-145, 2004 15271581
- Dwyer DS, Pinkofsky HB, Liu Y, et al: Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC12 cells. *Prog Neuropsychopharmacol Biol Psychiatry* 23(1):69-80, 1999 10368857
- Eli Lilly: Zyprexa (olanzapine tablets), Zyprexa (intramuscular olanzapine for injection), and Zyprexa Zydis (olanzapine orally disintegrating tablets), full prescribing information. August 2008. Available at: <http://pi.lilly.com/us/zyprexa-pi.pdf>. Accessed May 11, 2016.
- Essock SM, Covell NH, Davis SM, et al: Effectiveness of switching antipsychotic medications. *Am J Psychiatry* 163(12):2090-2095, 2006 17151159
- Everson G, Lasseter KC, Anderson KE, et al: The pharmacokinetics of ziprasidone in subjects with normal and impaired hepatic function. *Br J Clin Pharmacol* 49 (suppl 1):21S-26S, 2000 10771450
- Farber NB, Rubin EH, Newcomer JW, et al: Increased neocortical neurofibrillary tangle density in subjects with Alzheimer disease and psychosis. *Arch Gen Psychiatry* 57(12):1165-1173, 2000 11115331
- Findling RL, Cavus I, Pappadopulos E, et al: Efficacy, long-term safety, and tolerability of ziprasidone in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 23(8):545-557, 2013a 24111980
- Findling RL, Cavus I, Pappadopulos E, et al: Ziprasidone in adolescents with schizophrenia: results from a placebo-

controlled efficacy and long-term open-extension study. *J Child Adolesc Psychopharmacol* 23(8):531-544, 2013b 24111983

Fontaine KR, Heo M, Harrigan EP, et al: Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. *Psychiatry Res* 101(3):277-288, 2001 11311931

Frayne SM, Halanych JH, Miller DR, et al: Disparities in diabetes care: impact of mental illness. *Arch Intern Med* 165(22):2631-2638, 2005 16344421

Gandelman K, Alderman JA, Glue P, et al: The impact of calories and fat content of meals on oral ziprasidone absorption: a randomized, open-label, crossover trial. *J Clin Psychiatry* 70(1):58-62, 2009 19026256

Gao K, Pappadopulos E, Karayal ON, et al: Risk for adverse events and discontinuation due to adverse events of ziprasidone monotherapy relative to placebo in the acute treatment of bipolar depression, mania, and schizophrenia. *J Clin Psychopharmacol* 33(3):425-431, 2013 23609405

Garver DL, Holcomb JA, Christensen JD: Cerebral cortical gray expansion associated with two second-generation antipsychotics. *Biol Psychiatry* 58(1):62-66, 2005 15992524

Geddes J, Freemantle N, Harrison P, et al: Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 321(7273):1371-1376, 2000 11099280

Gerhard T, Huybrechts K, Olfson M, et al: Comparative mortality risks of antipsychotic medications in community-dwelling older adults. *Br J Psychiatry* 205(1):44-51, 2014 23929443

Glassman AH, Bigger JT Jr: Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 158(11):1774-1782, 2001 11691681

- Glick ID, Romano SJ, Simpson G, et al: Insulin resistance in olanzapine- and ziprasidone-treated patients: results of a double-blind, controlled 6-week trial. Paper presented at the annual meeting of the American Psychiatric Association, New Orleans, LA, May 5-10, 2001
- Goff DC, Posever T, Herz L, et al: An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 18(4):296-304, 1998 9690695
- Goff DC, McEvoy JP, Citrome L, et al: High-dose oral ziprasidone versus conventional dosing in schizophrenia patients with residual symptoms: the ZEBRAS study. *J Clin Psychopharmacol* 33(4):485-490, 2013 23775057
- Goldberg RJ, Bengtson J, Chen ZY, et al: Duration of the QT interval and total and cardiovascular mortality in healthy persons (The Framingham Heart Study experience). *Am J Cardiol* 67(1):55-58, 1991 1986505
- Gómez-Criado MS, Bernardo M, Florez TD, et al: Ziprasidone overdose: cases recorded in the database of Pfizer-Spain and literature review. *Pharmacotherapy* 25(11):1660-1665, 2005 16232029
- Gury C, Canceil O, Iaria P: [Antipsychotic drugs and cardiovascular safety: current studies of prolonged QT interval and risk of ventricular arrhythmia] (in French). *Encephale* 26(6):62-72, 2000 11217540
- Hamelin BA, Allard S, Laplante L, et al: The effect of timing of a standard meal on the pharmacokinetics and pharmacodynamics of the novel atypical antipsychotic agent ziprasidone. *Pharmacotherapy* 18(1):9-15, 1998 9469675
- Hardy TA, Poole-Hoffmann V, Lu Y, et al: Fasting glucose and lipid changes in patients with schizophrenia treated with olanzapine or ziprasidone. Poster presented at the annual meeting of the American College of



Neuropsychopharmacology, San Juan, PR, December 7-11, 2003

Harrigan EP, Miceli JJ, Anziano R, et al: A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol* 24(1):62-69, 2004 14709949

Harris EC, Barraclough B: Excess mortality of mental disorder. *Br J Psychiatry* 173:11-53, 1998 9850203

Harvey PD, Bowie CR: Ziprasidone: efficacy, tolerability, and emerging data on wide-ranging effectiveness. *Expert Opin Pharmacother* 6(2):337-346, 2005 15757429

Harvey PD, Siu CO, Romano S: Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Psychopharmacology (Berl)* 172(3):324-332, 2004 14615877

Harvey PD, Bowie CR, Loebel A: Neuropsychological normalization with long-term atypical antipsychotic treatment: results of a six-month randomized, double-blind comparison of ziprasidone vs. olanzapine. *J Neuropsychiatry Clin Neurosci* 18(1):54-63, 2006a 16525071

Harvey PD, Green MF, Bowie C, et al: The dimensions of clinical and cognitive change in schizophrenia: evidence for independence of improvements. *Psychopharmacology (Berl)* 187(3):356-363, 2006b 16783539

Harvey PD, Pappadopulos E, Lombardo I, et al: Reduction of functional disability with atypical antipsychotic treatment: a randomized long term comparison of ziprasidone and haloperidol. *Schizophr Res* 115(1):24-29, 2009 19189878

Hasnain M, Vieweg WV: QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. *CNS Drugs* 28(10):887-920, 2014 25168784

- Haupt DW, Fahnestock PA, Flavin KA, et al: Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients. *Neuropsychopharmacology* 32(12):2561-2569, 2007 17375138
- Heinrich TW, Biblo LA, Schneider J: Torsades de pointes associated with ziprasidone. *Psychosomatics* 47(3):264-268, 2006 16684946
- Heinrichs DW, Hanlon TE, Carpenter WT Jr: The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 10(3):388-398, 1984 6474101
- Hennekens CH, Hennekens AR, Hollar D, et al: Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 150(6):1115-1121, 2005 16338246
- Hippisley-Cox J, Parker C, Coupland CA, et al: Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. *Heart* 93(10):1256-1262, 2007 17344333
- Hirsch SR, Kissling W, Bäuml J, et al: A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. *J Clin Psychiatry* 63(6):516-523, 2002 12088164
- Hirschfeld RM, Keck PE Jr, Kramer M, et al: Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry* 161(6):1057-1065, 2004 15169694
- Holdridge KC, Sorsaburu S, Houston JP, et al: Characteristics and mortality among hospitalized patients treated with intramuscular antipsychotics: analysis of a United States hospital database. *Curr Drug Saf* 5(3):203-211, 2010 20210728
- Houseknecht KL, Robertson AS, Zavadowski W, et al: Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic

- effects. *Neuropsychopharmacology* 32(2):289–297, 2007 17035934
- Ichikawa J, Ishii H, Bonaccorso S, et al: 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. *J Neurochem* 76(5):1521–1531, 2001 11238736
- Insa Gómez FJ, Gutiérrez Casares JR: Ziprasidone overdose: cardiac safety. *Actas Esp Psiquiatr* 33(6):398–400, 2005 16292724
- Jarema M: Atypical antipsychotics in the treatment of mood disorders. *Curr Opin Psychiatry* 20(1):23–29, 2007 17143078
- Jensen KG, Juul K, Fink-Jensen A, et al: Corrected QT changes during antipsychotic treatment of children and adolescents: a systematic review and meta-analysis of clinical trials. *J Am Acad Child Adolesc Psychiatry* 54(1):25–36, 2015 25524787
- Johnsen E, Kroken RA, Wentzel-Larsen T, et al: Effectiveness of second-generation antipsychotics: a naturalistic, randomized comparison of olanzapine, quetiapine, risperidone, and ziprasidone. *BMC Psychiatry* 10:26, 2010 20334680
- Joukamaa M, Heliövaara M, Knekt P, et al: Mental disorders and cause-specific mortality. *Br J Psychiatry* 179:498–502, 2001 11731351
- Joyce AT, Harrison DJ, Loebel AD, et al: Effect of initial ziprasidone dose on length of therapy in schizophrenia. *Schizophr Res* 83(2–3):285–292, 2006 16545543
- Kahn RS, Fleischhacker WW, Boter H, et al; EUFEST study group: Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 371(9618):1085–1097, 2008 18374841
- Kane JM: Introduction. Ziprasidone in schizophrenia: from acute treatment to long-term management. *J Clin*

- Psychiatry 64 (suppl 19):3-5, 2003a 14728083
- Kane JM: Oral ziprasidone in the treatment of schizophrenia: a review of short-term trials. J Clin Psychiatry 64 (suppl 19):19-25, 2003b 14728086
- Kane J, Khanna S, Rajadhyaksha S, Giller E: Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol 21(1):21-28, 2006 16317313
- Kapur S, Remington G: Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 153(4):466-476, 1996 8599393
- Kapur S, Remington G: Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry 50(11): 873-883, 2001 11743942
- Kaufman KR, Stern L, Mohebati A, et al: Ziprasidone-induced priapism requiring surgical treatment. Eur Psychiatry 21(1):48-50, 2006 16356688
- Keck ME, Müller MB, Binder EB, et al: Ziprasidone-related tardive dyskinesia. Am J Psychiatry 161(1):175-176, 2004 14702272
- Keck P Jr, Buffenstein A, Ferguson J, et al: Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 140(2):173-184, 1998 9860108
- Keck PE Jr, Reeves KR, Harrigan EP; Ziprasidone Study Group: Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. J Clin Psychopharmacol 21(1):27-35, 2001 11199944
- Keck PE Jr, Marcus R, Tourkodimitris S, et al; Aripiprazole Study Group: A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 160(9):1651-1658, 2003a 12944341

- Keck PE Jr, Versiani M, Potkin S, et al; Ziprasidone in Mania Study Group: Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 160(4):741-748, 2003b 12668364
- Keck PE Jr, Potkin S, Warrington L, et al: Efficacy and safety of ziprasidone in bipolar disorder: short- and long-term data. Poster presented at the annual meeting of the American Psychiatric Association, New York, May 1-6, 2004
- Keck PE Jr, Versiani M, Warrington L, et al: Long-term safety and efficacy of ziprasidone in subpopulations of patients with bipolar mania. *J Clin Psychiatry* 70(6): 844-851, 2009 19573482
- Keefe RS, Bilder RM, Davis SM, et al; CATIE Investigators; Neurocognitive Working Group: Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry* 64(6):633-647, 2007 17548746
- Khanna S, Vieta E, Lyons B, et al: Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry* 187:229-234, 2005 16135859
- Kinon BJ, Lipkovich I, Edwards SB, et al: A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. *J Clin Psychopharmacol* 26(2):157-162, 2006 16633144
- Koro CE, Fedder DO, L'Italien GJ, et al: An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry* 59(11):1021-1026, 2002a 12418935
- Koro CE, Fedder DO, L'Italien GJ, et al: Assessment of independent effect of olanzapine and risperidone on risk

- of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 325(7358):243, 2002b 12153919
- Kreyenbuhl J, Marcus SC, West JC, et al: Adding or switching antipsychotic medications in treatment-refractory schizophrenia. *Psychiatr Serv* 58(7):983-990, 2007 17602016
- Kroeze WK, Hufeisen SJ, Popadak BA, et al: H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* 28(3):519-526, 2003 12629531
- Kudla D, Lambert M, Domin S, et al: Effectiveness, tolerability, and safety of ziprasidone in patients with schizophrenia or schizoaffective disorder: results of a multi-centre observational trial. *Eur Psychiatry* 22(3):195-202, 2007 17140769
- Kuehn BM: FDA panel OKs 3 antipsychotic drugs for pediatric use, cautions against overuse. *JAMA* 302(8):833-834, 2009 19706851
- Lesem MD, Zajecka JM, Swift RH, et al: Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry* 62(1):12-18, 2001 11235922
- Leucht S, Pitschel-Walz G, Abraham D, et al: Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res* 35(1):51-68, 1999 9988841
- Leucht S, Cipriani A, Spineli L, et al: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382(9896):951-962, 2013 23810019
- Levy WO, Robichaux-Keene NR, Nunez C: No significant QTc interval changes with high-dose ziprasidone: a case

- series. *J Psychiatr Pract* 10(4):227-232, 2004 15552544
- Lieberman JA: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia: efficacy, safety and cost outcomes of CATIE and other trials. *J Clin Psychiatry* 68(2):e04, 2007 17335312
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353(12):1209-1223, 2005 16172203
- Liebowitz MR, Salmán E, Mech A, et al: Ziprasidone monotherapy in bipolar II depression: an open trial. *J Affect Disord* 118(1-3):205-208, 2009 19264363
- Loebel A, Siu C, Romano S: Improvement in prosocial functioning after a switch to ziprasidone treatment. *CNS Spectr* 9(5):357-364, 2004 15115948
- Lombardo I, Alderman J, Preskorn S, et al: Effect of food on absorption of ziprasidone (abstract of poster presented at the International Congress on Schizophrenia Research, March 28-April 1, 2007, Colorado Springs, CO). *Schizophr Bull* 33(2):475-476, 2007
- Mamo D, Kapur S, Shammi CM, et al: A PET study of dopamine D2 and serotonin 5-HT<sub>2</sub> receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. *Am J Psychiatry* 161(5):818-825, 2004 15121646
- Mason MN, Johnson CE, Piasecki M: Ziprasidone-induced acute dystonia. *Am J Psychiatry* 162(3):625-626, 2005 15741487
- Mazei MS, Pluto CP, Kirkbride B, et al: Effects of catecholamine uptake blockers in the caudate-putamen and subregions of the medial prefrontal cortex of the rat. *Brain Res* 936(1-2):58-67, 2002 11988230
- McCue RE, Waheed R, Urcuyo L, et al: Comparative effectiveness of second-generation antipsychotics and

haloperidol in acute schizophrenia. *Br J Psychiatry* 189: 433-440, 2006 17077434

McEvoy JP, Meyer JM, Goff DC, et al: Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res* 80(1):19-32, 2005 16137860

McEvoy JP, Lieberman JA, Perkins DO, et al: Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry* 164(7):1050-1060, 2007 17606657

McIntyre RS, Brecher M, Paulsson B, et al: Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol* 15(5):573-585, 2005 16139175

McQuade RD, Marcus R, Sanchez R: Aripiprazole vs placebo in acute mania: safety and tolerability pooled analysis. Poster presented at the International Conference on Bipolar Disorder, Pittsburgh, PA, June 12-14, 2003

Miceli JJ, Anziano RJ, Robarge L, et al: The effect of carbamazepine on the steady-state pharmacokinetics of ziprasidone in healthy volunteers. *Br J Clin Pharmacol* 49 (suppl 1):65S-70S, 2000a 10771457

Miceli JJ, Smith M, Robarge L, et al: The effects of ketoconazole on ziprasidone pharmacokinetics—a placebo-controlled crossover study in healthy volunteers. *Br J Clin Pharmacol* 49 (suppl 1):71S-76S, 2000b 10771458

Miceli JJ, Wilner KD, Hansen RA, et al: Single- and multiple-dose pharmacokinetics of ziprasidone under non-fasting conditions in healthy male volunteers. *Br J Clin Pharmacol* 49 (suppl 1):5S-13S, 2000c 10771448



- Miceli JJ, Murray S, Sallee FR, et al: Pharmacokinetic and pharmacodynamic QTc profile of oral ziprasidone in pediatric and adult subjects following single-dose administration. Poster presented at the annual meeting of the American Psychiatric Association, New York, May 1-6, 2004
- Miceli JJ, Tensfeldt TG, Shiovitz T, et al: Effects of high-dose ziprasidone and haloperidol on the QTc interval after intramuscular administration: a randomized, single-blind, parallel-group study in patients with schizophrenia or schizoaffective disorder. *Clin Ther* 32(3):472-491, 2010 20399985
- Millan MJ: Improving the treatment of schizophrenia: focus on serotonin (5-HT)(1A) receptors. *J Pharmacol Exp Ther* 295(3): 853-861, 2000 11082417
- Miodownik C, Hausmann M, Frolova K, et al: Lithium intoxication associated with intramuscular ziprasidone in schizoaffective patients. *Clin Neuropharmacol* 28(6):295-297, 2005 16340388
- Montanez A, Ruskin JN, Hebert PR, et al: Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. *Arch Intern Med* 164(9):943-948, 2004 15136301
- Montes JM, Rodriguez JL, Balbo E, et al: Improvement in antipsychotic-related metabolic disturbances in patients with schizophrenia switched to ziprasidone. *Prog Neuropsychopharmacol Biol Psychiatry* 31(2):383-388, 2007 17129654
- Morrato EH, Newcomer JW, Allen RR, et al: Prevalence of baseline serum glucose and lipid testing in users of second-generation antipsychotic drugs: a retrospective, population-based study of Medicaid claims data. *J Clin Psychiatry* 69(2):316-322, 2008 18251625

- Mullins CD, Shaya FT, Zito JM, et al: Effect of initial ziprasidone dose on treatment persistence in schizophrenia. *Schizophr Res* 83(2-3):277-284, 2006 16545945
- Muralidharan K, Ali M, Silveira LE, et al: Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *J Affect Disord* 150(2):408-414, 2013 23735211
- Murray S, Mandel FS, Loebel A: Optimal initial dosing of ziprasidone: clinical trial data. Poster presented at the annual meeting of the American Psychiatric Association, New York, May 1-6, 2004
- Murty RG, Mistry SG, Chacko RC: Neuroleptic malignant syndrome with ziprasidone. *J Clin Psychopharmacol* 22(6):624-626, 2002 12454565
- Nasrallah HA, Meyer JM, Goff DC, et al: Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. *Schizophr Res* 86(1-3):15-22, 2006 16884895
- Nemeroff CB, Lieberman JA, Weiden PJ, et al: From clinical research to clinical practice: a 4-year review of ziprasidone. *CNS Spectr* 10 (11 suppl 17):1-20, 2005 16381088
- Newcomer JW: Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 19 (suppl 1):1-93, 2005 15998156
- Newcomer JW, Haupt DW: The metabolic effects of antipsychotic medications. *Can J Psychiatry* 51(8):480-491, 2006 16933585
- Newcomer JW, Hennekens CH: Severe mental illness and risk of cardiovascular disease. *JAMA* 298(15):1794-1796, 2007 17940236
- Obach RS, Huynh P, Allen MC, et al: Human liver aldehyde oxidase: inhibition by 239 drugs. *J Clin Pharmacol*

44(1):7-19, 2004 14681337

O'Brien JM, Rockwood RP, Suh KI: Haloperidol-induced torsade de pointes. *Ann Pharmacother* 33(10):1046-1050, 1999 10534216

O'Connor R, Schooler NR: Penultimate observation carried forward (POCF): a new approach to analysis of long-term symptom change in chronic relapsing conditions. *Schizophr Res* 60(2-3):319-320, 2003 12591593

Olfson M, Gerhard T, Huang C, et al: Comparative effectiveness of second-generation antipsychotic medications in early onset schizophrenia. *Schizophr Bull* 38(4):845-853, 2012 21307041

Osby U, Correia N, Brandt L, et al: Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* 45(1-2):21-28, 2000 10978869

Osby U, Brandt L, Correia N, et al: Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry* 58(9):844-850, 2001 11545667

Papakostas GI, Petersen TJ, Nierenberg AA, et al: Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *J Clin Psychiatry* 65(2):217-221, 2004 15003076

Papakostas GI, Vitolo OV, Ishak WW, et al: A 12-week, randomized, double-blind, placebo-controlled, sequential parallel comparison trial of ziprasidone as monotherapy for major depressive disorder. *J Clin Psychiatry* 73(12):1541-1547, 2012 23290327

Papakostas GI, Fava M, Baer L, et al: Ziprasidone augmentation of escitalopram for major depressive disorder: Efficacy results from a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 172(12):1251-1258, 2015 26085041

Papapetropoulos S, Wheeler S, Singer C: Tardive dystonia associated with ziprasidone. *Am J Psychiatry* 162(11):2191, 2005 16263868

- Patel NC, Keck PE Jr: Ziprasidone: efficacy and safety in patients with bipolar disorder. *Expert Rev Neurother* 6(8):1129-1138, 2006 16893341
- Perlis RH, Welge JA, Vornik LA, et al: Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry* 67(4):509-516, 2006 16669715
- Pfizer Inc: Dear Healthcare Practitioner letter, August 2004. Available at: <http://www.fda.gov/medwatch/SAFETY/2004/GeodonDearDoc.pdf>. Accessed May 12, 2016.
- Pfizer Inc: Geodon (ziprasidone HCl) capsules and Geodon (ziprasidone mesylate) for injection, full prescribing information, June 2008
- Potkin SG, Keck PE Jr, Segal S, et al: Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol* 25(4):301-310, 2005 16012271
- Potkin SG, Weiden PJ, Loebel AD, et al: Remission in schizophrenia: 196-week, double-blind treatment with ziprasidone vs. haloperidol. *Int J Neuropsychopharmacol* 12(9):1233-1248, 2009 19419595
- Pozzi L, Acconcia S, Ceglia I, et al: Stimulation of 5-hydroxytryptamine (5-HT<sub>(2C)</sub>) receptors in the ventro tegmental area inhibits stress-induced but not basal dopamine release in the rat prefrontal cortex. *J Neurochem* 82(1):93-100, 2002 12091469
- Prakash C, Kamel A, Cui D, et al: Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. *Br J Clin Pharmacol* 49 (suppl 1):35S-42S, 2000 10771452
- Purnine DM, Carey KB, Maisto SA, et al: Assessing positive and negative symptoms in outpatients with

- schizophrenia and mood disorders. *J Nerv Ment Dis* 188(10): 653–661, 2000 11048814
- Ramos AE, Shytle RD, Silver AA, et al: Ziprasidone-induced oculogyric crisis. *J Am Acad Child Adolesc Psychiatry* 42(9): 1013–1014, 2003 12964566
- Rettenbacher MA, Ebenbichler C, Hofer A, et al: Early changes of plasma lipids during treatment with atypical antipsychotics. *Int Clin Psychopharmacol* 21(6):369–372, 2006 17012984
- Rochon PA, Normand SL, Gomes T, et al: Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med* 168(10):1090–1096, 2008 18504337
- Rollema H, Lu Y, Schmidt AW, et al: 5-HT(1A) receptor activation contributes to ziprasidone-induced dopamine release in the rat prefrontal cortex. *Biol Psychiatry* 48(3):229–237, 2000 10924666
- Rosenfield PJ, Girgis RR, Gil R: High-dose ziprasidone-induced acute dystonia. *Prog Neuropsychopharmacol Biol Psychiatry* 31(2):546–547, 2007 17123682
- Rossi A, Cañas F, Fagiolini A, et al: Switching among antipsychotics in everyday clinical practice: focus on ziprasidone. *Postgrad Med* 123(1):135–159, 2011 21293094
- Rummel-Kluge C, Komossa K, Schwarz S, et al: Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull* 38(1):167–177, 2012 20513652
- Rybakowski JK, Vansteelandt K, Remlinger-Molenda A, et al; EUFEST Study Group: Extrapyramidal symptoms during treatment of first schizophrenia episode: results from EUFEST. *Eur Neuropsychopharmacol* 24(9):1500–1505, 2014 25085534
- Ryu S, Yoo JH, Kim JH, et al: Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in non-

elderly schizophrenic patients unexposed to first-generation antipsychotics: a cross-sectional and retrospective study. *J Clin Psychopharmacol* 35(1):13–21, 2015 25485636

Sacchetti E, Galluzzo A, Valsecchi P, et al; MOZART Study Group: Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. *Schizophr Res* 113(1):112–121, 2009 19606529

Sachs G, Sanchez R, Marcus R, et al; Aripiprazole Study Group: Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol* 20(4):536–546, 2006 16401666

Scherk H, Pajonk FG, Leucht S: Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry* 64(4):442–455, 2007 17404121

[Schizophrenia.com](http://www.schizophrenia.com/sznews/archives/005617.html): Eli Lilly updates label warning for Zyprexa to better inform on side-effects. October 5, 2007. Available at: <http://www.schizophrenia.com/sznews/archives/005617.html>. Accessed May 11, 2016.

Schmidt AW, Lebel LA, Howard HR Jr, et al: Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. *Eur J Pharmacol* 425(3):197–201, 2001 11513838

Schooler NR: Maintaining symptom control: review of ziprasidone long-term efficacy data. *J Clin Psychiatry* 64 (suppl 19):26–32, 2003 14728087

Seeger TF, Seymour PA, Schmidt AW, et al: Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *J Pharmacol Exp Ther* 275(1):101–113, 1995 7562537

- Simpson G, Weiden P, Pigott TA, et al: Ziprasidone vs olanzapine in schizophrenia: 6-month continuation study (abstract). *Eur Neuropsychopharmacol* 12 (suppl 3): S310, 2002
- Simpson GM, Glick ID, Weiden PJ, et al: Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry* 161(10):1837-1847, 2004a 15465981
- Simpson GM, Weiden PJ, Loebel A, et al: Ziprasidone: long-term post-switch efficacy in schizophrenia. Poster presented at the annual meeting of the American Psychiatric Association, New York, May 1-6, 2004b
- Simpson GM, Weiden P, Pigott T, et al: Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. *Am J Psychiatry* 162(8):1535-1538, 2005 16055779
- Smulevich AB, Khanna S, Eerdekens M, et al: Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *Eur Neuropsychopharmacol* 15(1):75-84, 2005 15572276
- Srisurapanont M, Maneeton N: Comparison of the efficacy and acceptability of atypical antipsychotic drugs: a meta-analysis of randomized, placebo-controlled trials. *J Med Assoc Thai* 82(4):341-346, 1999 10410494
- Stahl SM: Neurotransmission of cognition, part 2. Selective NRIs are smart drugs: exploiting regionally selective actions on both dopamine and norepinephrine to enhance cognition. *J Clin Psychiatry* 64(2):110-111, 2003 12633117
- Stahl SM, Shayegan DK: The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. *J Clin Psychiatry* 64 (suppl 19):6-12, 2003 14728084

- Stahl S, Lombardo I, Loebel A, et al: Efficacy of ziprasidone in dysphoric mania: pooled analysis of two double-blind studies. *J Affect Disord* 122(1-2):39-45, 2010a 19616304
- Stahl SM, Malla A, Newcomer JW, et al: A post hoc analysis of negative symptoms and psychosocial function in patients with schizophrenia: a 40-week randomized, double-blind study of ziprasidone versus haloperidol followed by a 3-year double-blind extension trial. *J Clin Psychopharmacol* 30(4):425-430, 2010b 20571437
- Strassnig M, Clarke J, Mann S, et al: Body composition, pre-diabetes and cardiovascular disease risk in early schizophrenia. *Early Interv Psychiatry* March 10, 2015 [Epub ahead of print] 25752319
- Strom BL, Eng SM, Faich G, et al: Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). *Am J Psychiatry* 168(2):193-201, 2011 21041245
- Stroup TS, Lieberman JA, McEvoy JP, et al; CATIE Investigators: Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 163(4):611-622, 2006 16585435
- Sumiyoshi T, Jayathilake K, Meltzer HY: The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. *Schizophr Res* 59(1):7-16, 2003 12413636
- Swainston Harrison T, Scott LJ: Ziprasidone: a review of its use in schizophrenia and schizoaffective disorder. *CNS Drugs* 20(12):1027-1052, 2006 17140281
- Swartz MS, Perkins DO, Stroup TS, et al; CATIE Investigators: Effects of antipsychotic medications on psychosocial functioning in patients with chronic



- schizophrenia: findings from the NIMH CATIE study. *Am J Psychiatry* 164(3):428-436, 2007 17329467
- Swift RH, Harrigan EP, van Kammen DP: A comparison of fixed-dose intramuscular (IM) ziprasidone with flexible-dose IM haloperidol. Poster presented at the annual meeting of the American Psychiatric Association, Toronto, ON, Canada, May 30-June 4, 1998
- Tan HH, Hoppe J, Heard K: A systematic review of cardiovascular effects after atypical antipsychotic medication overdose. *Am J Emerg Med* 27(5):607-616, 2009 19497468
- Tandon R, Fleischhacker WW: Comparative efficacy of antipsychotics in the treatment of schizophrenia: a critical assessment. *Schizophr Res* 79(2-3):145-155, 2005 16139989
- Tatsumi M, Jansen K, Blakely RD, et al: Pharmacological profile of neuroleptics at human monoamine transporters. *Eur J Pharmacol* 368(2-3):277-283, 1999 10193665
- Tauscher J, Kapur S, Verhoeff NP, et al: Brain serotonin 5-HT(1A) receptor binding in schizophrenia measured by positron emission tomography and [11C]WAY-100635. *Arch Gen Psychiatry* 59(6):514-520, 2002 12044193
- Taylor D: Ziprasidone in the management of schizophrenia: the QT interval issue in context. *CNS Drugs* 17(6):423-430, 2003 12697001
- Tecott LH, Sun LM, Akana SF, et al: Eating disorder and epilepsy in mice lacking 5-HT<sub>2c</sub> serotonin receptors. *Nature* 374(6522):542-546, 1995 7700379
- Thome J, Foley P, Riederer P: Neurotrophic factors and the maldevelopmental hypothesis of schizophrenic psychoses. Review article. *J Neural Transm (Vienna)* 105(1):85-100, 1998 9588763
- Tohen M, Sanger TM, McElroy SL, et al; Olanzapine HGEH Study Group: Olanzapine versus placebo in the

treatment of acute mania. *Am J Psychiatry* 156(5):702-709, 1999 10327902

Tohen M, Jacobs TG, Grundy SL, et al; The Olanzapine HGGW Study Group: Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 57(9):841-849, 2000 10986547

Versavel M, DelBello MP, Ice K, et al: Ziprasidone dosing study in pediatric patients with bipolar disorder, schizophrenia, or schizoaffective disorder (abstract). *Neuropsychopharmacology* 30 (suppl 1):S122-S123, 2005

Vieta E, Ramey T, Keller D, et al: Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. *J Psychopharmacol* 24(4):547-558, 2010 19074536

Villanueva N, Markham-Abedi C, McNeely C, et al: Probable association between ziprasidone and worsening hypertension. *Pharmacotherapy* 26(9):1352-1357, 2006 16945059

Weiden PJ, Iqbal N, Mendelowitz AJ, et al: Best clinical practice with ziprasidone: update after one year of experience. *J Psychiatr Pract* 8(2):81-97, 2002 15985861

Weiden PJ, Daniel DG, Simpson G, et al: Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol* 23(6):595-600, 2003a 14624190

Weiden PJ, Simpson GM, Potkin SG, et al: Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. *J Clin Psychiatry* 64(5):580-588, 2003b 12755663

Weiden PJ, Newcomer JW, Loebel AD, et al: Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. *Neuropsychopharmacology* 33(5):985-994, 2008 17637612

- Weinstein SK, Adler CM, Strakowski SM: Ziprasidone-induced acute dystonic reactions in patients with bipolar disorder. *J Clin Psychiatry* 67(2):327-328, 2006 16566635
- Weisler R, Dunn J, English P: Ziprasidone in adjunctive treatment of acute bipolar mania: double-blind, placebo-controlled trial. Poster presented at the annual meeting of the Institute on Psychiatric Services, Boston, MA, October 29-November 2, 2003
- Weisler R, Warrington L, Dunn J: Adjunctive ziprasidone in bipolar mania: short- and long-term data (abstract). *Biol Psychiatry* 55 (8 suppl):43S, 2004
- Yumru M, Savas HA, Selek S, et al: Acute dystonia after initial doses of ziprasidone: a case report. *Prog Neuropsychopharmacol Biol Psychiatry* 30(4):745-747, 2006 16580766
- Ziegenbein M, Schomerus G, Kropp S: Ziprasidone-induced Pisa syndrome after clozapine treatment. *J Neuropsychiatry Clin Neurosci* 15(4):458-459, 2003 14627778
- Zimbroff DL, Brook S, Benattia I: Safety and tolerability of IM ziprasidone: review of clinical trial data. Poster presented at the annual meeting of the American Psychiatric Association, Philadelphia, PA, May 18-23, 2002
- Zink M, Kuwilsky A, Krumm B, et al: Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomised controlled clinical trial. *J Psychopharmacol* 23(3):305-314, 2009 18562423
- Zhang H, Wang G, Zhao J, et al: Intramuscular ziprasidone versus haloperidol for managing agitation in Chinese patients with schizophrenia. *J Clin Psychopharmacol* 33(2):178-185, 2013 23422376
- Zorn SH, Bebel LA, Schmidt AW, et al: Pharmacological and neurochemical studies with the new antipsychotic

ziprasidone, in Interactive Monoaminergic Basis of Brain Disorders. Edited by Palomo T, Beninger R, Archer T. Madrid, Spain, Editorial Sintesis, 1998, pp 377-394

# CHAPTER 31

## Asenapine

Leslie L. Citrome, M.D., M.P.H.

---

### History and Discovery

---

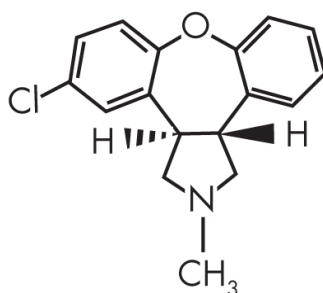
Asenapine as a sublingual tablet was initially approved by the U.S. Food and Drug Administration (FDA) in August 2009 for the treatment of acute schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults. It was subsequently approved for maintenance treatment of schizophrenia in adults, for adjunctive use with lithium or valproate in the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, and for bipolar mania in pediatric patients (ages 10–17 years) as a monotherapy ([Actavis 2015](#)). In addition to the original unflavored formulation, a black cherry-flavored version of asenapine was brought to the U.S. market in 2010.

---

## Pharmacological Profile

---

Asenapine is a second-generation (atypical) antipsychotic that belongs to the chemical class of dibenzo-oxepino pyrroles (Figure 31-1). Its receptor-binding profile is notable for high affinity ( $K_i$  [values in nM]) for several 5-hydroxytryptamine (5-HT; serotonin) receptor subtypes, including 5-HT<sub>2C</sub> (0.03), 5-HT<sub>2A</sub> (0.06), 5-HT<sub>7</sub> (0.13), 5-HT<sub>2B</sub> (0.16), and 5-HT<sub>6</sub> (0.25), and for several dopamine receptor subtypes, including D<sub>3</sub> (0.42), D<sub>2</sub> (1.3), D<sub>1</sub> (1.4), and D<sub>4</sub> (1.1) (Actavis 2015; Shahid et al. 2009). Asenapine also has high binding affinities to histamine H<sub>1</sub> (1.0) and to norepinephrine  $\alpha_1$  (1.2) and  $\alpha_2$  (1.2) receptors. Asenapine binds with somewhat lower affinity to serotonin 5-HT<sub>5</sub> (1.6), 5-HT<sub>1A</sub> (2.5), and 5-HT<sub>1B</sub> (4.0) receptors and histamine H<sub>2</sub> (6.2) receptors. Asenapine very weakly binds to muscarinic M<sub>1</sub> (8,128) receptors. Asenapine acts as an antagonist at all of the above receptors.



---

**FIGURE 31-1.** Chemical structure of asenapine.

Asenapine has approximately 38 metabolites, none of them highly prevalent; these metabolites have little clinically relevant effects either because of their lower

affinity for the relevant receptors or because of their inability to cross the blood-brain barrier ([Citrome 2009, 2014a](#); [U.S. Food and Drug Administration 2009](#)). Although the precise mechanism of action of asenapine in the treatment of schizophrenia is unknown, it is thought that antagonism at the dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> receptors mediates the drug's antipsychotic activity ([Actavis 2015](#)). In studies using positron emission tomography, asenapine has demonstrated dose-dependent dopamine D<sub>2</sub> receptor occupancy (dose range 0.1–4.8 mg), with a significant correlation between D<sub>2</sub> occupancy and plasma concentration ([U.S. Food and Drug Administration 2009](#)); sublingual administration of 4.8 mg twice daily resulted in a mean D<sub>2</sub> occupancy of 79% approximately 3–6 hours after dosing.

---

## Pharmacokinetics and Drug-Drug Interactions

---

Asenapine is the only commercially available antipsychotic that is absorbed primarily in the oral mucosa. It is formulated as a highly porous, rapid-dissolving tablet for sublingual administration, with a resulting bioavailability of approximately 35% ([Schering-Plough Research Institute 2009](#); [U.S. Food and Drug Administration 2009](#)). If the tablet is swallowed rather than allowed to orally dissolve, the drug's bioavailability is reduced to less than 2% because of high hepato-gastrointestinal first-pass metabolism ([Actavis 2015](#); [U.S. Food and Drug Administration 2009](#)). Patient instructions are to place the

tablet under the tongue and to refrain from eating or drinking for 10 minutes after administration, because drinking water sooner than 10 minutes can result in reduced bioavailability of asenapine ([Actavis 2015](#)).

Although asenapine was developed for sublingual administration, absorption will occur even if the tablet is placed elsewhere in the oral cavity, as was demonstrated in a study of healthy men who received single 5-mg doses of asenapine via sublingual, supralingual, and buccal routes ([Gerrits et al. 2010](#)). Drug exposure with buccal administration (i.e., “cheeking”) as measured by plasma levels was almost 25% higher than that with sublingual administration, whereas exposure with supralingual administration was 6% lower. However, these differences in exposure by oral administration site are small in relation to the wide variability in asenapine’s pharmacokinetics observed across the clinical studies used to obtain regulatory approval, where overall exposure varied by 37%, with a mean inter-individual variability of 26% and a mean intra-individual variability of 26% ([U.S. Food and Drug Administration 2009](#)). Doubling the dosage from 5 mg to 10 mg twice daily results in less than linear (1.7 times) increases in both the extent of exposure and the maximum concentration ([Actavis 2015](#)).

Peak plasma levels occur 30–90 minutes after administration, and asenapine has a mean terminal half-life of approximately 24 hours ([Actavis 2015](#); [Schering-Plough Research Institute 2009](#); [U.S. Food and Drug Administration 2009](#)). Barring any tolerability issues when starting treatment with asenapine, once-daily dosing in the evening is feasible given the half-life; however, the clinical trials supporting the approval of asenapine were conducted



using bid (twice-daily) dosing, resulting in the recommendation for bid dosing in product labeling.

Asenapine is metabolized in the liver primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 (CYP) isoenzymes (predominantly CYP1A2). Asenapine has a large volume of distribution and is highly bound (95%) to plasma proteins, including albumin and  $\alpha_1$ -acid glycoprotein. Despite the fact that smoking can induce CYP1A2, concomitant smoking had no substantial effect on the pharmacokinetics of asenapine when tested in healthy male subjects ([U.S. Food and Drug Administration 2009](#)). Fluvoxamine, a potent CYP1A2 inhibitor, can increase exposure to asenapine by 29% and therefore should be coadministered with caution ([Actavis 2015](#)).

Use of asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh class C); asenapine exposures are on average 7 times higher in patients with severe impairment than in those with normal hepatic function. However, no dosage adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. No dosage adjustment is required for patients with renal impairment.

Asenapine can inhibit CYP2D6, resulting in twofold increases in paroxetine concentrations ([U.S. Food and Drug Administration 2009](#)). The product label advises caution when coadministering asenapine with drugs that are both substrates and inhibitors of CYP2D6 ([Actavis 2015](#)).

---

## Indications and Efficacy

---

# Approved Indications

Asenapine's efficacy in acute schizophrenia in adults was tested in four pivotal short-term randomized, double-blind, placebo- and active comparator-controlled multicenter studies ([Citrome 2011b, 2014b](#)). Two studies were accepted by the FDA as supportive of asenapine's efficacy in the acute treatment of schizophrenia in adults ([Kane et al. 2010](#); [Potkin et al. 2007](#)). Asenapine's efficacy in the treatment of manic or mixed episodes of bipolar I disorder in adults was supported in both of two completed Phase III randomized, placebo- and active comparator-controlled 3-week trials ([McIntyre et al. 2009a, 2010a](#)). Approximately 1 year after the initial approval of asenapine for these indications, the FDA approved asenapine for the maintenance treatment of schizophrenia (based on a double-blind, placebo-controlled multicenter clinical trial [[Kane et al. 2011](#)]) and for use as adjunctive therapy with either lithium or valproate in the acute treatment of manic or mixed episodes associated with bipolar I disorder (again based on a placebo-controlled trial [[Szegedi et al. 2012](#)]). Approval of asenapine for the treatment of bipolar mania in pediatric patients (ages 10–17 years) was obtained in 2015 based on a placebo-controlled trial ([Findling et al. 2015b](#)).

In adults, the recommended dosage of asenapine for acute schizophrenia is 5 mg bid; that for bipolar manic or mixed episodes is 10 mg bid (5 mg bid if administered with lithium or valproate), based on the clinical trials used to obtain regulatory approval. Titration to these target dosages is not necessary. In a modeling and simulation study ([Friberg et al. 2009](#)), asenapine dosages of 5 and 10 mg bid had similar efficacy in the acute treatment of schizophrenia. In the maintenance study in schizophrenia

on which asenapine's approval for that indication was based, the most commonly used dosage was 10 mg bid ([Kane et al. 2011](#)).

In pediatric patients (ages 10–17 years) with bipolar mania, the recommended starting dosage of asenapine as monotherapy is 2.5 mg bid, with increases up to 10 mg bid possible.

## Schizophrenia

### Short-Term Efficacy

In one of the two positive trials, 458 patients with acute schizophrenia were randomly assigned to fixed-dosage treatment with asenapine at 5 mg bid, asenapine at 10 mg bid, placebo, or an active control for assay sensitivity (haloperidol at 4 mg bid) for 6 weeks ([Kane et al. 2010](#)). The primary efficacy endpoint was change from baseline in the Positive and Negative Syndrome Scale (PANSS; [Kay et al. 1987](#)) total score. On analyses of change in PANSS total score, asenapine at 5 mg bid and haloperidol were both superior to placebo, with statistically significant differences seen from day 21 onward. However, asenapine at 10 mg bid did not demonstrate an advantage over placebo, a finding that the authors suggested may have been due in part to the high placebo response rate in this trial. Rates of response—defined as a minimum reduction of 30% in the PANSS total score or a Clinical Global Impression-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved)—were 55% for asenapine 5 mg bid, 49% for asenapine 10 mg bid, 43% for haloperidol, and 33% for placebo, yielding numbers needed to treat (NNTs) ([Citrome 2008](#)) versus placebo of 5 for asenapine 5 mg bid, 7 for

asenapine 10 mg bid, and 10 for haloperidol ([Citrome 2011b](#)).

In the second short-term acute schizophrenia trial that was considered positive and supportive of asenapine's efficacy, 182 patients were randomly assigned to asenapine 5 mg bid, placebo, or an active control for assay sensitivity (risperidone 3 mg bid) for 6 weeks ([Potkin et al. 2007](#)). The primary efficacy endpoint was change from baseline in the PANSS total score. Compared with placebo, asenapine produced significantly greater decreases in PANSS total scores from week 2 onward. Risperidone did not statistically significantly separate from placebo. Using the criterion of reduction in the PANSS total score of at least 30%, 38% of the patients in the asenapine group were categorized as responders, compared with 39% of those in the risperidone group and 25% of those in the placebo group, yielding NNTs versus placebo of 8 for asenapine and 7 for risperidone ([Citrome 2011b](#)).

Two other 6-week acute schizophrenia trials were conducted ([Citrome 2011b](#); [U.S. Food and Drug Administration 2009](#)). One trial was considered negative because asenapine at 5 or 10 mg bid failed to separate from placebo, whereas the active control (olanzapine at 15 mg/day) did separate from placebo. The other trial was considered a failed trial because neither asenapine at 5 or 10 mg bid nor the active control (olanzapine 10–20 mg/day) separated from placebo. An additional double-blind trial was conducted in Asian patients where 532 adult participants from Japan, Korea, and Taiwan were randomly assigned to receive asenapine 5 mg bid, 10 mg bid, or placebo for 6 weeks ([Kinoshita et al. 2016](#)). The primary efficacy endpoint was change from baseline on the PANSS total score. Improvements from baseline on PANSS total

scores were significantly greater in the patients receiving asenapine 5 mg bid or 10 mg bid, compared with those receiving placebo, from days 14 and 7, respectively. Using the criterion of reduction in PANSS total score of at least 30%, 39% of the patients in the asenapine 5 mg bid group and 44% of those in the 10 mg bid group were categorized as responders, compared with 21% of those in the placebo group, yielding NNTs versus placebo of 6 for asenapine 5 mg bid and 5 for asenapine 10 mg bid.

An 8-week, placebo-controlled, double-blind trial in 306 adolescent (ages 12–17 years) patients with schizophrenia failed to demonstrate asenapine's efficacy at dosages of 2.5 and 5 mg twice daily ([Findling et al. 2015a](#)).

## **Longer-Term Efficacy**

Asenapine's longer-term efficacy in schizophrenia was examined in a published 1-year double-blind study in 1,225 patients with schizophrenia or schizoaffective disorder. Patients were randomly assigned to receive asenapine (5 mg bid for the first week and then flexible dosing of 5 or 10 mg bid) or olanzapine (10 mg/day for the first week and then flexible dosing of 10 or 20 mg/day) ([Schoemaker et al. 2010](#)). There was no placebo arm. Rates of discontinuation because of insufficient therapeutic effect were 25.1% for asenapine and 14.5% for olanzapine (NNT=10 for olanzapine versus asenapine to avoid discontinuation because of insufficient therapeutic effect). Changes from baseline in PANSS total score were similar for asenapine and olanzapine at week 6 but showed a statistically significant difference in favor of olanzapine at endpoint (last observation carried forward). Among the patients who completed the entire year-long trial, changes in PANSS total score were similar for asenapine and olanzapine at

week 6 and also at week 52. Completers were eligible to participate in an extension study in which clinical stability was further demonstrated ([Schoemaker et al. 2012](#)).

Asenapine's efficacy in the maintenance phase of schizophrenia was demonstrated in a published 26-week double-blind, placebo-controlled multicenter clinical trial ([Kane et al. 2011](#)). Patients were randomly assigned either to continue receiving asenapine or to receive placebo after establishing stability on asenapine during the 26 weeks of open-label treatment immediately prior. Of the 700 enrolled patients who were treated with open-label asenapine, 386 met stability criteria and entered the double-blind phase. Times to relapse/impending relapse and to discontinuation for any reason were significantly longer with asenapine than with placebo. The incidence of relapse or impending relapse was 12.1% for asenapine and 47.4% for placebo (NNT=3). Completion rates were 69.6% for asenapine and 37.5% for placebo (NNT=4). The most commonly used dosage of asenapine was 10 mg bid in both the open-label and the double-blind phases.

In two randomized, double-blind 26-week studies and their respective 26-week extensions, [Buchanan et al. \(2012\)](#) tested the hypothesis that asenapine is superior to olanzapine for persistent negative symptoms of schizophrenia and assessed the comparative long-term efficacy and safety of the two agents. Approximately 1,000 subjects participated. In the two core studies, 26-week completion rates with asenapine were 64.7% and 49.6%, versus 80.4% and 63.8%, respectively, with olanzapine. In the two extension studies, completion rates were 84.3% and 66.3% with asenapine versus 89.0% and 80.9%, respectively, with olanzapine. Asenapine was not superior to olanzapine in change in the 16-item Negative Symptom

Assessment Scale total score in either core study, but asenapine was superior to olanzapine at week 52 in one of the extension studies. Weight gain was consistently lower with asenapine. Extrapyramidal side effect (EPS)-related adverse-event incidence was higher with asenapine, but Extrapyramidal Symptom Rating Scale-Abbreviated total score changes did not differ significantly between treatments.

## Bipolar Disorder

In two identically designed 3-week acute studies of asenapine in the treatment of bipolar manic or mixed episodes ([McIntyre et al. 2009a](#), [2010a](#)), 977 subjects were randomly assigned to receive flexibly dosed asenapine 5–10 mg bid (starting dosage 10 mg bid), olanzapine 5–20 mg/day (starting dosage 15 mg/day), or placebo. The primary outcome measure for each of these studies was change from baseline in the Young Mania Rating Scale (YMRS; [Young et al. 1978](#)) total score. In the first study ([McIntyre et al. 2009a](#)), YMRS total scores were statistically significantly improved from baseline to day 21 for asenapine and olanzapine compared with placebo. Sustained statistically significant improvement in the YMRS score compared with placebo was noted for asenapine and olanzapine from day 2 onward. Percentages of subjects meeting criteria for response (50% decrease from baseline YMRS total score) and remission (YMRS total score  $\leq 12$ ) were higher with asenapine (42.3% and 40.2%, respectively) than with placebo (25.2% and 22.3%, respectively), yielding NNTs for response and for remission



versus placebo of 6. The NNT for response for olanzapine versus placebo was 5, and that for remission was 6.

In the second study ([McIntyre et al. 2010a](#)), YMRS total scores also were statistically significantly improved from baseline to day 21 for asenapine and olanzapine compared with placebo, with sustained statistically significant improvement in the YMRS total score versus placebo noted for asenapine and olanzapine from day 2 onward. In post hoc analyses, changes in YMRS total scores from baseline to day 21 were significantly greater for olanzapine than for asenapine with last observation carried forward analysis, but not with mixed model for repeated measures analysis. Rates of response (42.6%) and remission (35.5%) with asenapine did not differ significantly from those with placebo (34% and 30.9%, respectively), yielding NNTs of 12 and 22, respectively. Olanzapine was superior to placebo in rates of response (54.7%) and remission (46.3%), with NNTs for olanzapine versus placebo of 5 and 7, respectively, and for olanzapine versus asenapine of 9 and 10, respectively. Based on the above studies, the recommended starting dose of asenapine monotherapy for acute bipolar mania or mixed episodes in adults is 10 mg bid. However, additional information is available from a 3-week, double-blind, placebo-controlled, fixed-dose study of asenapine 5 mg bid and 10 mg bid in adults with an acute bipolar I disorder manic or mixed episode ([Landbloom et al. 2016](#)). Both asenapine doses were statistically superior to placebo in mean change from baseline to day 21 in YMRS total score, suggesting that 5 mg bid can be an adequate dose for adults with acute bipolar mania or mixed episodes. However, in this trial, neither asenapine dose had significantly more YMRS responders or remitters at day 21 than placebo.



Asenapine's longer-term efficacy in patients with manic or mixed episodes of bipolar disorder was assessed in a 9-week extension ([McIntyre et al. 2009b](#)) to the original two pivotal studies ([McIntyre et al. 2009a, 2010a](#)), followed by an additional 40-week extension ([McIntyre et al. 2010b](#)). A total of 504 subjects received at least one dose of double-blind trial medication during the 9-week extension trial and included 181 subjects who were treated with asenapine and 229 who were treated with olanzapine from the feeder trials (and who continued on the same treatment in the extension). In addition, 94 subjects who were treated with placebo in the feeder trials were blindly allocated to receive asenapine 5–10 mg bid in the extension trial. The primary efficacy analysis demonstrated that asenapine was statistically noninferior to olanzapine as measured by the YMRS total score from baseline to day 84 for the observed case subjects who had 3 weeks of previous exposure to study medication. The proportions of participants who were YMRS responders and remitters were similar in the asenapine and olanzapine groups: the rates of response at last observation carried forward endpoint were 77% and 82% with asenapine and olanzapine, respectively, and the rates of remission were 75% and 79%, respectively. For the 218 patients who were subsequently enrolled for another 40 weeks of double-blinded treatment, maintenance of efficacy was observed for both asenapine and olanzapine, with no differences in response or remission rates between the two agents.

Another study tested the efficacy of asenapine 5 mg bid in the treatment of an acute manic or mixed episode when combined with lithium or divalproex over 12 weeks ([Szegedi et al. 2012](#)), and its findings supported this indication as approved by the FDA ([Actavis 2015](#)).

Adjunctive asenapine significantly improved mania versus placebo at week 3 (primary endpoint) and weeks 2–12. The YMRS response rates were similar at week 3 but significantly better with asenapine at week 12. The YMRS remission rates and changes from baseline on the Clinical Global Impression–Bipolar (CGI-BP) for mania and overall illness were significantly better with asenapine at weeks 3 and 12. Patients completing the core study were eligible for a 40-week double-blind extension assessing safety and tolerability ([Szegedi et al. 2012](#)).

Asenapine's efficacy in the treatment of acute mania in pediatric patients (ages 10–17 years) was established in a single 3-week placebo-controlled, double-blind trial of 403 patients, of whom 302 received asenapine at fixed dosages of 2.5 mg, 5 mg, and 10 mg bid ([Findling et al. 2015b](#)). All patients were started on 2.5 mg bid, and dosages were titrated upward every 3 days in a stepwise fashion for patients randomly assigned to receive the higher dosages. Asenapine was statistically superior to placebo in improving YMRS total scores and CGI-BP severity of illness scores. YMRS responder rates were 42%, 54%, and 52% for asenapine 2.5 mg, 5 mg, and 10 mg bid, respectively, versus 28% for placebo, yielding corresponding NNT values for asenapine versus placebo of 8, 4, and 5.

## Agitation

Although asenapine is not approved for this indication, it was tested for the management of agitation in a randomized controlled trial ([Pratts et al. 2014](#)). Adults ages 18–65 years ( $N=120$ , any diagnosis) manifesting agitation in an emergency department and found to have a score of

$\geq 14$  on the PANSS-Excited Component (PANSS-EC) were randomly assigned to receive either a single sublingual 10-mg tablet of asenapine or matching placebo. Changes in PANSS-EC score at 2 hours were statistically significantly greater for the asenapine-treated subjects compared with the placebo-treated subjects, with an effect noted at 15 minutes, the earliest time point at which outcome was measured. The NNT value for response versus placebo was 3, an effect size comparable to that observed in prior studies of intramuscular antipsychotics. This study awaits replication.

---

## Side Effects and Toxicology

---

Common adverse reactions with asenapine observed in short-term trials (incidence  $\geq 5\%$  and twofold greater than placebo) were akathisia, oral hypoesthesia (numbness), and somnolence for adult patients with schizophrenia; somnolence, dizziness, EPS other than akathisia, and increased weight for monotherapy in adult patients with bipolar manic or mixed episodes; and somnolence and oral hypoesthesia for adjunctive therapy in adult patients with bipolar manic or mixed episodes ([Actavis 2015](#)). Among pediatric patients with bipolar disorder, common adverse reactions observed with asenapine as monotherapy were somnolence, dizziness, dysgeusia, oral paresthesias, nausea, increased appetite, fatigue, and increased weight ([Actavis 2015](#)).

Somnolence is the single most common adverse event associated with asenapine treatment. The product label describes this effect as usually transient, with the highest

incidence reported during the first week of treatment ([Actavis 2015](#)). The highest rates of somnolence in adults were observed in the short-term acute manic/mixed-episode bipolar trials (most common dosage=10 mg bid), where somnolence was reported in 24% of patients receiving asenapine versus 6% of patients receiving placebo, for a number needed to harm (NNH) of 6; rates of reported somnolence in the short-term schizophrenia trials (dosage=5 or 10 mg bid) were 13% for asenapine versus 7% for placebo, yielding a NNH of 17 ([Citrome 2009](#)). Comparisons of other antipsychotics against placebo on the outcome of somnolence in short-term acute trials of schizophrenia yielded a broad range of incidence rates, resulting in NNH values that ranged from 7 for olanzapine or quetiapine extended-release to a non-statistically significant 42 for paliperidone ([Citrome and Nasrallah 2012](#)). Although somnolence was frequently reported, somnolence/sedation led to discontinuation in only a small proportion (0.6%) of adult patients treated with asenapine ([Actavis 2015](#)).

Dizziness can also occur and is attributable to asenapine's  $\alpha_1$ -adrenergic antagonist activity; however, rates of syncope were observed to be low among patients in contrast to rates observed among healthy volunteers in the clinical pharmacology trials ([U.S. Food and Drug Administration 2009](#)). Asenapine has a dose-related association with EPS and akathisia, although the frequency of these events is substantially lower with asenapine than with haloperidol ([Citrome 2009](#)).

Unique to asenapine is the possibility of oral hypoesthesia, spontaneously reported as an adverse reaction in about 5% of the participants with acute schizophrenia in the clinical trials ([Actavis 2015](#)). Directly

asking patients about oral hypoesthesia may yield higher rates of this adverse effect, as was observed in a study that examined the effect of absorption site on the pharmacokinetics of asenapine in healthy male subjects ([Gerrits et al. 2010](#)). In this study, reported rates of oral paresthesias were 75.8%, 55.9%, and 45.7% for the sublingual, supralingual, and buccal absorption sites, respectively.

Asenapine has a mild effect on QTc interval, similar to that seen with quetiapine ([Chapel et al. 2009, 2011](#)). Hypersensitivity reactions have been reported with asenapine, in some cases occurring after the first dose, and this risk is now highlighted in product labeling ([Actavis 2015](#)). Asenapine's effects on prolactin levels in the short-term schizophrenia and bipolar manic/mixed-episode studies in adults revealed no clinically relevant changes.

In the 6-week acute schizophrenia trials, clinically relevant weight gain ( $\geq 7\%$  over baseline body weight) was observed in 4.9% of subjects receiving asenapine versus 2% of those receiving placebo. In the 3-week acute bipolar manic/mixed-episode studies, clinically relevant weight gain was observed in 5.8% of subjects receiving asenapine versus 0.5% of those receiving placebo. In addition to a favorable weight-gain profile, asenapine has shown minimal effects on glucose-related laboratory parameters such as fasting glucose and fasting insulin ([Schering-Plough Research Institute 2009](#)).

Of interest are longer-term safety and tolerability comparisons of asenapine with other antipsychotics. In a 1-year double-blind, randomized controlled trial comparing asenapine with olanzapine ([Schoemaker et al. 2010](#)), the incidence of treatment-emergent adverse events was 82% in both groups. Mean weight gain was 0.9 kg with

asenapine and 4.2 kg with olanzapine. The proportion of patients experiencing clinically relevant weight gain ( $\geq 7\%$  over baseline) was approximately 35% for olanzapine and approximately 15% for asenapine (olanzapine versus asenapine, NNH=5). No notable changes or between-group differences were seen in measures of total cholesterol or glucose, but triglyceride levels rose substantially with olanzapine and declined slightly with asenapine. In the 2-year blinded extension study ([Schoemaker et al. 2012](#)), mean body weight during the extension did not change beyond the weight gain in the core study. In the core study, EPS reported as adverse events were more common with asenapine (18%) than with olanzapine (8%) (asenapine versus olanzapine, NNH=10). The most commonly reported type of movement disorder in the asenapine and olanzapine groups was akathisia, with treatment-emergent rates of 10% for asenapine and 4% for olanzapine (asenapine versus olanzapine, NNH=17). In the 2-year blinded extension study, incidence rates of EPS-related adverse events that started during the extension were lower for both asenapine (4.5%) and olanzapine (3.3%) compared with those that started during the core study. Not many new cases of akathisia were reported during the extension period. There was little change in EPS severity during the extension of treatment.

Safety and tolerability outcomes are available from a 40-week extension to the acute bipolar trials ([McIntyre et al. 2010b](#)), where clinically relevant weight gain occurred in 21.9%, 39.2%, and 55.1% of patients in the placebo/asenapine, asenapine, and olanzapine groups, respectively. The NNH for clinically relevant weight gain for olanzapine versus asenapine was 7. The percentage of patients shifting to above a prespecified akathisia global

rating scale threshold was higher in the asenapine group compared with the placebo/asenapine and olanzapine groups.

Tolerability of asenapine in the pediatric patients (ages 10–17 years) in the 3-week bipolar mania trial differed from that in the adult trials in terms of higher reported rates of somnolence, oral paresthesias (oral hypoesthesia, oral paresthesia, and oral dysesthesia), and weight gain ([Actavis 2015](#)). Rates of somnolence were 49% for asenapine (all dosages) versus 12% for placebo, yielding an NNH of 3, with no clear dose-response relationship. Rates of fatigue were substantially lower (9% and 5% for asenapine and placebo, respectively), but with a dose-response effect and a rate of 14% for subjects receiving asenapine 10 mg bid. Rates of oral paresthesias were 27% for asenapine (all dosages) versus 4% for placebo, yielding an NNH of 5. The proportions of patients experiencing clinically relevant weight gain ( $\geq 7\%$  over baseline body weight) were 12%, 8.9%, and 8% for asenapine 2.5 mg bid, 5 mg bid, and 10 mg bid, respectively, versus 1.1% for placebo, yielding corresponding NNH values of 10, 13, and 15. A 50-week open-label, flexible-dose extension trial was available for those who completed the 3-week acute trial ([Findling et al. 2016](#)). Among the tolerability variables of interest, combined somnolence/sedation/hypersomnia occurred most frequently (42.4%). In total, 34.8% of the participants experienced clinically significant weight gain.

---

## Conclusion

---



Asenapine's efficacy is evidenced both in short-term acute clinical trials and in longer-term studies. In the mind of the clinician, asenapine will likely be measured against other "metabolically friendly" second-generation antipsychotics such as ziprasidone, aripiprazole, iloperidone, lurasidone, brexpiprazole, and cariprazine, as well as newer agents in the antipsychotic development pipeline ([Citrome 2011a, 2013, 2015](#)). Differences among these choices include dosing factors (daily versus twice-daily dosing, the need for dosage titration, special requirements for administration with or without food) as well as specific side-effect profiles.

Asenapine is unique in being the only antipsychotic that is absorbed primarily in the oral mucosa. Nonadherence by "cheeking" becomes moot. The possibility of oral hypoesthesia and dysgeusia (distorted or bad taste), a medication effect likely not experienced previously by the patient, necessitates advance warning.

In summary, asenapine's place in the treatment of schizophrenia and bipolar manic or mixed episodes is likely to be in patients for whom metabolic concerns are of import and in patients who would prefer a sublingual preparation. Substantial heterogeneity exists among the different antipsychotics and among individual patients ([Volavka and Citrome 2009](#)), so that asenapine has a legitimate place on a formulary.

Specific obstacles to the first-line use of asenapine are the recommendations for twice-daily versus once-daily administration and the recommendation to avoid food or liquids for 10 minutes after dosing. Cost may be a further impediment, given the availability of inexpensive generic versions of risperidone, quetiapine, ziprasidone, and olanzapine in the United States, as well as other generic second-generation antipsychotics in other countries.



---

# References

---

- Actavis: Saphris (asenapine) sublingual tablets. Product label, revised March 2015. Available at: [http://www.allergan.com/assets/pdf/saphris\\_pi](http://www.allergan.com/assets/pdf/saphris_pi). Accessed July 28, 2016.
- Buchanan RW, Panagides J, Zhao J, et al: Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia. *J Clin Psychopharmacol* 32(1):36-45, 2012 22198451
- Chapel S, Hutmacher MM, Haig G, et al: Exposure-response analysis in patients with schizophrenia to assess the effect of asenapine on QTc prolongation. *J Clin Pharmacol* 49(11):1297-1308, 2009 19843656
- Chapel S, Hutmacher MM, Bockbrader H, et al: Comparison of QTc data analysis methods recommended by the ICH E14 guidance and exposure-response analysis: case study of a thorough QT study of asenapine. *Clin Pharmacol Ther* 89(1):75-80, 2011 21107314
- Citrome L: Compelling or irrelevant? Using number needed to treat can help decide. *Acta Psychiatr Scand* 117(6):412-419, 2008 18479317
- Citrome L: Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract* 63(12):1762-1784, 2009 19840150
- Citrome L: Iloperidone, asenapine, and lurasidone: a brief overview of 3 new second-generation antipsychotics. *Postgrad Med* 123(2):153-162, 2011a 21474903
- Citrome L: Role of sublingual asenapine in treatment of schizophrenia. *Neuropsychiatr Dis Treat* 7:325-339, 2011b 21655346
- Citrome L: A review of the pharmacology, efficacy and tolerability of recently approved and upcoming oral

- antipsychotics: an evidence-based medicine approach. *CNS Drugs* 27(11):879-911, 2013 24062193
- Citrome L: Asenapine review, part I: chemistry, receptor affinity profile, pharmacokinetics and metabolism. *Expert Opin Drug Metab Toxicol* 10(6):893-903, 2014a 24793403
- Citrome L: Asenapine review, part II: clinical efficacy, safety and tolerability. *Expert Opin Drug Saf* 13(6):803-830, 2014b 24793161
- Citrome L: The ABC's of dopamine receptor partial agonists —aripiprazole, brexpiprazole and cariprazine: the 15-min challenge to sort these agents out. *Int J Clin Pract* 69(11):1211-1220, 2015 26477545
- Citrome L, Nasrallah HA: On-label on the table: what the package insert informs us about the tolerability profile of oral atypical antipsychotics, and what it does not. *Expert Opin Pharmacother* 13(11):1599-1613, 2012 22017361
- Findling RL, Landbloom RP, Mackle M, et al: Safety and efficacy from an 8 week double-blind trial and a 26 week open-label extension of asenapine in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol* 25(5):384-396, 2015a 26091193
- Findling RL, Landbloom RL, Szegedi A, et al: Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry* 54(12):1032-1041, 2015b 26598478
- Findling RL, Landbloom RL, Mackle M, et al: Long-term safety of asenapine in pediatric patients diagnosed with bipolar I disorder: a 50-week open-label, flexible-dose trial. *Paediatr Drugs* 18(5):367-378, 2016 27461426
- Friberg LE, de Greef R, Kerbusch T, et al: Modeling and simulation of the time course of asenapine exposure response and dropout patterns in acute schizophrenia. *Clin Pharmacol Ther* 86(1):84-91, 2009 19387434
- Gerrits M, de Greef R, Peeters P: Effect of absorption site on the pharmacokinetics of sublingual asenapine in

- healthy male subjects. *Biopharm Drug Dispos* 31(5-6):351-357, 2010 20549835
- Kane JM, Cohen M, Zhao J, et al: Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol* 30(2):106-115, 2010 20520283
- Kane JM, Mackle M, Snow-Adami L, et al: A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry* 72(3):349-355, 2011 21367356
- Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13(2):261-276, 1987 3616518
- Kinoshita T, Bai YM, Kim JH, et al: Efficacy and safety of asenapine in Asian patients with an acute exacerbation of schizophrenia: a multicentre, randomized, double-blind, 6-week, placebo-controlled study. *Psychopharmacology (Berl)* 233(14):2663-2674, 2016 27271087
- Landbloom RL, Mackle M, Wu X, et al: Asenapine: efficacy and safety of 5 and 10mg bid in a 3-week, randomized, double-blind, placebo-controlled trial in adults with a manic or mixed episode associated with bipolar I disorder. *J Affect Disord* 190:103-110, 2016 26496015
- McIntyre RS, Cohen M, Zhao J, et al: A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord* 11(7):673-686, 2009a 19839993
- McIntyre RS, Cohen M, Zhao J, et al: Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar Disord* 11(8):815-826, 2009b 19832806
- McIntyre RS, Cohen M, Zhao J, et al: Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 122(1-2):27-38, 2010a 20096936

- McIntyre RS, Cohen M, Zhao J, et al: Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *J Affect Disord* 126(3):358–365, 2010b 20537396
- Potkin SG, Cohen M, Panagides J: Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 68(10):1492–1500, 2007 17960962
- Pratts M, Citrome L, Grant W, et al: A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. *Acta Psychiatr Scand* 130(1):61–68, 2014 24606117
- Schering-Plough Research Institute: Saphris (asenapine) Sublingual Tablets. Briefing Document (Background Package). 30 July 2009. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM173876.pdf>. Accessed July 28, 2016.
- Schoemaker J, Naber D, Vrijland P, et al: Long-term assessment of asenapine vs. olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry* 43(4):138–146, 2010 20205074
- Schoemaker J, Stet L, Vrijland P, et al: Long-term efficacy and safety of asenapine or olanzapine in patients with schizophrenia or schizoaffective disorder: an extension study. *Pharmacopsychiatry* 45(5):196–203, 2012 22454251
- Shahid M, Walker GB, Zorn SH, et al: Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol* 23(1):65–73, 2009 18308814
- Szegedi A, Calabrese JR, Stet L, et al; Apollo Study Group: Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week

core study and 40-week extension. J Clin Psychopharmacol 32(1):46-55, 2012 22198448

U.S. Food and Drug Administration: Saphris (asenapine) Sublingual Tablets. Briefing Book. 30 July 2009. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM173877.pdf>. Accessed July 28, 2016.

Volavka J, Citrome L: Oral antipsychotics for the treatment of schizophrenia: heterogeneity in efficacy and tolerability should drive decision-making. Expert Opin Pharmacother 10(12):1917-1928, 2009 19558339

Young RC, Biggs JT, Ziegler VE, et al: A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:429-435, 1978 728692

## CHAPTER 32

### Iloperidone

Peter F. Buckley, M.D.

Adriana E. Foster, M.D.

Oliver Freudenreich, M.D.

Scott Van Sant, M.D.

---

#### History and Discovery

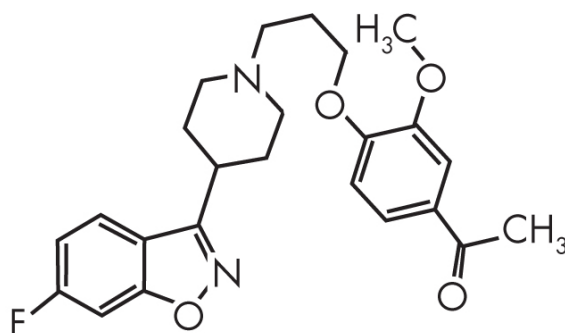
Iloperidone was approved by the U.S. Food and Drug Administration (FDA) in 2009 for the treatment of schizophrenia. It meets the now generally appreciated profile of second-generation antipsychotics (SGAs), in that it has a complex pharmacology (with a predilection for dopamine and serotonin antagonism) and little propensity for extrapyramidal side effects (EPS), as well as efficacy against key symptoms of schizophrenia, as shown in placebo-controlled clinical trials ([Rado and Janicak 2010](#); [Weiden 2012](#)). Iloperidone's efficacy has been demonstrated at a dosage range of 12–24 mg/day, with no clear advantage evident at higher dosages. To minimize the risk of dizziness and postural hypotension consequent to iloperidone's antagonism of noradrenergic  $\alpha_1$  receptors, it is recommended that the drug be initiated and titrated upward with caution. Clinical experience with iloperidone is accruing, as is comparative information for iloperidone in relation to other SGAs ([Potkin et al. 2013](#); [Rado and Janicak 2014](#); [Tarazi and Stahl 2012](#)). Additional clinical trials of iloperidone are ongoing (see [www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

---

#### Structure-Activity Relations and Pharmacological Profile

Iloperidone is an SGA of the piperidiny-benzisoxazole class ([Figure 32-1](#)). Structurally similar benzisoxazole derivatives include risperidone and its metabolite paliperidone, as well as ziprasidone. Iloperidone's chemistry and specific binding profile across multiple neuroreceptors are complex ([Citrome 2010](#); [Kalkman et al. 2003](#)). In brief, similar to several other SGAs, iloperidone is a serotonin 2A (5-HT<sub>2A</sub>) and dopamine 2 (D<sub>2</sub>) receptor antagonist. It has strong affinity for dopamine D<sub>3</sub> receptors and a lesser (but still more pronounced compared with other SGAs) affinity for D<sub>4</sub> receptors. It also has affinity for both 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors. Iloperidone is further distinguished by its antagonism of

noradrenergic  $\alpha_1$  receptors. The strength of iloperidone's  $\alpha_1$ -receptor affinity exceeds that of all other SGAs except clozapine. In contrast, iloperidone has low affinity for 5-HT<sub>1A</sub> and histamine H<sub>1</sub> receptors. Collectively, this receptor affinity constellation may account for iloperidone's adverse-effect attributes of postural hypotension risk, prolactin-elevating capacity, modest weight-gain propensity, and mild sedative effects.



**FIGURE 32-1.** Chemical structure of iloperidone.

## Pharmacokinetics and Disposition

Iloperidone is readily absorbed from the gastrointestinal tract and reaches peak plasma concentrations approximately 2 hours after ingestion. Its absorption is slowed by food, but its bioavailability is unaffected; thus, it can be given either with or without food.

Iloperidone is extensively metabolized by the cytochrome P450 (CYP) enzyme system, particularly the 3A4 and 2D6 isoenzymes. Iloperidone's average half-life in "regular" (extensive) CYP2D6 metabolizers is approximately 24 hours. Clinicians need to be cautious when prescribing iloperidone concurrently with agents that inhibit CYP2D6 and CYP3A4 enzymes, a category that includes several antidepressant medications. It has been shown that a statistically significantly greater proportion of iloperidone responders than of nonresponders have average plasma concentrations of  $\geq 5$  ng/mL. That being said, blood levels of iloperidone are not available for use in clinical practice (Weiden 2012).

Iloperidone is currently available only in tablet form. No liquid or short-term intramuscular formulations or long-acting injectable forms have been developed.

There is currently no clinical evidence that the dosage of iloperidone requires adjustment on the basis of age or gender, although it is noteworthy that the potential for postural hypotension may be markedly higher in the elderly. Clinical studies of iloperidone in schizophrenia did not include sufficient numbers of patients ages 65 years and older to determine whether older persons respond differently from younger adults. Among more than 3,000 patients treated with iloperidone in the early registration trials, only 25 patients (0.5%) were  $\geq 65$  years old, and there were no patients  $\geq 75$  years old. Iloperidone's safety and effectiveness in pediatric patients have not yet been well studied; therefore, the drug should not be prescribed in children or adolescents. Additionally, iloperidone's teratogenic risk is unknown. It is therefore advised that lactating women who are being treated with iloperidone refrain from breast-feeding their newborns. The most recent FDA recommendations regarding use of antipsychotics during pregnancy and the neonatal period also apply to iloperidone (see FDA MedWatch; [www.fda.gov/Safety/MedWatch](http://www.fda.gov/Safety/MedWatch)).

# Indications and Efficacy

Iloperidone is FDA approved for the acute treatment of schizophrenia. No other indications for iloperidone were under consideration by the FDA at the time of this writing. However, the clinical trials program for this drug now includes investigative studies in mood disorders that are currently ongoing (see [www.clinicaltrials.com](http://www.clinicaltrials.com)).

## Schizophrenia

### Pivotal Clinical Trials

Iloperidone's FDA approval for the treatment of schizophrenia was predominantly based on four short-term placebo-controlled trials, highlighted in [Table 32-1](#). In addition, two long-term trials have been published ([Cutler et al. 2013](#); [Kane et al. 2008](#)). These studies are described in the following paragraphs. A more complete review of drug development and initial trials in humans is provided elsewhere ([Citrome 2010](#); [Rado and Janicak 2014](#)).

**TABLE 32-1. Pivotal clinical trials of iloperidone efficacy in patients with schizophrenia or schizoaffective disorder**

Study	N and diagnosis	Iloperidone and comparator drug dosages (mg/day)	Efficacy outcome measure	Symptom change from baseline to endpoint
<a href="#">Potkin et al. 2008</a> Three 6-week randomized, double-blind studies comparing ILO against PLA	1,943 patients with schizophrenia or schizoaffective disorder	<i>Study 1:</i> ILO 4, 8, 12; HAL 15; PLA <i>Study 2:</i> ILO 4-8, 10-16; RIS 4-8; PLA <i>Study 3:</i> ILO 12-16, 20-24; RIS 6-8; PLA	<b>Primary:</b> PANSS-T or PANSS-derived BPRS change from baseline to endpoint  <b>Secondary:</b> PANSS-P, PANSS-N, PANSS-GP, BPRS, CDSS, CGI-S, CGI-C	<i>Study 1</i> • Changes in PANSS-T from baseline were significant with ILO 12 ( $P=0.04$ ) and HAL 15 ( $P<0.01$ ).
<i>Note.</i> HAL=haloperidol; ILO=iloperidone; PLA=placebo; RIS=risperidone; ZIP=ziprasidone. NS=nonsignificant. BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; PANSS=Positive and Negative Syndrome Scale (PANSS-T=total; PANSS-P=positive symptoms; PANSS-N=negative symptoms; PANSS-GP=general psychopathology); CGI=Clinical Global Impressions (CGI-S=severity; CGI-C=change). *Relapse=25% increase in PANSS-T scores; discontinuation due to lack of efficacy hospitalization, or CGI increase by 2 points.				



Study	N and diagnosis	Iloperidone and comparator drug dosages (mg/day)	Efficacy outcome measure	Symptom change from baseline to endpoint
				<ul style="list-style-type: none"> <li>• Changes with combined ILO 8 and ILO 12 groups were NS vs. PLA.</li> <li>• Changes with HAL vs. PLA were significant (<math>P&lt;0.001</math>).</li> </ul> <p><i>Studies 2 and 3</i></p> <ul style="list-style-type: none"> <li>• All ILO dosages as well as RIS changed BPRS from baseline in Studies 2 and 3.</li> <li>• Compared with PLA, changes were significant with ILO 4-8 (<math>P=0.012</math>) and ILO 10-16 (<math>P=0.001</math>) in Study 2 and ILO 20-24</li> </ul>

*Note.* HAL=haloperidol; ILO=iloperidone; PLA=placebo; RIS=risperidone ZIP=ziprasidone. NS=nonsignificant. BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; PANSS=Positive and Negative Syndrome Scale (PANSS-T=total; PANSS-P=positive symptoms; PANSS-N=negative symptoms; PANSS-GP=general psychopathology); CGI=Clinical Global Impressions (CGI-S=severity; CGI-C=change).

\*Relapse=25% increase in PANSS-T scores; discontinuation due to lack of efficacy hospitalization, or CGI increase by 2 points.

Study	N and diagnosis	Iloperidone and comparator drug dosages (mg/day)	Efficacy outcome measure	Symptom change from baseline to endpoint
				( $P=0.01$ ) in Study 3. <ul style="list-style-type: none"> <li>• ILO 12-16 vs. PLA was NS in Study 3.</li> <li>• RIS vs. PLA was significant in all studies (<math>P&lt;0.001</math>).</li> <li>• All ILO dosages improved each variable vs. PLA except ILC 4-8 for PANSS N in Study 2.</li> </ul>
Potkin et al. 2008 Combined analysis of three studies	1,553 patients who remained in the studies at least 2 weeks			All ILO dosages as well as HAL and RIS were statistically significant vs. PLA ( $P<0.05$ ).

*Note.* HAL=haloperidol; ILO=iloperidone; PLA=placebo; RIS=risperidone ZIP=ziprasidone. NS=nonsignificant. BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; PANSS=Positive and Negative Syndrome Scale (PANSS-T=total; PANSS-P=positive symptoms; PANSS-N=negative symptoms; PANSS-GP=general psychopathology); CGI=Clinical Global Impressions (CGI-S=severity; CGI-C=change).

\*Relapse=25% increase in PANSS-T scores; discontinuation due to lack of efficacy hospitalization, or CGI increase by 2 points.

Study	N and diagnosis	lloperidone and comparator drug dosages (mg/day)	Efficacy outcome measure	Symptom change from baseline to endpoint
Cutler et al. 2008 4-week study 1-week titration 3-week double-blind treatment for acute exacerbation	593 patients with schizophrenia	ILO 24; ZIP 160; PLA	<b>Primary:</b> change from baseline in PANSS-T for ILO vs. PLA <b>Secondary:</b> change from baseline in BPRS, PANSS-P, PANSS-N, PANSS-GP, CGI-S, CGI-C, CDSS	ILO reduced PANSS-T significantly vs. PLA ( $P<0.01$ ). ILO and ZIP significantly reduced all measures except PANSS-GP. ILO reduced PANSS-P, CGI-S, and CGI-C significantly vs. PLA. Neither ILO nor ZIP reduced CDSS significantly.

*Note.* HAL=haloperidol; ILO=iloperidone; PLA=placebo; RIS=risperidone ZIP=ziprasidone. NS=nonsignificant. BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; PANSS=Positive and Negative Syndrome Scale (PANSS-T=total; PANSS-P=positive symptoms; PANSS-N=negative symptoms; PANSS-GP=general psychopathology); CGI=Clinical Global Impressions (CGI-S=severity; CGI-C=change).

\*Relapse=25% increase in PANSS-T scores; discontinuation due to lack of efficacy hospitalization, or CGI increase by 2 points.

Study	N and diagnosis	Iloperidone and comparator drug dosages (mg/day)	Efficacy outcome measure	Symptom change from baseline to endpoint
<a href="#">Kane et al. 2008</a> Long-term (46-week) double-blind maintenance phase after 6-week stabilization	473 patients with schizophrenia or schizoaffective disorder who had responded to ILO ( <i>n</i> =371) or HAL ( <i>n</i> =118) during stabilization phase (36.6% responded to ILO and 37.8% to HAL in the acute phase)	ILO 4-16; HAL 5-20 Mean dosage at end of maintenance=12.5 for both drugs	<b>Primary:</b> time to relapse* <b>Secondary:</b> change from baseline to endpoint on PANSS, BPRS, and CGI-C	Difference in time to relapse between ILO (89.8 days) and HAL (101.8 days) was not significant. Relapse rate was 43.5% for ILO vs. 41.2% for HAL. Both groups improved; PANSS scores were not significantly different at endpoint between ILO and HAL.

*Note.* HAL=haloperidol; ILO=iloperidone; PLA=placebo; RIS=risperidone ZIP=ziprasidone. NS=nonsignificant. BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; PANSS=Positive and Negative Syndrome Scale (PANSS-T=total; PANSS-P=positive symptoms; PANSS-N=negative symptoms; PANSS-GP=general psychopathology); CGI=Clinical Global Impressions (CGI-S=severity; CGI C=change).

\*Relapse=25% increase in PANSS-T scores; discontinuation due to lack of efficacy hospitalization, or CGI increase by 2 points.

[Potkin et al. \(2008\)](#) reviewed the 6-week double-blind period of the pivotal trials that evaluated iloperidone's efficacy in the treatment of schizophrenia. All of these trials included screening, an acute double-blind phase, and a long-term maintenance phase.

Study 1 enrolled patients ages 18-65 years with acute or subacute exacerbations of schizophrenia or schizoaffective disorder and with Positive and Negative Syndrome Scale (PANSS) scores of 60 or greater. One hundred twenty-one patients were randomly assigned to receive iloperidone 4 mg/day, 125 to iloperidone 8 mg/day, 124 to iloperidone 24 mg/day, 124 to haloperidol 15 mg/day, and 127 to placebo. After a screening and a 3-day placebo run-in period as well as a 7-day fixed-titration period, patients were placed on

study medication for 5 weeks. The primary objective was to determine the efficacy of iloperidone versus placebo. The primary efficacy variable was change in PANSS total score (PANSS-T) from baseline to endpoint (day 42 or last visit before discontinuation). Although PANSS-T scores improved significantly from baseline for the iloperidone 12 mg/day ( $P=0.047$ ) and the haloperidol ( $P<0.001$ ) groups, improvement for the combined iloperidone 8 mg/day and 12 mg/day group was not significantly different from that for the placebo group. The all-cause discontinuation rates were 57%, 64%, and 58% for iloperidone 4 mg/day, 8 mg/day, and 12 mg/day, respectively; 65% for haloperidol; and 69% for placebo (Potkin et al. 2008).

In Study 2, patients selected according to the same inclusion criteria used in Study 1 were randomly assigned to receive iloperidone 4–8 mg/day ( $n=53$ ; 52% discontinued the study before endpoint) or 10–16 mg/day ( $n=154$ ; 44% discontinued), risperidone 4–8 mg/day ( $n=153$ ; 42% discontinued), or placebo ( $n=156$ ; 60% discontinued). The primary objective was again to determine the efficacy of iloperidone versus placebo. Both dosage ranges of iloperidone resulted in significant symptom improvement (as measured by Brief Psychiatric Rating Scale [BPRS] scores) from baseline compared with placebo (Potkin et al. 2008).

In Study 3, patients selected according to the previously described criteria were randomly assigned to receive iloperidone 12–16 mg/day ( $n=244$ ; 46% discontinued) or 20–24 mg/day ( $n=145$ ; 41% discontinued), risperidone 6–8 mg/day ( $n=157$ ; 29% discontinued), or placebo ( $n=160$ ; 46% discontinued). In this study, the iloperidone 12–16 mg/day dosage failed to separate from placebo (Potkin et al. 2008).

A combined analysis of all three studies was performed to eliminate the impact of early discontinuations (i.e., those occurring in the initial 2 weeks of the studies, during which the drug reaches steady state). When the analysis was restricted to patients who had remained in double-blind treatment for at least 2 weeks ( $n=1,553$ ), it showed that each of the iloperidone dosage ranges (4–8, 10–16, and 20–24 mg/day) separated significantly from placebo (Potkin et al. 2008).

A 4-week double-blind study (Cutler et al. 2008) evaluated the efficacy of iloperidone 24 mg/day against that of placebo and of ziprasidone 160 mg/day in patients with an acute exacerbation of schizophrenia by measuring change from baseline in the PANSS-T score and the PANSS positive, negative, and general psychopathology scale scores; the Calgary Depression Scale for Schizophrenia (CDSS) score; and the Clinical Global Impression–Severity (CGI-S) score. Iloperidone significantly reduced PANSS-T scores at 4 weeks compared with placebo. Although both iloperidone and ziprasidone significantly improved negative and positive PANSS and CGI-S scores compared with placebo, none of the drugs improved PANSS general psychopathology scores significantly, nor did any drug affect CDSS scores.

Kane et al. (2008) conducted a long-term efficacy analysis using data from patients who had completed the 6-week double-blind phase of the three pivotal studies described above. Patients who had at least a 20% reduction in PANSS-T scores and a CGI score of less than 4 and who had received at least one dose of long-term-phase medication were randomly assigned to iloperidone or haloperidol for 48 weeks of double-blind maintenance treatment (mean dosage at endpoint=12.5 mg/day for both drugs). The primary efficacy variable was relapse (defined as an increase of 25% or greater on the PANSS score). Differences between the iloperidone group and the haloperidol group in time to relapse were not significant—63.6% of patients in both groups completed the long-term phase of the trial.

Cutler et al. (2013) reported on a 25-week open-label extension study. More than 58% of patients discontinued iloperidone. Overall improvement was seen in 80% of patients.

Weiden et al. (2014) reported on a 12-week trial in which schizophrenia patients who were taking risperidone, olanzapine, or aripiprazole but were experiencing problems with tolerability or efficacy were switched to iloperidone (up to 12 mg twice daily) via random assignment to either an immediate-cessation or a gradual-downtitration strategy. The results were similar across all groups, and the two switching strategies yielded comparable efficacy and tolerability.

## Pharmacogenetic Studies

Clinical trials of iloperidone sought to establish the drug's pharmacogenetic characteristics (Volpi et al. 2009a, 2009b) by exploring the relationship between iloperidone's efficacy and various candidate genes related to dopamine receptors, dopamine  $\beta$ -hydroxylase, the serotonin 1B (5-HT<sub>1B</sub>) receptor, and the ciliary neurotrophic factor (CNTF). CNTF is a cytokine in the interleukin-6 cytokine family that suppresses noradrenergic and serotonergic function (Galter and Unsicker 1999). A null mutation in the CNTF gene leads to a non-G/G rs1800169 genotype that cannot produce a functional protein and has been linked to an increased risk of psychosis (Thome et al. 1996). However, a meta-analysis involving more than 1,000 patients and a similar number of control subjects (Lin and Tsai 2004) found no association between *CNTF* and schizophrenia risk.

In a 4-week randomized, placebo-controlled study in 417 patients genotyped for *CNTF*, 279 received iloperidone and 138 received placebo (Lavedan et al. 2008). Iloperidone improved symptom scores significantly versus placebo in patients with an active *CNTF* gene, whereas patients with the *CNTF* null allele showed no greater response to iloperidone than to placebo.

In a whole-genome study of 407 patients from the same sample, of which 218 patients received iloperidone, six single-nucleotide polymorphisms (SNPs) associated with iloperidone efficacy were identified (Volpi et al. 2009b). The identified loci included SNPs of the neuronal PAS domain protein 3 gene (*NPAS3*); of the XK Kell blood group complex subunit-related family member 4 gene (*XKR4*); of the tenascin-R gene (*TNR*); of the glutamate receptor ionotropic AMPA 4 gene (*GRIA4*); of the glial cell line-derived neurotrophic factor receptor alpha 2 gene (*GFRA2*); and of the NUDT9P1 pseudogene located in the chromosomal region of the serotonin receptor 7 gene (*HTR7*). More than 75% of the iloperidone-treated patients in the group with the optimal genotype combinations showed a  $\geq 20\%$  symptom improvement, whereas only 37% of patients with other genotypes showed a  $\geq 20\%$  improvement.

Another whole-genome association study (Volpi et al. 2009a) was conducted in 183 patients with schizophrenia who received an electrocardiogram (ECG) on day 14 of treatment with iloperidone, after the drug had reached steady state. DNA polymorphisms associated with QT prolongation were found in six loci, including *CERKL*, thought to be part of the ceramide pathway; *SLCO3A1*, which encodes the organic anion-transporting polypeptide; various genes involved in myocardial infarction (*PALLD*), cardiac structure and function (*BRUNOL4*), and cardiac development (*NRG3*); and an SNP on *NUBPL* with unknown function. Each SNP defined two genotype groups associated with a low mean QT interval change or a higher mean QT interval prolongation.

Although these findings have attracted considerable interest from the field, pharmacogenomic approaches to drug optimization need to be tested further in larger studies before these findings can be of clinical use. Nevertheless, the incorporation of

pharmacogenetic testing into the regulatory registration trials of this drug represents an important new aspect of psychopharmacological drug development.

## Other Indications

Little information is available on the use of iloperidone in patients with first-episode psychosis. Similarly, there are no studies to inform the use of iloperidone in patients with treatment-refractory schizophrenia. There is no information on the efficacy or tolerability of iloperidone in patients with comorbid substance use disorders. Information on the use of iloperidone in other comorbid conditions and/or in other primary psychiatric and neuropsychiatric disorders is scant. Given the paucity of data to guide treatment, off-label use of this drug cannot be recommended.

## Side Effects and Toxicology

### Common Adverse Events in Early Studies

The safety of iloperidone in short-term studies was examined in a pooled analysis of the three 6-week Phase II studies in acute schizophrenia ( $N=1,943$ ) conducted between 1998 and 2002 (Potkin et al. 2008). A total of 1,912 patients received at least one dose of study medication and were included in this pooled analysis. The safety cohort included 440 patients on placebo, 463 on iloperidone 4–8 mg/day, 456 on iloperidone 10–16 mg/day, 125 on iloperidone 20–24 mg/day, 118 on haloperidol 15 mg/day, and 306 on risperidone 4–8 mg/day. The most common treatment-related adverse events associated with iloperidone across all three dosage groups were dizziness, dry mouth, somnolence, and dyspepsia (Table 32-2).

**TABLE 32-2. Safety profile of iloperidone in short- and long-term studies: adverse events occurring in at least 5% of patients in any active-treatment group**

Event (%)	Short-term studies <sup>a</sup>					Long-term studies <sup>b</sup>	
	ILO 4-8 mg/day ( <i>n</i> =463)	ILO 10-16 mg/day ( <i>n</i> =456)	ILO 20-24 mg/day ( <i>n</i> =125)	HAL 15 mg/day ( <i>n</i> =118)	RIS 4-8 mg/day ( <i>n</i> =306)	ILO ( <i>n</i> =371)	HAL ( <i>n</i> =118)
Akathisia	3.7	1.5	4.8	13.6	6.9	3.8	14.4
Dizziness	12.1	10.3	23.2	5.1	7.2	5.1	4.2
EPS	5.4	4.8	4.0	20.3	9.5	0.8	5.9
Tremor	2.8	2.6	4.8	22.0	6.9	4.9	12.7
Dry mouth	5.2	7.9	10.4	2.5	2.9	*	*
Dyspepsia	7.8	5.5	4.8	11.0	5.9	*	*
Dystonia	0.9	0.9	0.8	11.9	2.6	*	*
Fatigue	4.3	4.6	6.4	7.6	1.6	*	*
Flatulence	1.9	1.3	1.6	5.1	2.3	*	*

Event (%)	Short-term studies <sup>a</sup>					Long-term studies <sup>b</sup>	
	ILO 4-8 mg/day (n=463)	ILO 10-16 mg/day (n=456)	ILO 20-24 mg/day (n=125)	HAL 15 mg/day (n=118)	RIS 4-8 mg/day (n=306)	ILO (n=371)	HAL (n=118)
Nasal congestion	4.8	5.0	5.6	1.7	2.6	*	*
Somnolence	5.0	5.7	8.0	6.8	5.9	*	*
Insomnia	*	*	*	*	*	18.1	16.9
Anxiety	*	*	*	*	*	10.8	11.0
Headache	*	*	*	*	*	6.2	4.2
Agitation	*	*	*	*	*	5.7	5.1
Muscle rigidity	*	*	*	*	*	4.0	12.7
Restlessness	*	*	*	*	*	3.5	6.8
Constipation	*	*	*	*	*	2.2	5.1

*Note.* “Schizophrenia aggravated” and “psychosis aggravated” were listed as adverse events in the [Kane et al. 2008](#) study but were not included in this table. EPS=extrapyramidal side effects; HAL=haloperidol; ILO=iloperidone; RIS=risperidone.

\*Did not occur in at least 5% of comparators.

<sup>a</sup>Pooled analysis of 6-week studies.

<sup>b</sup>Long-term (46 weeks) maintenance treatment (mean dosage 12.5 mg/day at study end for both drugs).

*Source.* Adapted from [Kane et al. 2008](#) and [Weiden et al. 2008](#).

With respect to available data from long-term studies, three prospective multicenter studies—each with a 6-week stabilization period followed by a 46-week double-blind maintenance phase—inform our understanding of iloperidone’s longer-term tolerability ([Kane et al. 2008](#); see [Table 32-2](#)). Patients were randomly assigned to receive iloperidone 4-16 mg/day or haloperidol 5-20 mg/day. Of the 1,644 patients who underwent random assignment and the 1,326 who completed the 6-week stabilization period, 473 (iloperidone 359, haloperidol 114) were included in the long-term efficacy analysis and 489 (iloperidone 371, haloperidol 118) were included in the safety analysis. The most common adverse events reported for iloperidone were insomnia, anxiety, and headache.

## Extrapyramidal Side Effects

In the pooled analysis of pivotal short-term trials comparing iloperidone (4-8 mg/day, 10-16 mg/day, and 20-24 mg/day), risperidone, and haloperidol, all iloperidone dosages demonstrated significant improvement (as measured by overall EPS ratings from baseline



to endpoint on the Extrapyramidal Symptom Rating Scale [ESRS]; [Chouinard and Margolese 2005](#)). By comparison, there was no significant change with risperidone and significant worsening with haloperidol. Akathisia items on the ESRS all showed significant improvement from baseline for iloperidone at the 10–16 mg/day and 20–24 mg/day dosage ranges ([Weiden et al. 2008](#)). The low EPS profile of iloperidone is an advantage clinically, even in this era of predominantly SGA prescribing in which one's risk of EPS is much lower than heretofore ([Weiden 2012](#)). Moreover, the absence of a dose-related increase in EPS across dosage ranges in clinical trials of iloperidone is conspicuous and encouraging.

## Orthostatic Hypotension

In view of its antagonism at  $\alpha_1$ -noradrenergic receptors, iloperidone possesses the potential for autonomic side effects. In its clinical trials program, iloperidone was associated with decreases in supine and standing systolic and diastolic blood pressures in all dosage groups. Decreases in blood pressure were mostly observed within the first week of treatment and were generally not sustained. Orthostatic hypotension was observed more frequently in all active-treatment groups (iloperidone, risperidone, and haloperidol) than in the placebo group. Sustained orthostatic hypotension was observed in 0.4% ( $n=2$ ), 3.8% ( $n=17$ ), and 4.8% ( $n=6$ ) of patients receiving iloperidone 4–8 mg/day, 10–16 mg/day, and 20–24 mg/day, respectively. According to the manufacturer's full prescribing information ([Vanda Pharmaceuticals 2016](#)), iloperidone must be initiated slowly and gradually so as to avoid orthostatic hypotension, with a starting dosage of 1 mg twice daily, increasing to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively, to a target dosage range of 12–24 mg/day. Clinicians should therefore pay particular attention to dizziness early in treatment with iloperidone. It is also important to go even slower with initial titration in patients who may be at risk for postural hypotension ([Weiden 2012](#)).

## Weight Gain and Metabolic Effects

One of the potential advantages of iloperidone could be its profile with respect to metabolic issues and weight gain ([De Hert et al. 2012](#); [Tarazi and Stahl 2012](#)). Compared with patients receiving placebo, patients receiving iloperidone exhibited a small but statistically significant increase in weight across all dosages. For all patients completing the respective studies, the mean weight gain was 2.4 kg in each iloperidone dosing group. Clinically significant weight gain (defined as  $\geq 7\%$  increase in body weight from baseline) occurred in 12.3% of all iloperidone groups ([Weiden et al. 2008](#)). The majority of the weight gain occurred within the first 6 weeks of the studies (6.4%). Long-term treatment with iloperidone also produced slight increases in total cholesterol, triglycerides, and glucose levels ([Kane et al. 2008](#)). Increased prolactin levels were not observed in the pooled analysis of the three 6-week trials. The prescribing information ([Vanda Pharmaceuticals 2016](#)), however, emphasizes findings from the 4-week iloperidone versus ziprasidone versus placebo trial, in which 26% of subjects receiving iloperidone, versus 12% of those receiving placebo, exhibited elevated plasma prolactin levels. Thus, the relatively more favorable weight and metabolic profiles of iloperidone constitute a distinction that might guide the selection and use of iloperidone in particular patient groups ([Weiden 2012](#)).

On the other hand, in a provocative preclinical study in which rats were exposed to iloperidone, asenapine, or olanzapine ([Boyda et al. 2013](#)) the iloperidone-exposed rats developed glucose intolerance. In a 12-month head-to-head study of lurasidone and risperidone in 611 patients with schizophrenia, baseline rates of metabolic syndrome were similar for both groups (33% for lurasidone; 33% for risperidone), whereas after 12 months, the incidence of new-onset metabolic syndrome was 16% in lurasidone-treated patients and 27% in risperidone-treated patients ([Newcomer 2014](#)).

## QT Interval Prolongation

With respect to potentially life-threatening side effects, there was evidence of significant QT/QTc interval prolongation across all iloperidone groups in the drug's pivotal study program, and this potential drug effect was a focus of review by the FDA. Specifically, the least square mean changes in QTc intervals from baseline to endpoint in these studies were 2.9 msec, 3.9 msec, and 9.1 msec for iloperidone 4–8 mg/day, 10–16 mg/day, and 20–24 mg/day, respectively. It is noteworthy that no deaths or serious arrhythmias attributable to QT prolongation occurred in these studies ([Weiden 2012](#); [Weiden et al. 2008](#)). [Potkin et al. \(2013\)](#) examined the incidence of QTc prolongation in patients randomly assigned to receive iloperidone, quetiapine, or ziprasidone. To further test for metabolic inhibition, there was a period of coadministration of paroxetine and paroxetine plus ketoconazole. These conditions revealed QTc intervals of 60 mg or greater in approximately 10% of patients receiving iloperidone. However, no patients had clinical symptoms, and none had a QTc interval that reached or exceeded 500 mg.

## Contraindications

According to the manufacturer's prescribing information ([Vanda Pharmaceuticals 2016](#)), iloperidone should be avoided in combination with other drugs that are known to prolong the QTc interval, a group that includes Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications, and antibiotics. This prohibition makes sense, given iloperidone's metabolism through these cytochrome pathways. In addition, it is recommended that iloperidone be avoided in persons with congenital long-QT syndrome or cardiac arrhythmias.

In common with all other SGAs, iloperidone carries a black box warning regarding the increased mortality risk associated with use of antipsychotic drugs in elderly patients with dementia-related psychosis. That said, iloperidone is not approved for the treatment of patients with dementia-related psychosis, and use in the elderly should be avoided pending future clinical trials.

---

## Conclusion

---

Iloperidone is an FDA-approved antipsychotic with proven efficacy in the treatment of schizophrenia. There remains much to be studied regarding its use in specific subgroups of psychotic patients. Iloperidone's utility in nonapproved mood disorder indications is currently unknown. There is a need for additional dose-finding studies to guide the optimal use of this drug.

---

## References

---

- Boyda HN, Procyshyn RM, Pang CCY, et al: Metabolic side-effects of the novel second-generation antipsychotic drugs asenapine and iloperidone: a comparison with olanzapine. *PLoS ONE* 8(1):e53459, 2013 23326434
- Citrome L: Iloperidone: chemistry, pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety and tolerability, regulatory affairs, and an opinion. *Expert Opin Drug Metab Toxicol* 6(12):1551-1564, 2010 21034370
- Chouinard G, Margolese HC: Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res* 76(2-3):247-265, 2005 15949657
- Cutler AJ, Kalali AH, Weiden PJ, et al: Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol* 28 (2 suppl 1):S20-S28, 2008 18334909
- Cutler AJ, Kalali AH, Mattingly GW, et al: Long-term safety and tolerability of iloperidone: results from a 25-week, open-label extension trial. *CNS Spectr* 18(1):43-54, 2013 23312567
- De Hert M, Yu W, Detraux J, et al: Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. *CNS Drugs* 26(9):733-759, 2012 22900950
- Galter D, Unsicker K: Regulation of the transmitter phenotype of rostral and caudal groups of cultured serotonergic raphe neurons. *Neuroscience* 88(2):549-559, 1999 10197774
- Kalkman HO, Feuerbach D, Lötscher E, Schoeffter P: Functional characterization of the novel antipsychotic iloperidone at human D2, D3, alpha 2C, 5-HT6, and 5-HT1A receptors. *Life Sci* 73(9):1151-1159, 2003 12818723
- Kane JM, Lauriello J, Laska E, et al: Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol* 28 (2 suppl 1):S29-S35, 2008 18334910
- Lavedan C, Volpi S, Polymeropoulos MH, Wolfgang CD: Effect of a ciliary neurotrophic factor polymorphism on schizophrenia symptom improvement in an iloperidone clinical trial. *Pharmacogenomics* 9(3):289-301, 2008 18303965
- Lin PY, Tsai G: Meta-analyses of the association between genetic polymorphisms of neurotrophic factors and schizophrenia. *Schizophr Res* 71(2-3):353-360, 2004 15474906
- Newcomer JW: Lurasidone and metabolic syndrome. Presentation at European College of Neuropsychopharmacology, September 2014
- Potkin SG, Litman RE, Torres R, Wolfgang CD: Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. *J Clin Psychopharmacol* 28 (2 suppl 1):S4-S11, 2008 18334911
- Potkin SG, Preskorn S, Hochfeld M, Meng X: A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. *J Clin Psychopharmacol* 33(1):3-10, 2013 23277250
- Rado J, Janicak PG: Iloperidone for schizophrenia. *Expert Opin Pharmacother* 11(12):2087-2093, 2010 20586713
- Rado JT, Janicak PG: Long-term efficacy and safety of iloperidone: an update. *Neuropsychiatr Dis Treat* 10:409-415, 2014 24600226
- Tarazi FI, Stahl SM: Iloperidone, asenapine and lurasidone: a primer on their current status. *Expert Opin Pharmacother* 13(13):1911-1922, 2012 22849428
- Thome J, Durany N, Harsányi A, et al: A null mutation allele in the CNTF gene and schizophrenic psychoses. *Neuroreport* 7(8):1413-1416, 1996 8856688
- Vanda Pharmaceuticals: FANAPT (iloperidone) tablets, full prescribing information. Washington, DC, Vanda Pharmaceuticals Inc., May 2016. Available at:

<https://www.fanapt.com/product/pi/pdf/fanapt.pdf>. Accessed September 6, 2016.

- Volpi S, Heaton C, Mack K, et al: Whole genome association study identifies polymorphisms associated with QT prolongation during iloperidone treatment of schizophrenia. *Mol Psychiatry* 14(11): 1024-1031, 2009a 18521091
- Volpi S, Potkin SG, Malhotra AK, et al: Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia. *J Clin Psychiatry* 70(6):801-809, 2009b 19573479
- Weiden PJ: Iloperidone for the treatment of schizophrenia: an updated clinical review. *Clin Schizophr Relat Psychoses* 6(1):34-44, 2012 22453868
- Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD: Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. *J Clin Psychopharmacol* 28 (2 suppl 1):S12-S19, 2008 18334908
- Weiden PJ, Citrome L, Alva G, et al: A trial evaluating gradual- or immediate-switch strategies from risperidone, olanzapine, or aripiprazole to iloperidone in patients with schizophrenia. *Schizophr Res* 153(1-3):160-168, 2014 24529610

# CHAPTER 33

## Lurasidone

Philip D. Harvey, Ph.D.

**Lurasidone** (Latuda), one of the most recent additions to the atypical antipsychotic class, received U.S. Food and Drug Administration (FDA) approval for the treatment of schizophrenia in October 2010 and for the treatment of bipolar depression in June 2013. As with all currently registered antipsychotic medications, lurasidone is a dopamine D<sub>2</sub> receptor antagonist. In addition, this compound is a full antagonist at the serotonin 2A (5-HT<sub>2A</sub>) receptor, similar to other atypical antipsychotic medications. Lurasidone has other receptor affinities that may contribute to additional beneficial or adverse effects. Because lurasidone is relatively new, its database is limited compared with that of other medications, although the recently approved indication for bipolar depression has led to several additional publications. A current interesting line of investigation is lurasidone's potential utility in the treatment of a new entity defined in DSM-5 ([American](#)

[Psychiatric Association 2013](#)), bipolar depression with mixed features.

In this chapter, I review the pharmacological properties and efficacy basis of lurasidone, the side effects and adverse events from the pivotal studies, and other features of the compound that may prove to be important in later studies as well as in the clinical applications of this agent. I also consider the question of what, if anything, seems unique about lurasidone compared with other available antipsychotic medications.

---

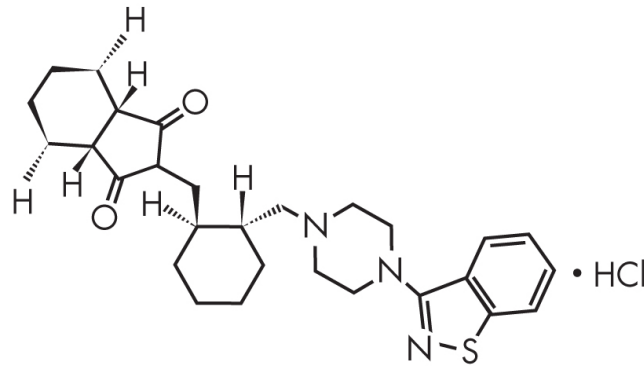
## Pharmacological Properties

---

### Receptor-Binding Profile

Lurasidone belongs to the chemical class of benzisothiazole derivatives ([Figure 33-1](#)). The compound is a full antagonist at dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> receptors, a profile it shares with other atypical antipsychotics. Lurasidone also has high affinity for 5-HT<sub>7</sub> receptors, with in vitro affinity for 5-HT<sub>7</sub> being relatively higher than that shown by the drug for D<sub>2</sub> and 5-HT<sub>2A</sub> receptors. Lurasidone is a partial agonist at 5-HT<sub>1A</sub> receptors ([Ishibashi et al. 2010](#)), and it has moderate affinity for noradrenergic receptors. Lurasidone's minimal affinity for α<sub>1</sub>-adrenergic receptors would be expected to convey a reduced risk for orthostatic hypotension in comparison with compounds that have higher affinity for this receptor. Lurasidone appears to have weak affinity for 5-HT<sub>2C</sub> receptors and no affinity for histamine H<sub>1</sub> receptors, a profile that should carry

relatively low risk for weight gain. Lurasidone lacks affinity for muscarinic acetylcholine M<sub>1</sub> receptors, which suggests reduced risk for cholinergic cognitive deficits and other side effects.



**FIGURE 33-1.** Chemical structure of lurasidone.

## Pharmacokinetics and Dosing

Lurasidone is rapidly absorbed and reaches peak concentrations within 3 hours for the lowest effective antipsychotic dose, 40 mg. Steady state is reached within 7 days ([Sunovion Pharmaceuticals 2013](#)). The molecule is metabolized in the liver via the cytochrome P450 (CYP) 3A4 enzyme system, leading to the conclusion that lurasidone should not be used in the presence of strong inducers (e.g., rifampin) or inhibitors (e.g., ketoconazole) of CYP3A4. Lurasidone does show a food effect. A study examining food effects on lurasidone concentrations found that taking the drug with meals containing 350 calories or more, with either low or high fat content, led to a doubling of the bioavailability of lurasidone compared with dosing during fasting ([Chiu et al. 2010](#)).

The recommended starting dosage of lurasidone is 40 mg/day taken concurrently with at least 350 calories of food. Dosages up to 160 mg/day are currently approved for schizophrenia and up to 120 mg/day for bipolar depression. As previously noted, lurasidone should not be used by patients taking medications that are strong metabolic inducers or inhibitors of CYP3A4. There are no suggested dosage adjustments based on age, gender, ethnicity, or smoking, but individuals with renal or hepatic impairment should not be prescribed dosages greater than 40 mg/day. Lurasidone is currently available in 20-, 40-, 80-, and 120-mg tablets ([Sunovion Pharmaceuticals 2013](#)).

Lurasidone lacks a requirement for initial dosage titration and appears to require minimal adjustment and tinkering. Having a starting dose with substantial efficacy is a strong point for many patients. Food effects are an issue, given that optimal exposure requires the medication to be taken with at least 350 calories of food (with no minimum fat content specified); however, the lack of a need for titration and the uncomplicated requirements for suitable meals will make it easier to apply this treatment to patients who may be challenged in their ability to adhere to complex regimens.

---

## **Efficacy and Tolerability**

---

### **Pivotal Registration Trials in Schizophrenia**



In the standard drug development program, lurasidone at daily dosages of 40 mg, 80 mg, and 120 mg was compared with placebo in four separate studies ([Meltzer et al. 2011](#); [Nakamura et al. 2009](#); [Nasrallah et al. 2013](#); [Ogasa et al. 2013](#)), with several different dosing and comparator strategies. A fifth study ([Loebel et al. 2013](#)) added a 160-mg/day dosage. [Citrome \(2011a, 2011b\)](#) reviewed data based on conference presentations for the schizophrenia development program. Patients ranged in age from 18 to 74 years and were symptomatic with an acute exacerbation of psychosis. In the early clinical studies, the dosage that most consistently separated from placebo was 80 mg/day, although 40 mg/day and 120 mg/day did as well in some trials. Lurasidone at 120 mg/day did not confer additional clinical benefit on the primary outcomes—improved scores on either the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS)—across the different studies. However, clinical data submitted to the FDA led to an increase in the approved dosage to a maximum of 160 mg/day.

## Comparative Efficacy Studies

### Schizophrenia

Four blinded and randomized studies compared lurasidone with other agents in the treatment of schizophrenia.

In the first study ([Potkin et al. 2011](#)), lurasidone was compared with ziprasidone in a 3-week randomized trial in 301 patients with schizophrenia. Both treatments improved symptoms as measured by the PANSS, and there was no significant difference in endpoint PANSS scores.

In the second study ([Meltzer et al. 2011](#)), lurasidone was compared with olanzapine in clinically unstable patients with schizophrenia who had been admitted to inpatient care. Both olanzapine and lurasidone were superior to placebo for clinical response. In addition, the weight gain with olanzapine was significantly greater than that with either lurasidone or placebo, whereas rates of akathisia were significantly higher in the lurasidone group compared with the other two groups.

In the third study ([Loebel et al. 2013](#)), two dosages of lurasidone (80 and 160 mg/day) were compared with quetiapine extended release (XR) 600 mg/day and placebo in inpatients experiencing an acute exacerbation of schizophrenia. Both lurasidone (at both dosages) and quetiapine separated from placebo, and weight gain and sedation/sleepiness were more frequent with quetiapine than with either dosage of lurasidone.

In the fourth study ([Citrome et al. 2012](#)), clinically stable patients with schizophrenia were randomly assigned to receive either risperidone or lurasidone and were followed for 12 months to assess potential differences in long-term safety. Findings included greater weight gain with risperidone, minimal differences between lurasidone and risperidone in efficacy, and no differences between the two agents in relapse rates. All-cause discontinuation rates were higher for lurasidone, possibly due to slight elevations in nausea in the lurasidone group.

## **Bipolar Depression**

Two randomized placebo-controlled trials of lurasidone were conducted in patients with bipolar depression. In the first study ([Loebel et al. 2014a](#); monotherapy), lurasidone at two different dosage ranges (20–60 mg/day and 80–120

mg/day) was compared with placebo. Both dosage ranges separated from placebo, with similar effect sizes. In the second study ([Loebel et al. 2014b](#); adjunctive therapy), lurasidone at 20–120 mg/day was added to stable treatment with either valproate or lithium. Statistically significant separation from placebo was found. Lurasidone treatment was administered at a mean modal dose of 75 mg/day, which translates to an available dose of 80 mg/day. The results of these two studies led to lurasidone's approval by the FDA for both augmentation of lithium or valproate therapy and monotherapy of bipolar depression in June 2013.

In an additional post hoc analysis of the results of the monotherapy study, [McIntyre et al. \(2015\)](#) reported that lurasidone was effective in the treatment of bipolar depression with mixed features, an entity newly defined in DSM-5. The presence of mixed features was defined as having a Young Mania Rating Scale (YMRS; [Young et al. 1978](#)) score of 4 or greater. Fifty-six percent of the patients in the study were found to have mixed features (272 out of 485 patients). Of the patients with mixed features, 182 received treatment with active lurasidone and 90 received placebo treatment. Efficacy for the treatment of depression in patients with and without mixed features was essentially equivalent: 15.7-point decreases in Montgomery-Åsberg Depression Rating Scale (MADRS; [Montgomery and Åsberg 1979](#)) scores were seen for patients without mixed features, and 15.2-point decreases were found for those with mixed features. Eighty-two percent of the patients without mixed features completed the trial when treated with active lurasidone, and 73% of the patients with mixed features completed the study with active treatment. These data indicate that the presence of mixed features in bipolar

depression should not be viewed as a contraindication to treatment with lurasidone.

In a very recent study ([Suppes et al. 2016](#)), lurasidone was tested for efficacy in major depression with mixed features. This newly defined condition is characterized by the coexistence within a major depressive episode of a limited set of manic symptoms ([American Psychiatric Association 2013](#)). Patients selected for the presence of DSM-IV-TR ([American Psychiatric Association 2000](#))-defined major depressive disorder and two or three manic symptoms were randomly assigned to lurasidone ( $n=109$ ) or placebo ( $n=100$ ) for a 6-week trial. Lurasidone was superior to placebo, leading to a 20.5-point change on the MADRS for active treatment compared with a 13-point change for placebo ( $P<0.001$ ; effect size  $d=.80$ ). Completion rates were similar for active treatment and placebo (94% and 85%, respectively), and the remission rate was 49% for active treatment. Switch into mania did not occur with lurasidone treatment, and patients who received lurasidone manifested a 7-point decrease in their YMRS scores. These data suggest efficacy for lurasidone in the treatment of depression with mixed features as well as bipolar depression.

## Summary of Efficacy and Tolerability Data

The risk-benefit evaluation for lurasidone suggests a lower potential for metabolic consequences and QTc prolongation combined with a slightly higher risk of extrapyramidal side effects (EPS) and akathisia compared with some of the other atypical antipsychotic medications. Prolactin elevation

appears to be minimal within the approved dosage range. Given our limited clinical experience with lurasidone, it may be premature to target an optimal patient for this medication; however, the reduced metabolic consequences of lurasidone would seem to be a very strong point. Patients who are extraordinarily vulnerable to EPS may require close monitoring.

Lurasidone's efficacy in schizophrenia relative to other agents has been examined in four active comparison studies ([Citrome et al. 2012](#); [Loebel et al. 2013](#); [Meltzer et al. 2011](#); [Potkin et al. 2011](#)), none of which found lurasidone to be inferior. It is not yet possible to assess lurasidone's relative efficacy in bipolar depression, given the absence of comparative trials to date.

---

## Side Effects and Safety

---

### Class Warnings

The typical class warnings are present on the lurasidone label ([Sunovion Pharmaceuticals 2013](#)), including the black box warning about increased stroke risk in elderly individuals and a variety of other class warnings regarding neuroleptic malignant syndrome, tardive dyskinesia, diabetes, hyperlipidemia, weight gain, glucose abnormalities, hyperprolactinemia, agranulocytosis, suicide, and seizures. Lurasidone has no warning for QTc alteration; a dedicated cardiac safety study (referenced in the package insert) found no evidence of QTc prolongation with lurasidone treatment.

# Adverse-Event Reports

Safety information is available from the manufacturer's safety database (see also [www.sunovionprofile.com/sp/latuda-bp.html](http://www.sunovionprofile.com/sp/latuda-bp.html)). Dose-related adverse effects that separated from placebo included somnolence, akathisia, and EPS (as measured by total scores on clinical rating scales for EPS). Of note, weight and metabolic parameters were only minimally affected in patients with schizophrenia or bipolar depression in clinical trials. Although short-term changes in cholesterol, triglycerides, and glucose are likely to be attributable to transition from medications with more substantial adverse profiles in these domains, the weight-gain data for lurasidone are very noticeable and consistent.

---

## Promising Features

---

### Favorable Metabolic Profile

Lurasidone appears to have the promise of weight neutrality. Weight gain in the pooled 6-week studies across doses was 0.75 kg; in the pooled 12-month database from extension studies, patients lost an average of 0.4 kg ([Meyer et al. 2015](#)). These statistics compare favorably with those for other antipsychotics in wide clinical use (see review by [Citrome 2011b](#)). It is important to note that specific populations outside the current label may have a greater weight-gain risk compared with the typical patient with chronic schizophrenia in these trials. Data are not yet

available for lurasidone's profile in the long-term treatment of bipolar depression. Nevertheless, the suggestion of no weight gain after a year's treatment, even for patients who may have gained weight with previous treatments, is quite promising.

## Potential Cognitive Benefits

### Basic Science Rationale

Compounds that interact with the 5-HT<sub>7</sub> receptor as their primary binding profile have historically been shown to produce beneficial cognitive effects in animal models ([Ballaz et al. 2007](#)). Furthermore, it is postulated that agents with partial agonist properties at the 5-HT<sub>1A</sub> receptor may have potential benefit in regard to reduction of flat affect and related negative symptoms in schizophrenia ([Newman-Tancredi 2010](#)).

MK-801 is a glutamate receptor antagonist that is used to induce cognitive impairments in healthy individuals that are quite similar to those seen in schizophrenia. Like other *N*-methyl-D-aspartate (NMDA) antagonists, MK-801 is capable of inducing deficits in memory and problem solving. Given that NMDA antagonists such as ketamine and phencyclidine can induce a reliable analog of schizophrenia in healthy people (and exacerbate psychosis in patients with schizophrenia), such manipulations have more intrinsic validity than cholinergic manipulations such as scopolamine challenge. In rats, lurasidone has shown the potential to reverse MK-801-induced learning and memory deficits in the passive avoidance test ([Ishiyama et al. 2007](#)) and the Morris water maze ([Enomoto et al. 2008](#)).

Research using analogs of cognitive impairment derived from animal models has notoriously failed to yield paradigms with adequate translational relevance to the specific cognitive domains affected in schizophrenia, particularly in terms of reliably predicting beneficial cognitive effects associated with pharmacological treatment ([Harvey 2009](#)). A possible reason for this failure may be that the adverse influences on human cognition of dopamine D<sub>2</sub> receptor antagonism associated with antipsychotic treatment may override the influences of a “secondary” receptor profile, preventing its beneficial effects from being realized ([Harvey and McClure 2006](#)). For example, ziprasidone, a partial agonist at the 5-HT<sub>1A</sub> receptor, has never demonstrated greater cognitive benefit versus antipsychotics that do not interact with that receptor (e.g., olanzapine; [Harvey et al. 2004](#)). Thus, clear evidence of cognitive enhancement in patients with schizophrenia treated with the medication of interest, compared with other treatments in similar populations, is the “bottom line” requirement for demonstration of meaningful cognitive benefit.

## **Studies in Schizophrenia**

Three published studies in patients with schizophrenia have addressed the issue of lurasidone’s cognitive benefit compared with that of other antipsychotics ([Harvey et al. 2011, 2013, 2015](#)).

The first study, which was conducted during the early development phases of lurasidone, was a 3-week double-blind, randomized head-to-head comparison of lurasidone versus ziprasidone in generally clinically stable outpatients with schizophrenia ([Harvey et al. 2011](#)). At the time this



study was conducted, no U.S. patients had ever been exposed to lurasidone. Patients were selected for being naive to treatment with ziprasidone as well. The study examined changes in performance on a neuropsychological assessment consisting of most of the tests in the widely used Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB; [Nuechterlein et al. 2008](#)) and an interview-based assessment of cognitive functioning, the Schizophrenia Cognition Rating Scale (SCoRS; [Keefe et al. 2006](#)). The study found that lurasidone was associated with improvements on neuropsychological tests that were generally consistent with practice effects ([Harvey et al. 2011](#)). There was one exception, processing speed, which manifested relatively greater improvement with lurasidone than with ziprasidone. However, improvements seen with lurasidone on the SCoRS were double the size of improvements seen on the neuropsychological assessments and nearly significantly larger than the improvements associated with ziprasidone. These results cannot be attributed to practice effects, given that the SCoRS is an interview, not a performance-based measure. Furthermore, the fact that the differential effects of lurasidone and ziprasidone were nearly significant ( $P<0.06$ ) argues against a generalized bias effect, because the lurasidone effects were clearly larger.

The second study ([Harvey et al. 2013](#)) compared two dosages of lurasidone (80 and 160 mg/day) with 600 mg/day of quetiapine XR and placebo. This double-blind, placebo-controlled trial was conducted in patients experiencing an acute exacerbation of psychosis. Lurasidone 160 mg/day was compared with placebo, quetiapine XR, or lurasidone 80 mg/day over a 6-week

period, followed by a 6-month double-blind extension. Follow-ups were conducted at 3 and 6 months, and placebo patients were switched to lurasidone at flexible dosages; quetiapine XR patients remained on the same treatment. The CogState Computerized Cognitive Battery ([Pietrzak et al. 2009](#)) and the University of California San Diego (UCSD) Performance-based Skills Assessment—Brief version (UPSA-B; [Mausbach et al. 2007](#); [Patterson et al. 2001](#)) were administered at baseline and at each assessment point. When patients who provided invalid baseline CogState data were censored from the analysis, lurasidone at 160 mg/day separated from placebo on composite cognitive improvement at the 6-week endpoint, whereas lurasidone at 80 mg/day and quetiapine XR did not.

[Harvey et al. \(2015\)](#) presented an analysis of the dose-response relationships of lurasidone compared with quetiapine during the full 6-month duration of the trial. The full sample, regardless of the validity of baseline performance, was examined at two follow-up assessments (at 3 and 6 months). Both dosages of lurasidone were found to be superior to quetiapine XR at both assessments ([Harvey et al. 2015](#)). Scores on the UPSA-B improved with all active treatments at each of the assessment time points, with no between-group differences in improvements.

Although these results clearly require replication, they suggest that lurasidone may have beneficial cognitive effects. In all three studies, performance- and interview-based assessments of functionally relevant cognitive processes showed treatment-related improvements. In the [Harvey et al. \(2013\)](#) study, the performance-based cognitive assessments also showed improvements that were superior to those seen with placebo or the active comparator. This superiority to the comparator was confirmed across all

dosages of lurasidone in the [Harvey et al. \(2015\)](#) study. The sleepiness-inducing effects of quetiapine XR may have contributed to the difference between this compound and lurasidone ([Loebel et al. 2014c](#)); however, that circumstance would not have explained the separation of lurasidone from placebo.

---

## Conclusion

---

Lurasidone is a new antipsychotic with some benefits compared with other available medications, including low weight-gain propensity and reduced risk for metabolic side effects. Little of the published data have been supported by sources other than the sponsor of the medication. We will watch this medication carefully to continue to determine its benefit over time. Since the previous edition of this textbook, the indication for bipolar depression has been added and additional cognitive and long-term safety data have become available. No new safety concerns have emerged, and no new data raising efficacy questions have appeared.

---

## References

---

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013

- Ballaz SJ, Akil H, Watson SJ: The 5-HT<sub>7</sub> receptor: role in novel object discrimination and relation to novelty-seeking behavior. *Neuroscience* 149(1):192-202, 2007 17869441
- Chiu YY, Preskorn S, Sarubbi D, et al: Effect of food on lurasidone absorption. Poster presented at the NCDEU Meeting, Boca Raton, FL, June 14-17, 2010
- Citrome L: Lurasidone for schizophrenia: a brief review of a new second-generation antipsychotic. *Clin Schizophr Relat Psychoses* 4(4):251-257, 2011a 21177242
- Citrome L: Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. *Int J Clin Pract* 65(2):189-210, 2011b 21129135
- Citrome L, Cucchiaro J, Sarma K, et al: Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. *Int Clin Psychopharmacol* 27(3):165-176, 2012 22395527
- Enomoto T, Ishibashi T, Tokuda K, et al: Lurasidone reverses MK-801-induced impairment of learning and memory in the Morris water maze and radial-arm maze tests in rats. *Behav Brain Res* 186(2):197-207, 2008 17881065
- Harvey PD: Pharmacological cognitive enhancement in schizophrenia. *Neuropsychol Rev* 19(3):324-335, 2009 19507034
- Harvey PD, McClure MM: Pharmacological approaches to the management of cognitive dysfunction in schizophrenia. *Drugs* 66(11):1465-1473, 2006 16906778
- Harvey PD, Siu CO, Romano S: Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Psychopharmacology (Berl)* 172(3):324-332, 2004 14615877

- Harvey PD, Ogasa M, Cucchiaro J, et al: Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs. ziprasidone. *Schizophr Res* 127(1-3):188-194, 2011 21277745
- Harvey PD, Siu CO, Hsu J, et al: Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension. *Eur Neuropsychopharmacol* 23(11):1373-1382, 2013 24035633
- Harvey PD, Siu CO, Ogasa M, Loebel A: Effect of lurasidone dose on cognition in patients with schizophrenia: post-hoc analysis of a long-term, double-blind continuation study. *Schizophr Res* 166(1-3): 334-338, 2015 26117157
- Ishibashi T, Horisawa T, Tokuda K, et al: Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT<sub>7</sub>) and 5-HT<sub>1A</sub> receptor activity. *J Pharmacol Exp Ther* 334(1):171-181, 2010 20404009
- Ishiyama T, Tokuda K, Ishibashi T, et al: Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test. *Eur J Pharmacol* 572(2-3):160-170, 2007 17662268
- Keefe RS, Poe M, Walker TM, et al: The Schizophrenia Cognition Rating Scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. *Am J Psychiatry* 163(3):426-432, 2006 16513863
- Loebel A, Cucchiaro J, Sarma K, et al: Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. *Schizophr Res* 145(1-3):101-109, 2013 23415311

- Loebel A, Cucchiaro J, Silva R, et al: Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 171(2):160-168, 2014a 24170180
- Loebel A, Cucchiaro J, Silva R, et al: Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 171(2):169-177, 2014b 24170221
- Loebel AD, Siu CO, Cucchiaro JB, et al: Daytime sleepiness associated with lurasidone and quetiapine XR: results from a randomized double-blind, placebo-controlled trial in patients with schizophrenia. *CNS Spectr* 19(2):197-205, 2014c 24330860
- Mausbach BT, Harvey PD, Goldman SR, et al: Development of a brief scale of everyday functioning in persons with serious mental illness. *Schizophr Bull* 33(6):1364-1372, 2007 17341468
- McIntyre RS, Cucchiaro J, Pikalov A, et al: Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. *J Clin Psychiatry* 76(4):398-405, 2015 25844756
- Meltzer HY, Cucchiaro J, Silva R, et al: Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry* 168(9):957-967, 2011 21676992
- Meyer JM, Mao Y, Pikalov A, et al: Weight change during long-term treatment with lurasidone: pooled analysis of studies in patients with schizophrenia. *Int Clin Psychopharmacol* 30(6):342-350, 2015 26196189
- Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382-389, 1979 444788
- Nakamura M, Ogasa M, Guarino J, et al: Lurasidone in the treatment of acute schizophrenia: a double-blind,

- placebo-controlled trial. *J Clin Psychiatry* 70(6):829–836, 2009 19497249
- Nasrallah HA, Silva R, Phillips D, et al: Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. *J Psychiatr Res* 47(5):670–677, 2013 23421963
- Newman-Tancredi A: The importance of 5-HT<sub>1A</sub> receptor agonism in antipsychotic drug action: rationale and perspectives. *Curr Opin Investig Drugs* 11(7):802–812, 2010 20571976
- Nuechterlein KH, Green MF, Kern RS, et al: The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry* 165(2):203–213, 2008 18172019
- Ogasa M, Kimura T, Nakamura M, Guarino J: Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. *Psychopharmacology (Berl)* 225(3): 519–530, 2013 22903391
- Patterson TL, Goldman S, McKibbin CL, et al: UCSD Performance-based Skills Assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophr Bull* 27(2):235–245, 2001 11354591
- Pietrzak RH, Olver J, Norman T, et al: A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. *J Clin Exp Neuropsychol* 31(7):848–859, 2009 19142774
- Potkin SG, Ogasa M, Cucchiaro J, Loebel A: Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophr Res* 132(2–3):101–107, 2011 21889878
- Sunovion Pharmaceuticals: Latuda (lurasidone HCl) tablets: prescribing information. Revised July 2013. Available at:

<http://www.latuda.com/LatudaPrescribingInformation.pdf>. Accessed September 8, 2015.

Suppes R, Silva R, Cucchiaro J, et al: Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 173(4): 400–407, 2016 26552942

Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 133:429–435, 1978 728692



# CHAPTER 34

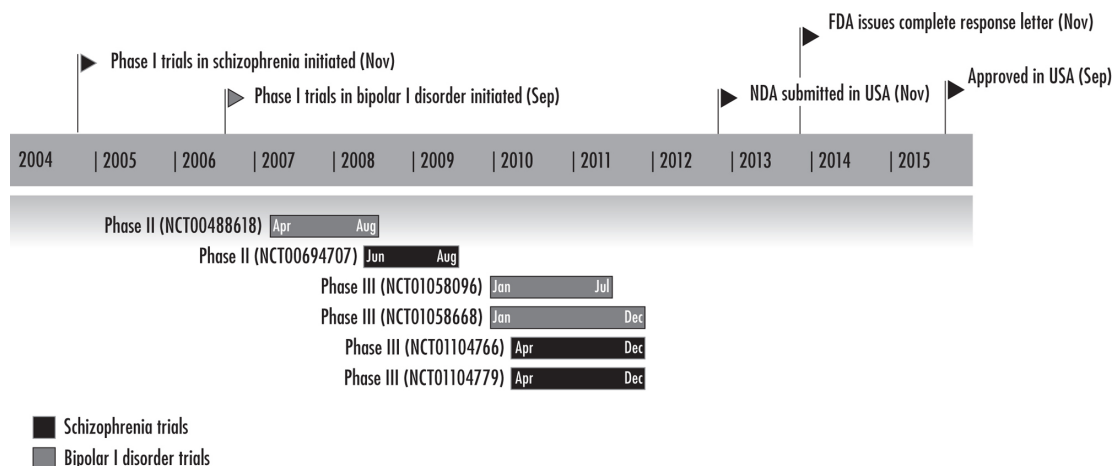
## Cariprazine

Sultan Albrahim, M.D.

Joseph H. Henry, M.D.

Charles B. Nemeroff, M.D., Ph.D.

Cariprazine (Vraylar) was initially discovered by the Hungarian company Gedeon Richter Ltd. (November 2004) and was developed by Forest Laboratories and submitted to the U.S. Food and Drug Administration (FDA) in November 2012 ([Forest Laboratories 2012](#)). In September 2015, cariprazine was approved by the FDA for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults ([Actavis Inc. 2015](#)) ([Figure 34-1](#)). Cariprazine is also in development in a variety of countries for use in the treatment of schizophrenia with predominantly negative symptoms (Phase III), for use as an adjunct in the treatment of major depressive disorder (Phase II/III), and for use in the treatment of bipolar depression (Phase II) ([McCormack 2015](#)).



---

**FIGURE 34-1.** Key development milestones for cariprazine.

Note. FDA=U.S. Food and Drug Administration; NDA=new drug application.

Source. Reprinted from McCormack PL: "Cariprazine: First Global Approval." *Drugs* 75(17):2035-2043, 2015. Copyright © 2015, Springer International Publishing. Used with permission.

Cariprazine, a piperazine/piperidine derivative, is classified as an atypical antipsychotic on the basis of its dopamine receptor partial agonist mechanism. Cariprazine is the third agent with a dopamine receptor partial agonist mechanism to become available (aripiprazole was approved in 2002, and brexpiprazole received FDA approval on July 13, 2015, both for schizophrenia; see [Chapter 29](#) in this volume, "Aripiprazole and Brexpiprazole," by Gonzalez and Strassnig). In common with aripiprazole and brexpiprazole, cariprazine has partial agonist effects at dopamine 2 ( $D_2$ ) and dopamine 3 ( $D_3$ ) receptors and serotonin 1A ( $5-HT_{1A}$ ) receptors and antagonist effects at serotonin 2A ( $5-HT_{2A}$ ) receptors. What is unique about cariprazine is its higher affinity for and more selective binding to  $D_3$  receptors compared with other currently marketed typical and atypical antipsychotics.

---

## Comparison With Other Dopamine Receptor Partial Agonists

---

The theory behind the use of partial agonists, including cariprazine, is that these agents restore homeostatic balance to neurochemical circuits by 1) decreasing the effects of endogenous neurotransmitters (dopamine tone) in regions of the brain where their transmission is excessive, such as in the mesolimbic regions in schizophrenia or mania; 2) simultaneously increasing neurotransmission in regions where transmission of endogenous neurotransmitters is low, such as in the prefrontal cortex in schizophrenia; and 3) exerting little effect in regions where neurotransmitter activity is normal, such as the pituitary gland.

Aripiprazole and brexpiprazole are dopamine  $D_2$  receptor-preferring partial agonists, with minimal  $D_3$  effects. In contrast, cariprazine has a six- to eightfold greater affinity for  $D_3$  receptors than for  $D_2$  receptors, with a specificity for the  $D_3$  receptor that is 3–10 times greater than aripiprazole's specificity for that receptor ([Mattingly and Anderson 2016](#)).

Aripiprazole binds more potently than cariprazine to human and rat  $5-HT_{2A}$ ,  $5-HT_{2C}$ , and adrenergic receptors. In contrast, cariprazine has lesser

affinity for human and rat hippocampal 5-HT<sub>1A</sub> receptors (and demonstrates low intrinsic efficacy), low affinity for human 5-HT<sub>2A</sub> receptors, moderate or low affinity for histamine H<sub>1</sub> and 5-HT<sub>2C</sub> receptors, and negligible affinity for cholinergic or adrenergic receptors, all of which suggest a reduced propensity for side effects related to these receptors (Kiss et al. 2010).

In addition to its labeled indications for schizophrenia and manic or mixed episodes associated with bipolar I disorder, aripiprazole is approved as an adjunctive treatment for depression or bipolar maintenance, and for irritability associated with autistic disorder. In addition to its approved use in schizophrenia, brexpiprazole has an FDA indication for use as an adjunct to antidepressant treatment in major depressive disorder. Cariprazine has not been directly compared with aripiprazole, brexpiprazole, or other antipsychotic agents in clinical studies of schizophrenia or bipolar I disorder, and it has not yet received approval for indications other than schizophrenia and bipolar I disorder. In contrast to the variety of formulations available for aripiprazole, cariprazine is currently available only in a capsule for oral administration.

Although their mechanisms of action are in some ways similar, the three agents differ in terms of their pharmacodynamic profile and receptor affinities, as summarized in Table 34-1.

**TABLE 34-1. Pharmacodynamic profiles of cariprazine, aripiprazole, and brexpiprazole: in vitro binding affinities for human receptors**

Receptor <sup>b</sup>		Activity	Affinity K <sub>i</sub> <sup>a</sup> (in vitro)		
			Cariprazine	Aripiprazole	Brexpiprazole
Dopamine	D <sub>3</sub>	Partial agonist	0.085	0.8	1.1

<sup>a</sup>Receptor binding affinity K<sub>i</sub> [nM], inverse relationship.

<sup>b</sup>Cariprazine and aripiprazole demonstrated negligible (percentage displacement less than 20% at 1 μM test concentration) affinities for adrenergic (α<sub>2B</sub>, α<sub>2C</sub>), cannabinoid (CB<sub>1</sub>, CB<sub>2</sub>), dopamine (D<sub>1</sub>, D<sub>4.2</sub>, D<sub>5</sub>), histamine (H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>), muscarinic (M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub>, M<sub>5</sub>), nicotinic, and serotonin (5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5A</sub>, 5-HT<sub>6</sub>) receptors (Kiss et al. 2010).

*Source.* Adapted from Citrome L: “The ABC’s of Dopamine Receptor Partial Agonists—Aripiprazole, Brexpiprazole and Cariprazine: The 15-Min Challenge to Sort These Agents Out.” *International Journal of Clinical Practice* 69(11):1211-1220, 2015. Copyright © 2015, John Wiley & Sons Ltd. Used with permission.

Receptor <sup>b</sup>	Activity	Affinity K <sub>i</sub> <sup>a</sup> (in vitro)		
		Cariprazine	Aripiprazole	Brexpiprazole
	D <sub>2L</sub> Partial agonist	0.49	0.34	0.30
	D <sub>2S</sub> Partial agonist	0.69		
Serotonin	5-HT <sub>1A</sub> Partial agonist	2.6	1.7	0.12
	5-HT <sub>2A</sub> Antagonist	18.8	3.4	0.47
	5-HT <sub>2B</sub> Antagonist	0.58	0.36	1.9
	5-HT <sub>2C</sub> Antagonist	134	15	34
	5-HT <sub>7</sub> Antagonist	111	39	3.7
Histamine	H <sub>1</sub> Antagonist	23.2	61	19
Adrenergic	α <sub>1A</sub> Antagonist	155	57	15

<sup>a</sup>Receptor binding affinity K<sub>i</sub> [nM], inverse relationship.

<sup>b</sup>Cariprazine and aripiprazole demonstrated negligible (percentage displacement less than 20% at 1 μM test concentration) affinities for adrenergic (α<sub>2B</sub>, α<sub>2C</sub>), cannabinoid (CB<sub>1</sub>, CB<sub>2</sub>), dopamine (D<sub>1</sub>, D<sub>4.2</sub>, D<sub>5</sub>), histamine (H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>), muscarinic (M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub>, M<sub>5</sub>), nicotinic, and serotonin (5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5A</sub>, 5-HT<sub>6</sub>) receptors ([Kiss et al. 2010](#)).

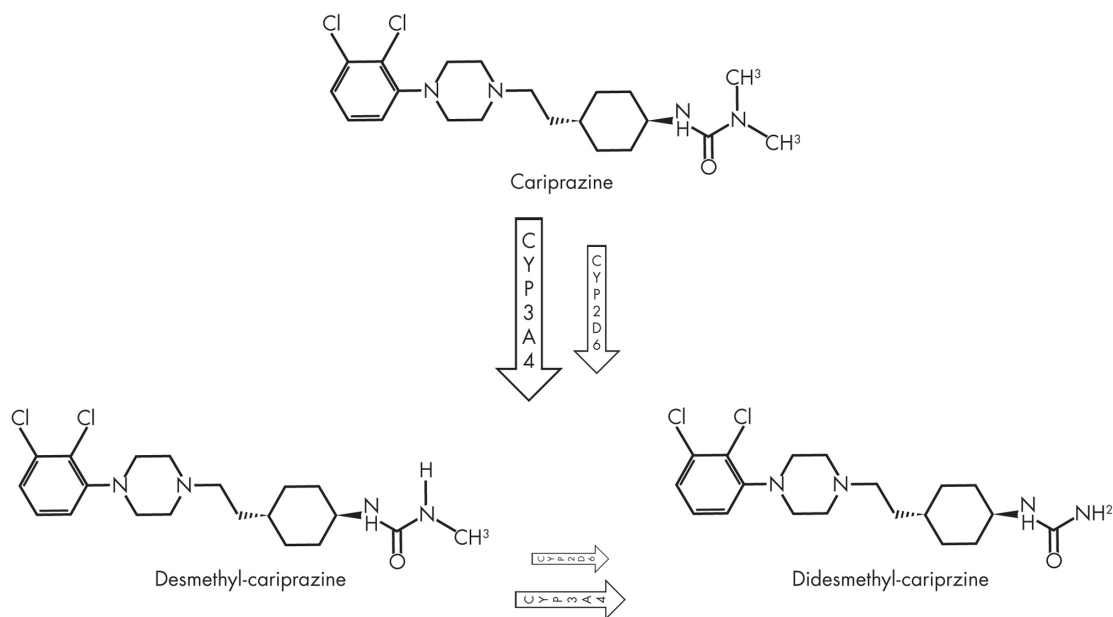
*Source.* Adapted from Citrome L: “The ABC’s of Dopamine Receptor Partial Agonists—Aripiprazole, Brexpiprazole and Cariprazine: The 15-Min Challenge to Sort These Agents Out.” *International Journal of Clinical Practice* 69(11):1211-1220, 2015. Copyright © 2015, John Wiley & Sons Ltd. Used with permission.

## Pharmacodynamics

### Structure

Cariprazine, also known as RGH-188 and MP-214, is 3-[4-{2-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethyl} cyclohexyl]-1,1-dimethylurea ([Figure 34-2](#)). The active ingredient is cariprazine hydrochloride, a compound synthesized and selected for development on the basis of its high selectivity for dopamine D<sub>3</sub> receptors over D<sub>2</sub> receptors ([Veselinovic et al. 2013](#)).

Cariprazine has two clinically relevant active metabolites: desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR) ([Citrome 2013b](#)).



**FIGURE 34-2.** Chemical structures of cariprazine and its major metabolites, desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR).

## Receptor-Binding Profile

Cariprazine is a potent dopamine D<sub>3</sub> and D<sub>2</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors, which is a unique pharmacological profile among known antipsychotic medications ([Kiss et al. 2010](#)).

Whereas D<sub>2</sub> receptor antagonism is required for antipsychotic efficacy, D<sub>3</sub> receptor antagonism may impart beneficial effects on cognition while attenuating the risk of extrapyramidal side effects (EPS) ([Veselinovic et al. 2013](#)).

Cariprazine acts as a partial agonist at dopamine D<sub>3</sub> and D<sub>2</sub> receptors with very high binding affinity and at serotonin 5-HT<sub>1A</sub> receptors with high binding affinity (see [Table 34-1](#)). Cariprazine acts as an antagonist at serotonin 5-HT<sub>2B</sub> and 5-HT<sub>2A</sub> receptors with very high and moderate binding affinity, respectively, and at histamine H<sub>1</sub> receptors with moderate binding affinity. Cariprazine shows weak binding affinity for serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors, very low affinity for  $\alpha_{1A}$ -adrenergic receptors,

and no appreciable affinity for cholinergic muscarinic receptors ([Actavis Inc. 2015](#)).

## Dopamine Receptors

**D<sub>3</sub> and D<sub>2</sub>.** Dopamine, the neurotransmitter primarily linked to psychosis, has very high affinity for D<sub>3</sub> receptors. In vitro, virtually all of the first- and second-generation antipsychotics in clinical use are D<sub>2</sub> nonselective and therefore show considerable affinity for the D<sub>3</sub> receptor subtype. D<sub>3</sub> receptors have pre- and postsynaptic localizations in brain stem nuclei, limbic parts of the striatum, and cortex and exert a widespread influence on dopamine release, on dopaminergic function, and on several other neurotransmitters. The D<sub>2</sub> receptor's assumed role as an autoreceptor is suggested by its high expression in regions such as the ventral tegmental area and substantia nigra.

The signaling pathways of D<sub>3</sub> receptors are distinct from those of other members of the D<sub>2</sub>-like receptor family. Although the role of D<sub>3</sub> receptor blockade in alleviating positive symptoms is still controversial, selective D<sub>3</sub> receptor antagonism has therapeutic effects in schizophrenia and beyond, as demonstrated by several animal models: improved cognitive function, emotional processing, executive function, flexibility, and social behavior. D<sub>3</sub> receptor antagonism seems to contribute to the atypicality of antipsychotics by reducing motor EPS; has no direct influence on prolactin release; and does not cause anhedonia, weight gain, or metabolic dysfunction ([Gross and Drescher 2012](#)).

D<sub>3</sub>, an autoreceptor primarily located in the limbic system, controls phasic (not tonic) activity of dopamine nerve cells and mediates behavioral abnormalities induced by glutamate and *N*-methyl-D-aspartate receptor antagonists ([Veselinovic et al. 2013](#)).

Animal models and preclinical studies have demonstrated antipsychotic-like and procognitive effects potentially attributable to dopamine D<sub>3</sub> receptor-preferring agents. D<sub>3</sub> receptor blockade appears to enhance—whereas D<sub>3</sub> receptor agonism seems to impair—cognitive function in animals ([Gyertyán et al. 2011](#)).

The overall function of dopamine D<sub>3</sub> receptors in the human brain remains incompletely understood.

## Serotonin Receptors

**5-HT<sub>1A</sub>.** Cariprazine has a high affinity for human serotonin 5-HT<sub>1A</sub> receptors and acts as a partial agonist at these receptors. The effect of cariprazine depends on the serotonin concentration at the site.

In vivo, at lower dosages, cariprazine's partial agonism at 5-HT<sub>1A</sub> receptors may contribute minimally to its antipsychotic-like activity and side-effect profile; at higher dosages, the 5-HT<sub>1A</sub> receptor partial agonism may contribute to cariprazine's favorable side-effect profile (i.e., lack of EPS) ([Kiss et al. 2010](#)).

Cariprazine's 5-HT<sub>1A</sub> receptor partial agonism may also contribute to its antidepressant efficacy ([Bluer and Ward 2003](#)) and to its beneficial effects on negative symptoms and cognitive dysfunction ([Bantick et al. 2001](#)), as suggested by preclinical studies.

**5-HT<sub>2B</sub>.** Cariprazine has very high binding affinity for human serotonin 5-HT<sub>2B</sub> receptors ( $K_i=0.58$  nM). Activity at these receptors may modulate dopamine release in the nucleus accumbens ([Citrome 2013a](#)).

Cariprazine's antagonist activity at 5-HT<sub>2B</sub> receptors may contribute to its postulated effects on mood and cognition, as observed in preclinical studies.

**5-HT<sub>2A</sub>.** Cariprazine's binding affinity for human serotonin 5-HT<sub>2A</sub> receptors is lower than that of aripiprazole and brexpiprazole. Theoretically, antagonist effects at serotonin 5-HT<sub>2A</sub> receptors are essential for "atypicality" of antipsychotics. It is unknown whether cariprazine's relatively low affinity for 5-HT<sub>2A</sub> receptors has any clinical implications.

## Histamine H<sub>1</sub> Receptors

Cariprazine's moderate affinity for H<sub>1</sub> receptors is roughly equivalent to the affinity of aripiprazole and brexpiprazole for these receptors. Sedation and orthostatic hypotension with high dosages of cariprazine might be related to this property.

## Positron Emission Tomography Studies

Although several marketed antipsychotics have shown moderate in vitro affinity for the D<sub>3</sub> receptor, positron emission tomography (PET) studies have suggested that these compounds do not demonstrate D<sub>3</sub> receptor occupancy in vivo at therapeutic dosages ([Girgis et al. 2016](#)).

Three PET studies have demonstrated cariprazine's excellent brain penetration, showing high and dose-dependent in vivo occupancy of both



dopamine D<sub>3</sub> and D<sub>2</sub> receptors in rodents ([Gyertyán et al. 2011](#)), in monkeys ([Seneca et al. 2011](#)), and in patients with schizophrenia ([Girgis et al. 2016](#)).

In a Phase I open-label three-cohort study, patients with schizophrenia ( $n=3$ ) received multiple-dose cariprazine treatment for 15 days. Cariprazine treatment resulted in high D<sub>2</sub> and D<sub>3</sub> receptor occupancy at all dosages (range, 0.5–12.0 mg/day) and conditions (i.e., acute [day 1], day 4/5, and subchronic [day 15]). A clear dose-occupancy relationship existed for acute, day 4/5, and subchronic treatment, with the highest occupancy for both D<sub>2</sub> and D<sub>3</sub> receptors observed with the highest dosage (12 mg/day).

For dosages of 12 mg/day, 3 mg/day, and 1 mg/day, respectively, the mean D<sub>3</sub> receptor occupancies were 99%, 92%, and 76%, and the mean D<sub>2</sub> receptor occupancies were 95%, 79%, and 45%.

For acute (day 1/4) dosing, the median effective dose (ED<sub>50</sub>) was 1.52 mg for D<sub>3</sub> receptor occupancy and 1.84 mg for D<sub>2</sub> occupancy, with a D<sub>3</sub>/D<sub>2</sub> selectivity ratio range of 1.21–1.31. For subchronic [day 15] dosing, the ED<sub>50</sub> was 0.30 mg for D<sub>3</sub> receptor occupancy and 1.03 mg for D<sub>2</sub> occupancy, with a D<sub>3</sub>/D<sub>2</sub> selectivity ratio range of 3.43–5.75.

Cariprazine showed high and dose-dependent in vivo occupancy of both dopamine D<sub>3</sub> and D<sub>2</sub> receptors in patients with schizophrenia. After subchronic (15-day) administration, cariprazine showed a threefold greater preference for D<sub>3</sub> versus D<sub>2</sub> receptors. The increased D<sub>3</sub>/D<sub>2</sub> selectivity after subchronic dosing compared with acute dosing may be related to the pharmacological activity of cariprazine's metabolites ([Girgis et al. 2016](#)).

---

## Pharmacokinetics

---

In a Phase II double-blind, placebo-controlled tolerance study, the pharmacokinetic properties of cariprazine were similar in healthy volunteers and schizophrenia patients, and there were no significant clinical changes in pharmacokinetic properties by age, sex, or race/ethnicity ([Kapás et al. 2008](#)).

In premarketing studies investigating cariprazine's tolerability in specific populations, patients with either mild or moderate hepatic impairment (Child-Pugh score between 5 and 9), in comparison with healthy subjects, had approximately 25% higher exposure (peak serum concentration [ $C_{\max}$ ] and AUC [area under the concentration curve]) to the parent drug, and approximately 45% lower exposure to the major active metabolites (DCAR and DDCA), following a single daily dose of 1 mg cariprazine or 0.5 mg cariprazine for 14 days). Pharmacokinetic analyses in patients with renal



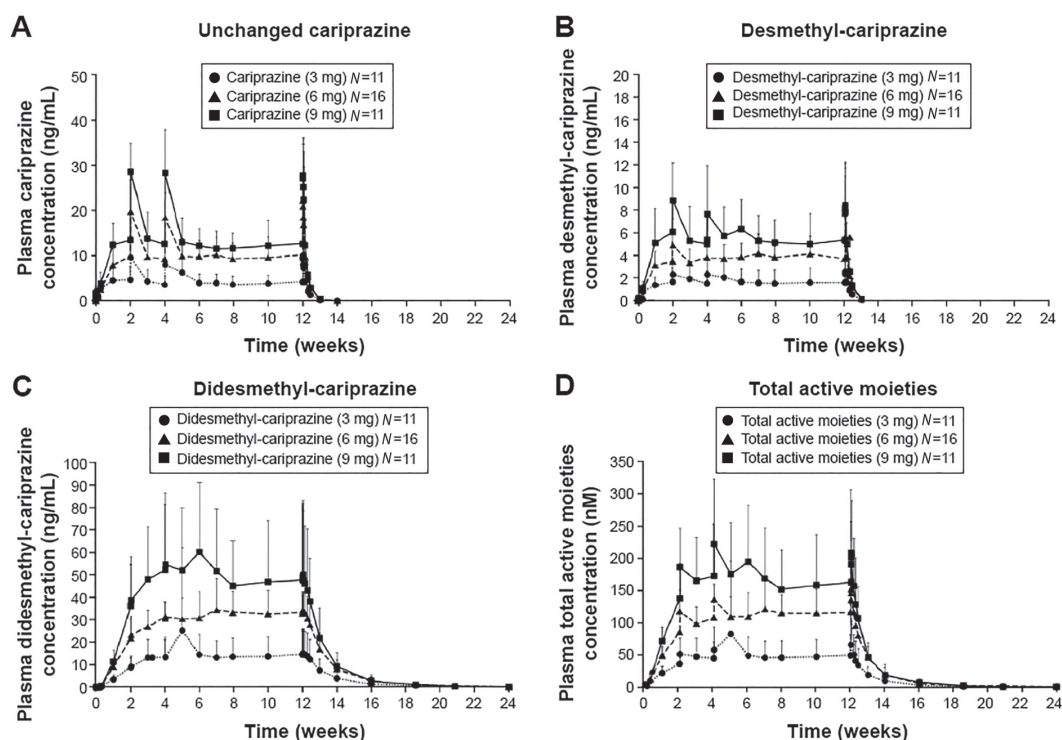
impairment showed no significant relationship between plasma clearance and creatinine clearance ([Actavis Inc. 2015](#)).

## Absorption and Distribution

Cariprazine can be taken with or without food. Food causes a slight delay but has no significant effect on the extent of absorption ([Citrome 2013a](#)).

The effect of a meal on the pharmacokinetics of cariprazine was evaluated in an open-label randomized crossover study in 12 healthy male volunteers who received a single oral dose of 2 mg.  $T_{max}$  was observed at 3–4 hours under fasting conditions. Previous consumption of a meal delayed absorption of the drug but did not affect the final extent of absorption. The plasma profile of cariprazine followed a multi-exponential disposition, with a terminal half-life of 5–6 days ([Veselinovic et al. 2013](#)).

Peak serum concentrations are reached between 3 and 6 hours. There is a linear relationship between dose and plasma concentration. Cariprazine and its major active metabolites are highly bound (91%–97%) to plasma proteins ([Actavis Inc. 2015](#)). Cariprazine and DCAR reach steady-state concentrations within 1–2 weeks ([Figure 34-3](#)); by contrast, DDCAR requires 4–8 weeks of daily cariprazine administration to reach steady-state levels.



---

**FIGURE 34-3.** Plasma concentrations of cariprazine **(A)**, desmethyl-cariprazine **(B)**, didesmethyl-cariprazine **(C)**, and total active moieties (sum of cariprazine, desmethyl-cariprazine and didesmethyl-cariprazine) **(D)** for each dosage group during the treatment and follow-up periods.

*Note.* Data are mean  $\pm$  standard deviation. The lower limit of quantification of analytes was 0.02 ng/mL. The mean was not plotted when at least half of the results were below the lower limit of detection except at time=0.

*Source.* Reprinted from Nakamura T, Kubota T, Iwakaji A, et al.: "Clinical Pharmacology Study of Cariprazine (MP-214) in Patients With Schizophrenia (12-Week Treatment)." *Drug Design, Development and Therapy* 10:327-338, 2016. Copyright © 2016, Dove Medical Press Ltd. Used with permission.

Effective half-life (calculated from time to steady state) of total active moieties was  $\pm 1$  week. Terminal half-lives of cariprazine, DCAR, and DDCAR range from 31.6 to 68.4, 29.7 to 37.5, and 314 to 446 hours, respectively ([Nakamura et al. 2016](#)).

The mean half-life of cariprazine is 2-5 days over a dosage range of 1.5-12.5 mg/day, which is considerably longer (days) than the mean half-life in laboratory animal studies (hours in rats and dogs) ([Mészáros et al. 2008](#)).

On the first day of dosing, systemic exposure to the metabolites (DCAR and DDCAR) was relatively low compared with exposure to the parent drug. However, on day 37, with the 12.5-mg/day dosage, systemic exposure to DDCAR was threefold greater than that to cariprazine for the AUC over 24 hours and sixfold greater for the AUC over 7 days, indicating a slower elimination and a substantially longer half-life for this metabolite than for the parent compound ([Veselinovic et al. 2013](#)).

After initiating cariprazine therapy or changing the dosage, response and side effects should be monitored for several weeks because of the long half-life of cariprazine's active metabolite DDCAR.

## Metabolism and Elimination

Cariprazine is extensively metabolized by hydroxylation and demethylation in the liver cytochrome P450 (CYP) enzyme system, mainly by the 3A4 enzyme and to a lesser extent by the 2D6 enzyme. Eight metabolites for cariprazine were identified in liver microsomes, but only two active metabolites, DCAR and DDCAR, were clinically relevant (equipotent to cariprazine with similar receptor partial agonism) ([Veselinovic et al. 2013](#)).

Cariprazine's main metabolite, DCAR, is further metabolized by CYP3A4 and CYP2D6 to DDCAR, which is metabolized by CYP3A4 to a hydroxylated

metabolite ([Actavis Inc. 2015](#)).

Cariprazine and DCAR levels had decreased by more than 90% at 1 week after the last dose, whereas DDCAR levels had decreased by approximately 50% at 1 week; total active moieties had decreased by approximately 90% at 4 weeks. Cariprazine and its metabolites were eliminated almost completely in the 12 weeks following the last cariprazine dose ([Nakamura et al. 2016](#)).

Following administration of cariprazine 12.5 mg/day to patients with schizophrenia for 27 days, about 21% of the daily dosage was found in urine, with approximately 1.2% of the daily dosage excreted in urine as unchanged cariprazine ([Actavis Inc. 2015](#)).

## Drug–Drug Interactions

Cariprazine and its major active metabolites are weak competitive inhibitors of the human CYP2D6 and CYP3A4 isozymes. They have no induction effect on the CYP enzyme system in human hepatocytes. Cariprazine is a weak inhibitor of a number of CYP450 isoenzymes in vitro: 1A2, 2C9, 2D6, 3A4, 2C19, 2A6, and 2E1.

Because cariprazine is highly metabolized by CYP3A4 and to some degree by CYP2D6, changes in steady-state plasma concentrations would be expected if the drug were coadministered with potent CYP3A4 inhibitors or inducers. However, CYP2D6 inducers or inhibitors are not expected to have this effect on cariprazine metabolism, because CYP2D6 is known to be a poor metabolizer of cariprazine and its metabolites.

Taking a strong CYP3A4 inhibitor (e.g., ketoconazole, fluoxetine, grapefruit juice) with cariprazine will increase concentrations of the parent drug by about 3.5-fold, decrease DCAR by about one-third, and increase DDCAR by about 1.5-fold. The concomitant use of CYP3A4 inducers with cariprazine has not yet been evaluated. When cariprazine is to be added to an existing regimen of a strong CYP3A4 inhibitor, the recommended starting dosage is 1.5 mg every other day, with a maximum dosage of 3 mg/day ([Actavis Inc. 2015](#)).

The absence of any significant effect on the CYP system permits cariprazine to be used in combination with other psychotropics if needed clinically without significant drug–drug interactions. No such combination studies have been published to date.

---

## Indications, Dosing, and Efficacy

---

Cariprazine has a half-life greater than 24 hours, which allows once-daily dosing, an advantage in terms of antipsychotic adherence. Cariprazine has a relatively broad therapeutic index, in that dosages in the range of 0.5–12.5 mg/day are well tolerated. The minimum cariprazine starting dosage is 1.5 mg/day. The minimum therapeutic dosage for schizophrenia is 1.5 mg/day, and that for bipolar disorder is 3 mg/day; however, the maximum recommended target dosage is 6 mg/day for both illnesses. Any dosage changes will be reflected fully in the serum level 2 weeks after initial dosing. In short-term controlled trials, dosages above 6 mg/day did not confer increased effectiveness sufficient to outweigh dose-related adverse reactions. The use of cariprazine in geriatric or pediatric patients has not been studied ([Actavis Inc. 2015](#)).

## FDA-Approved Indications

### Schizophrenia

In the treatment of patients with schizophrenia, the recommended dosage of cariprazine is 1.5–6 mg/day. The recommended starting dosage is 1.5 mg/day, which can be increased to 3 mg/day on day 2, with further upward dosage increments of 1.5 or 3 mg/day as necessary, depending on clinical response and tolerability.

FDA approval for the schizophrenia was based on data from three positive 6-week double-blind, randomized controlled studies of cariprazine that were conducted in adult patients with schizophrenia between 2008 and 2011. Two of the studies used fixed dosages and included active drug comparators (risperidone and aripiprazole) and placebo. All three trials consisted of a washout period of up to 1 week, 6 weeks of double-blind treatment, and a 2-week safety follow-up. The primary efficacy measure in each study was change from baseline in Positive and Negative Syndrome Scale (PANSS) Total score; assessments were conducted at screening, at baseline, and at the end of each double-blind treatment week (weeks 1–6) ([Table 34–2](#)).

**TABLE 34–2. Three 6-week randomized, placebo-controlled trials establishing the efficacy of cariprazine in treating acute schizophrenia**

Trial <sup>a</sup>	Randomization (N)	Efficacy <sup>b</sup>	Side effects
--------------------	----------------------	-----------------------	--------------

<b>Trial<sup>a</sup></b>	<b>Randomization (N)</b>	<b>Efficacy<sup>b</sup></b>	<b>Side effects</b>
NCT00694707 RGH-MD-16 Phase II (Durgam et al. 2014)	Total N: 732 64% completed the study Placebo (151) Cariprazine fixed dosages: 1.5 mg/day (145) 3 mg/day (147) 4.5 mg/day (148) Active control: Risperidone 4 mg/day (141) <sup>c</sup>	At week 6, statistically significant ( $P<0.001$ [LOCF]) LSMD in favor of cariprazine versus placebo were observed for <ul style="list-style-type: none"> <li>PANSS-Total (1.5 mg/day: −7.6; 3 mg/day: −8.8; 4.5 mg/day: −10.4)</li> <li>CGI-S (1.5 mg/day: −0.4; 3 mg/day: −0.5; 4.5 mg/day: −0.6)</li> </ul> Risperidone was superior to placebo on both measures (LSMD: PANSS=−15.1, $P<0.001$ [LOCF]; CGI-S=−0.8, $P<0.05$ [LOCF]).	The most frequent cariprazine adverse events (≥5% and twice the rate of placebo) were akathisia, extrapyramidal disorder, insomnia, sedation, nausea, dizziness, and constipation. Mean changes in metabolic parameters were small and similar between groups.

<b>Trial<sup>a</sup></b>	<b>Randomization (N)</b>	<b>Efficacy<sup>b</sup></b>	<b>Side effects</b>
NCT01104766 RGH-MD-04 Phase III ( <a href="#">Laszlovszky et al. 2014</a> )	Total N: 617 Placebo (153) Cariprazine fixed dosages: 3 mg/day (155) 6 mg/day (157) Active control: Aripiprazole 10 mg/day (152) <sup>c</sup>	At week 6, statistically significant LSMD in favor of cariprazine versus placebo were observed for <ul style="list-style-type: none"> <li>• PANSS-Total (3 mg/day: -6.0, <math>P=0.0044</math>; 6 mg/day: -8.8, <math>P&lt;0.0001</math>)</li> <li>• CGI-S (3 mg/day: -0.4, <math>P=0.0044</math>; 6 mg/day: -0.5, <math>P&lt;0.0001</math>)</li> </ul> Aripiprazole was superior to placebo on both measures (LSMD: PANSS- Total=-7.0, $P=0.0008$ ; CGI- S=-0.4, $P=0.0001$ ).	Akathisia was reported ( $\geq 5\%$ ; twice the rate of placebo). Changes in metabolic parameters were small and similar to those with placebo.

<b>Trial<sup>a</sup></b>	<b>Randomization (N)</b>	<b>Efficacy<sup>b</sup></b>	<b>Side effects</b>
NCT01104779 RGH-MD-05 Phase III (Kane et al. 2015)	Total N: 446 60.5% completed the study Placebo (147) Cariprazine flexible dosing: 3-6 mg/day (151) 6-9 mg/day (148) No active control group	At week 6, statistically significant LSMD in favor of cariprazine versus placebo were observed for <ul style="list-style-type: none"> <li>• PANSS-Total (3-6 mg/day: -6.8, <math>P=0.003</math>; 6-9 mg/day: -9.9, <math>P&lt;0.001</math>)</li> <li>• CGI-S (3-6 mg/day: -0.3, <math>P=0.012</math>; 6-9 mg/day: -0.5, <math>P&lt;0.001</math>)</li> </ul>	The most frequent cariprazine adverse events ( $\geq 5\%$ ; twice the rate of placebo) in both cariprazine groups were akathisia, extrapyramidal disorder, and tremor; most were mild to moderate in severity. Mean changes in metabolic parameters were generally small and similar between groups. Prolactin levels decreased in all groups.

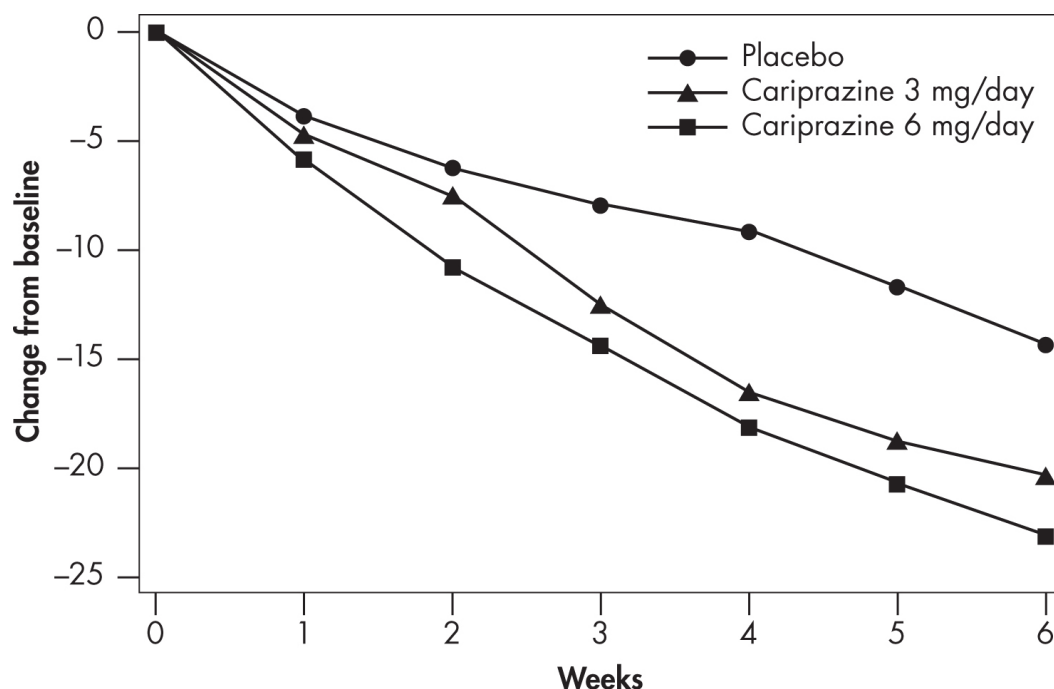
*Note.* CGI-S=Clinical Global Impression-Severity; LOCF=last observation carried forward; LSMD=least squares mean differences; PANSS=Positive and Negative Syndrome Scale.

<sup>a</sup>Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) identifiers NCT00694707, NCT01104766, and NCT01104779.

<sup>b</sup>In each study, the PANSS was used as the primary measure and the CGI-S rating scale was used as the secondary efficacy measure. The primary endpoint was change from baseline in PANSS total score at the end of week 6. The change from baseline for cariprazine and for all active control groups was superior to placebo in all three trials.

<sup>c</sup>The active control medications (aripiprazole and risperidone) were included for use in assessment of assay sensitivity and not for efficacy comparisons. However, they were superior to placebo.

As indicated in [Table 34-2](#), patients were randomly assigned to receive cariprazine (1.5 mg/day, 3 mg/day, or 4.5 mg/day); risperidone (4 mg/day); or placebo in the NCT00694707 study; cariprazine (3 mg/day or 6 mg/day), aripiprazole (10 mg/day), or placebo in the NCT01104766 study; and cariprazine (3–6 mg/day or 6–9 mg/day) or placebo in the NCT01104779 study. The efficacy of cariprazine compared with placebo was demonstrated at dosages ranging from 1.5 to 9 mg/day. There was, however, a dose-related increase in certain adverse effects (e.g., EPS), particularly at dosages above 6 mg/day. Findings on the time course of efficacy in the NCT01104766 study are shown in [Figure 34-4](#).



**FIGURE 34-4.** Change from baseline in Positive and Negative Syndrome Scale (PANSS) Total score, by weekly visit (Study ID: NCT01104766).

Source. [Actavis Inc. 2015](#).

In Phase III clinical trials, dosages of 3–9 mg/day produced significant improvement on the PANSS and on the Clinical Global Impression scale. Higher dosages (6–9 mg/day) showed early separation from placebo (by the end of week 1) but carried a dosage-related risk of adverse events, leading the FDA to recommend 6 mg/day as the maximum dosage ([Mattingly and Anderson 2016](#)).

The effects of cariprazine on human cognition were evaluated in the NCT 01104779 study (weeks 0, 3, and 6). No significant differences were



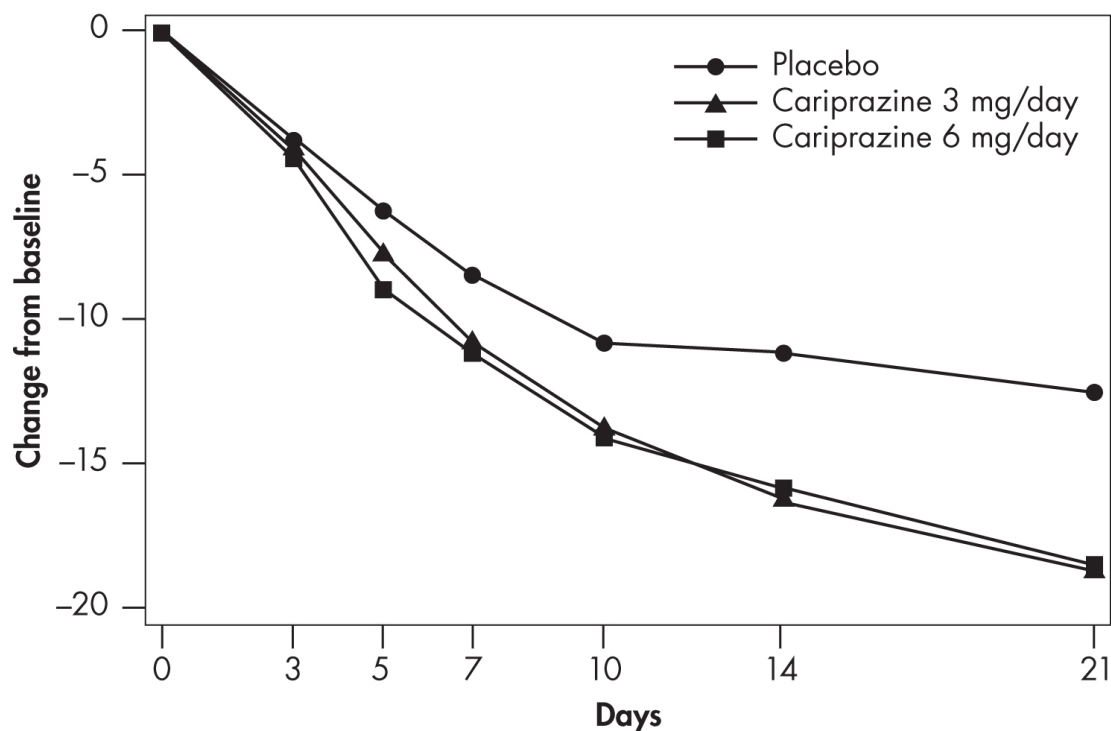
observed for the cariprazine group versus the placebo group on the Cognitive Drug Research System Attention Battery Tests or the Color Trails Test ([Kane et al. 2015](#)).

Data on direct comparisons of clinical efficacy between cariprazine and aripiprazole or risperidone are not yet available ([Veselinovic et al. 2013](#)).

A recent 6-week double-blind, placebo-controlled proof-of-concept study (NCT00404573) evaluated the efficacy, safety, and tolerability of low-dosage (1.5–4.5 mg/day) versus high-dosage (6–12 mg/day) cariprazine in patients with schizophrenia. Surprisingly, no significant differences between the two dosages of cariprazine and placebo were noted on PANSS Total score changes or any other efficacy parameters (Clinical Global Impression–Severity [CGI-S] scale or PANSS subscales) after multiplicity adjustment ([Durgam et al. 2016b](#)).

### Acute Manic or Mixed Episodes Associated With Bipolar I Disorder

Cariprazine’s efficacy in the treatment of bipolar manic or mixed episodes was established at dosages ranging from 3 to 12 mg/day. Dosages above 6 mg/day did not appear to add additional benefit over lower dosages, and there was a dose-related increase in certain adverse effects (e.g., EPS). Therefore, the maximum recommended dosage is 6 mg/day. Findings on the time course of efficacy in the NCT01058668 study are shown in [Figure 34-5](#) ([Vraylar 2015](#)).



**FIGURE 34-5.** Change from baseline in Young Mania Rating Scale (YMRS) Total score, by study visit (Study ID: NCT01058668).

Source. Actavis Inc. 2015.

FDA approval for the bipolar disorder indication was based on data from three 3-week placebo-controlled trials in adults with manic or mixed episodes of bipolar I disorder with or without psychotic features. All three studies demonstrated cariprazine's superiority over placebo (Table 34-3).

**TABLE 34-3. Three 3-week randomized, placebo-controlled, flexibly dosed trials establishing the efficacy of cariprazine in acute manic/mixed episodes of bipolar I disorder**

<b>Trial<sup>a</sup></b>	<b>Randomization (N)</b>	<b>Efficacy<sup>b</sup></b>	<b>Side effects</b>
NCT01058668 Phase III (Calabrese et al. 2015)	Total N: 497 74% completed the study Cariprazine flexible dosing: 3-6 mg/day (169) 6-9 mg/day (167) Placebo (161)	At week 3, statistically significant LSMD in favor of cariprazine versus placebo were observed for <ul style="list-style-type: none"> <li>• YMRS-Total (3-6 mg/day, -6.1; 6-12 mg/day, -5.9; <math>P &lt; 0.001</math> [both])</li> <li>• CGI-S (3-6 mg/day, -0.6; 6-12 mg/day, -0.6; <math>P &lt; 0.001</math> [both])</li> </ul>	The most common ( $\geq 5\%$ ; twice the rate of placebo) treatment-related adverse events for cariprazine were akathisia (both groups) and nausea, constipation, and tremor (6-12 mg/day only).

<b>Trial<sup>a</sup></b>	<b>Randomization (N)</b>	<b>Efficacy<sup>b</sup></b>	<b>Side effects</b>
NCT00488618 Phase II ( <a href="#">Durgam et al. 2015</a> )	Total N: (235) 61.9% of placebo group and 63.6% of cariprazine group completed the study Cariprazine flexible dosing: 3-12 mg/day (118) Placebo (117)	At week 3, statistically significant LSMD in favor of cariprazine versus placebo were observed for <ul style="list-style-type: none"> <li>• YMRS-Total (3-12 mg/day, -6.1; <math>P&lt;0.001</math>)</li> <li>• CGI-S (3-12 mg/day, -0.6; <math>P&lt;0.001</math>)</li> </ul>	The most common adverse events (>10% for cariprazine) were akathisia (cariprazine: 22%; placebo: 6%), extrapyramidal symptoms (parkinsonism) (cariprazine: 16%; placebo: 1%), headache, constipation, nausea, and dyspepsia.  Changes in metabolic parameters were similar between groups, with the exception of fasting glucose change.

<b>Trial<sup>a</sup></b>	<b>Randomization (N)</b>	<b>Efficacy<sup>b</sup></b>	<b>Side effects</b>
NCT01058096 Phase III ( <a href="#">Sachs et al. 2015</a> )	Total N: 310 68.4% completed the study Cariprazine flexible dosing: 3-12 mg/day (158) Placebo (152)	At week 3, statistically significant LSMD in favor of cariprazine versus placebo were observed for <ul style="list-style-type: none"> <li>• YMRS-Total (3-12 mg/day, -4.3; <math>P=0.0004</math>)</li> <li>• CGI-S (3-12 mg/day, -0.4; <math>P=0.0027</math>)</li> </ul>	The most common cariprazine-related (>10%; twice the rate of placebo) treatment-emergent adverse events were akathisia, extrapyramidal disorder, tremor, dyspepsia, and vomiting. Mean changes from baseline in metabolic parameters were generally small and similar between groups.

*Note.* CGI-S=Clinical Global Impression-Severity; LSMD=least squares mean differences; YMRS-Total=Young Mania Rating Scale total score.

<sup>a</sup>Trial registration: [ClinicalTrials.gov](#) identifiers NCT01058668, NCT00488618, and NCT01058096.

<sup>b</sup>In all trials, patients were adults (ages 18-65 years; mean age=39 years) whose symptoms met DSM-IV-TR criteria for bipolar I disorder with manic or mixed episodes and with or without psychotic features (YMRS score $\geq$ 20). YMRS and CGI-S were used as the primary and secondary efficacy measures, respectively; the primary endpoint was decrease from baseline in YMRS-Total score at the end of week 3. The change from baseline for cariprazine was superior to placebo in all three trials. All three trials lacked an active comparator arm and had a short duration.

As indicated in [Table 34-3](#), patients were randomly assigned to receive flexible dosages (3-12 mg/day) of cariprazine or placebo. No active comparator arm was included.

# Possible Future Indications

## Bipolar Depression

Two studies failed to establish cariprazine's efficacy in patients with bipolar depression. In a Phase II ( $N=233$ ) 8-week randomized, double-blind, parallel-group, flexible-dose multicenter trial of cariprazine (0.25–0.75 mg/day or 1.5–3.0 mg/day) in bipolar depression, improvement with cariprazine versus placebo did not reach significance on the primary efficacy measure (change from baseline to week 8 on the Montgomery-Åsberg Depression Rating Scale (MADRS) using mixed model repeated measures [MMRM] analyses). The authors speculated that high placebo response may have contributed to the outcome ([Ahuja et al. 2011](#)).

In a recent 8-week multinational randomized, double-blind, placebo-controlled, parallel-group, fixed-dose (0.75, 1.5, or 3 mg/day) multicenter study of cariprazine in adults ( $N=571$ ) experiencing a current major depressive episode in bipolar I disorder, improvement with cariprazine versus placebo did not reach significance on the primary assessment (MADRS change from baseline to week 6 using MMRM analyses). The 0.75 mg/day dosage did not separate from placebo; however, the 1.5 mg/day dosage produced greater improvement on the MADRS total score change compared with the 3 mg/day dosage ([Durgam et al. 2016a](#)).

## Major Depressive Disorder (Adjunctive Therapy)

A Phase III trial of cariprazine as an adjunct to antidepressant treatment in adult patients with major depressive disorder (NCT01715805) is in progress. In this randomized, double-blind trial, patients will receive oral cariprazine 1.5–4.5 mg/day or placebo for 8 weeks in addition to antidepressant therapy. The primary endpoint is change on the MADRS score at 8 weeks, and the secondary endpoint is change on the Sheehan Disability Scale score at 8 weeks. The trial is recruiting approximately 1,100 patients in the United States and Puerto Rico ([McCormack 2015](#)).

Another Phase III extension trial to assess the long-term safety and tolerability of cariprazine as an adjunct to antidepressant therapy in adult patients with major depressive disorder (NCT01838876) is under way. This 26-week open-label, flexible-dose (1.5–4.5 mg/day) study has enrolled 347 patients, and the final data collection point was scheduled for July 2015 ([McCormack 2015](#)).

## Substance Use Disorders

Cariprazine is being investigated for its potential anti-abuse/relapse-preventing effects in preclinical studies. In a study by [Román et al. \(2013\)](#),

cariprazine, as well as aripiprazole and bifeprunox, reduced the rewarding effects of cocaine (minimum effective doses were 0.17, 1.0, and 0.1 mg/kg for cariprazine, aripiprazole, and bifeprunox, respectively) and delayed relapse to cocaine seeking, with ED<sub>50</sub> values of 0.2, 4.2, and 0.17 mg/kg, respectively. The behavioral effects of cariprazine were as potent as those of bifeprunox and were more potent than those of aripiprazole ([Román et al. 2013](#)).

## Hostility

Using pooled data from the three positive randomized controlled trials in schizophrenia conducted between 2008 and 2011, a post hoc analysis was performed to investigate the effect of cariprazine on hostility in patients with schizophrenia ([Citrome et al. 2016](#)).

Statistically significant improvement (as assessed by mean change from baseline to week 6 on the PANSS Hostility item) was seen in cariprazine-treated versus placebo-treated patients. Antihostility effects were partially independent of improvement on PANSS Positive symptom items, were independent of sedation effects, and were greater in cariprazine-treated patients with higher versus lower baseline levels of hostility ([Citrome et al. 2016](#)).

---

## Side Effects and Toxicology

---

Cariprazine generally was well tolerated in short-term trials for schizophrenia and bipolar I disorder. No significant anticholinergic or antiadrenergic side effects were documented, because cariprazine has negligible affinity for cholinergic or adrenergic receptors.

## Common Treatment-Emergent Adverse Events in Clinical Trials

### 12-Week Open-Label Study

In a 12-week open-label, fixed-dose (3, 6, or 9 mg/day) study of 38 adult patients with schizophrenia ([Nakamura et al. 2016](#)), the overall completion rate was 63.2%; 15.8% of patients discontinued the medication because of adverse events.

Incidence of treatment-emergent adverse events (TEAEs) was 97.4%. No abnormal laboratory values or major differences from baseline in EPS were

observed. A total of 37 (97.4%) patients reported at least one TEAE, and 31 (81.6%) patients experienced at least one adverse drug reaction (defined as adverse events for which a causal relationship with cariprazine was determined to be “reasonably possible”). Side effects observed in this study were similar to those reported in previous studies. Across all dosage groups, akathisia was observed in 21% of patients during cariprazine treatment. One case of cataract (deemed mild in severity) was reported (Nakamura et al. 2016).

## 48-Week Open-Label Studies

In two 48-week studies ( $N=679$ ) of open-label, flexible-dose cariprazine in adult patients with schizophrenia (NCT01104792, 3–9 mg/day; NCT00839852, 1.5–4.5 mg/day) (reported by Nasrallah et al. 2014), the overall completion rate was 40.1%. The mean duration of treatment with cariprazine (days $\pm$ SD) was 188.4 $\pm$ 136.8; 211 patients (31.1%) were exposed to cariprazine for at least 1 year.

Incidence of TEAEs was 81.4%. TEAEs reported in at least 10% of patients were akathisia (15.5%), insomnia (13.1%), headache (12.7%), and weight gain (10.5%) (Table 34-4). The mean increase in body weight was 2.46 kg. Mean changes from baseline to the end of study in metabolic parameters and other clinical laboratory values, blood pressure, and electrocardiographic parameters were generally small. No patients met criteria for Hy’s law (regarding risk of fatal drug-induced liver injury). Mean prolactin levels decreased from baseline to the end of study. The incidence of treatment-emergent parkinsonism (Simpson-Angus Scale score  $>3$ ) was 10.7%, and the incidence of treatment-emergent akathisia (Barnes Akathisia Rating Scale score  $>2$ ) was 17.8%. Ophthalmological testing revealed no significant changes.

**TABLE 34-4. Most frequent<sup>a</sup> treatment-emergent adverse events (TEAEs) during long-term treatment with cariprazine ( $N=679$ )**

TEAE	<i>n</i> (%)
Akathisia	105 (15.5)
Insomnia	89 (13.1)

<sup>a</sup>Reported by  $\geq 5\%$  of patients.

Source. Reprinted from Nasrallah HA, Cutler AJ, Wang Y, et al.: “P.3.d.025 Safety and Tolerability of Cariprazine in Long-Term Treatment of Schizophrenia: Integrated Summary of Safety Data” (poster & abstract). *European Neuropsychopharmacology* 24 (Suppl 2):S536, 2014, Table 2. Copyright © 2014, Elsevier. Used with permission.

**TEAE*****n (%)***

---

Headache	86 (13.1)
Weight increase	71 (10.5)
Anxiety	58 (8.5)
Tremor	47 (6.9)
Extrapyramidal disorder	45 (6.6)
Schizophrenia	38 (5.6)
Nausea	38 (5.6)
Restlessness	38 (5.6)
Dyspepsia	37 (5.4)
Nasopharyngitis	34 (5.0)

---

<sup>a</sup>Reported by  $\geq 5\%$  of patients.

*Source.* Reprinted from Nasrallah HA, Cutler AJ, Wang Y, et al.: "P.3.d.025 Safety and Tolerability of Cariprazine in Long-Term Treatment of Schizophrenia: Integrated Summary of Safety Data" (poster & abstract). *European Neuropsychopharmacology* 24 (Suppl 2):S536, 2014, Table 2. Copyright © 2014, Elsevier. Used with permission.

Serious adverse events were reported in 79 patients (11.6%), including one death (suicide) during the open-label treatment period. The most common serious adverse events were worsening of schizophrenia (4.4%) and psychotic disorder (2.1%) ([Nasrallah et al. 2014](#)).

### **16-Week Open-Label Study**

In a 16-week study ( $N=402$ ) of open-label, flexible-dose cariprazine 3–12 mg/day in adult patients with bipolar mania ([Ketter et al. 2013](#)), the overall completion rate was 33%; 16% of patients discontinued the medication because of adverse events. The mean treatment duration was 57.7 days, and the mean cariprazine dosage was 6.2 mg/day. No deaths were reported.

Incidence of TEAEs was 83%. TEAEs reported in at least 10% of patients were akathisia (33%), headache (17%), constipation (11%), and nausea (10%); overall, EPS-related TEAEs were reported in 46% of patients.



Suicidal ideation and behavior (assessed with the Columbia Suicide Severity Rating Scale) occurred in 9% and 1% of patients, respectively; suicidal ideation and suicide attempt occurred in 4 and 3 patients, respectively. The mean body weight increase was <1 kg; 9% of patients had  $\geq 7\%$  weight gain. Mean changes in laboratory values, vital signs, electrocardiogram results, and ophthalmology parameters were generally small. Cariprazine treatment was not associated with an increase in prolactin levels.

Serious adverse events occurred in 8% of patients; most serious adverse events were associated with worsening of mania, depression, or akathisia. The most common adverse events leading to discontinuation were akathisia (5%) and depression (2%) ([Ketter et al. 2013](#)).

## Atypical Antipsychotic Class Warnings

Cariprazine has not been approved for use in the treatment of pediatric or geriatric patients.

Numerous risks are associated with the use of atypical antipsychotic medications in general. As a member of this class, cariprazine carries the following risks ([Actavis Inc. 2015](#)):

1. Increased mortality in elderly patients with dementia-related psychosis
2. Increased risk of cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis
3. Neuroleptic malignant syndrome
4. Tardive dyskinesia
5. Leukopenia, neutropenia, and agranulocytosis
6. Seizures
7. Potential for cognitive and motor impairment
8. Body temperature dysregulation
9. Dysphagia

The boxed warnings are based on the pharmacological actions of this class. No such effects were observed in the cariprazine studies, possibly because of the short lengths of the trials.

## Late-Occurring Adverse Drug Reactions

Cariprazine has a long half-life, but the half-lives of its major metabolites are even longer. Therefore, plasma levels accumulate over time, and side effects may appear weeks after the initiation of treatment. As a result, the incidence of adverse reactions in short-term trials may not reflect the rates after

longer-term exposure. Clinicians are advised to monitor for adverse reactions for several weeks after starting a patient on cariprazine and after any dosage increase. If side effects are noted, dosage reduction or medication discontinuation should be considered.

## Akathisia

Across clinical trials for both FDA-approved disorders, akathisia and parkinsonism were among the more common side effects of cariprazine. Both were usually mild, resulting in relatively few premature discontinuations. Parkinsonism appeared to be somewhat dosage-related, whereas akathisia had no clear relationship to dosage ([Mattingly and Anderson 2016](#)).

## Changes in Metabolic and/or Clinical Laboratory Parameters

In the pooled analysis of safety and tolerability data from the two open-label long-term studies discussed earlier ([Nasrallah et al. 2014](#); see “48-Week Open-Label Studies” subsection), mean changes from baseline in plasma lipid levels during long-term cariprazine treatment were small and not clinically meaningful ([Table 34-5](#)). The mean increase in fasting glucose (4.5 mg/dL) was similar to that observed during the 6-week lead-in studies. Mean change from baseline in weight was 1.6 kg. A potentially clinically significant increase in body weight was seen in 27% of patients; a potentially clinically significant decrease was seen in 11% of patients. Mean prolactin levels decreased during long-term cariprazine treatment (see [Table 34-5](#)). Mean alanine transaminase and aspartate transaminase values increased slightly. Creatine kinase levels increased slightly during open-label treatment; however, the large standard deviation indicates that the data were highly variable ([Nasrallah et al. 2014](#)).

<b>TABLE 34-5. Mean changes in metabolic and clinical laboratory parameters after long-term treatment with cariprazine (N=679)</b>
<b>Mean change (SD)</b>

---

**Mean change (SD)**

---

**Metabolic laboratory parameters**

Total cholesterol, mg/dL	−5.3 (31.1)
LDL cholesterol, mg/dL	−3.5 (26.4)
HDL cholesterol, mg/dL	−0.8 (11.3)
Triglycerides, mg/dL	1.2 (87.2)
Fasting glucose, mg/dL	4.5 (23.2)

**Body weight**

Body weight, kg	1.6 (5.4)
Waist circumference, cm	1.6 (7.4)
PCS changes ( $\geq 7\%$ ) in body weight, %:	
$\geq 7\%$ increase from baseline:	27.2
$\geq 7\%$ decrease from baseline:	10.9

**Prolactin**

Prolactin, ng/mL	−15.4 (39.6)
------------------	--------------

**Creatine kinase**

Creatine kinase, U/L	18.5 (264.0)
----------------------	--------------

**Liver function**

---

*Note.* ALT=alanine aminotransferase; AST=aspartate aminotransferase; PCS=potentially clinically significant; SD=standard deviation.

*Source.* Reprinted from Nasrallah HA, Cutler AJ, Wang Y, et al.: “P.3.d.025 Safety and Tolerability of Cariprazine in Long-Term Treatment of Schizophrenia: Integrated Summary of Safety Data” (poster & abstract). *European Neuropsychopharmacology* 24 (Suppl 2):S536, 2014, Tables 4 and 5. Copyright © 2014, Elsevier. Used with permission.

	Mean change (SD)
ALT, U/L	2.4 (27.8)
AST, U/L	0.5 (15.5)
Total bilirubin, mg/dL	0.02 (0.28)

*Note.* ALT=alanine aminotransferase; AST=aspartate aminotransferase; PCS=potentially clinically significant; SD=standard deviation.

*Source.* Reprinted from Nasrallah HA, Cutler AJ, Wang Y, et al.: "P.3.d.025 Safety and Tolerability of Cariprazine in Long-Term Treatment of Schizophrenia: Integrated Summary of Safety Data" (poster & abstract). *European Neuropsychopharmacology* 24 (Suppl 2):S536, 2014, Tables 4 and 5. Copyright © 2014, Elsevier. Used with permission.

In schizophrenia clinical trials that included active control medications, the proportion of patients with potentially significant ( $\geq 7\%$ ) weight gain was greater for aripiprazole and risperidone than for cariprazine ([Durgam et al. 2014](#)).

## High Dosage and Overdose

In clinical trials, the 12.5 mg/day dosage was well tolerated in most cases. Several cases of overdose were reported (Trials RGH-PK-15 and RGH-MD-36), at dosages of up to 48 mg/day in one accidental overdose, but in none of those cases was more than supportive measures required ([Citrome 2013a, 2013b](#)).

## Use During Pregnancy and Lactation

There have been no well-controlled studies of cariprazine in pregnant women, but neonates whose mothers have been exposed to other antipsychotic medications during the third trimester of pregnancy are at risk for extrapyramidal and withdrawal symptoms following delivery.

Administration of cariprazine to rats during the period of organogenesis caused malformations, reduced pup survival, and developmental delays at drug exposures less than the human exposure at the maximum recommended human dosage (MRHD) of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the MRHD of 6 mg/day. Based on animal data, cariprazine may cause fetal harm. Pregnant women should be advised of the potential risk to the fetus ([Actavis Inc. 2015](#)).

---

## Ongoing Cariprazine Trials

---

Numerous trials of cariprazine are currently ongoing or under way ([McCormack 2015](#)):

- Phase III trial of cariprazine in the treatment of schizophrenia or bipolar disorder in some countries of the European Union, India, Russia, South Africa, Serbia, Colombia, and Ukraine
- Phase III trial of cariprazine in the treatment of schizophrenia with predominant negative symptoms in the Czech Republic, Hungary, Spain, Poland, Croatia, France, Serbia, Romania, Russia, Ukraine, and Bulgaria
- Phase III trial of cariprazine in the prevention of relapse of schizophrenia in India, Romania, Slovakia, the United States, and Ukraine
- Phase II/III trial of cariprazine in the treatment of schizophrenia in Japan, South Korea, and Taiwan
- Phase III trial of cariprazine as an adjunct to antidepressant treatment of major depressive disorder in Puerto Rico and the United States
- Phase II trial of cariprazine as an adjunct to antidepressant treatment of major depressive disorder in Estonia, Finland, Slovakia, Sweden, Ukraine, and the United Kingdom
- Phase II trial of cariprazine in the treatment of bipolar depression in Bulgaria, Canada, Colombia, Russia, Ukraine, and the United States

---

## Conclusion

---

Cariprazine combines functional selectivity at dopamine D<sub>3</sub> and D<sub>2</sub> receptors, partial agonist activity at serotonin 5-HT<sub>1A</sub> receptors, and antagonism at serotonin 5-HT<sub>2B</sub> and 5-HT<sub>2A</sub> receptors. Cariprazine's receptor-binding profile is unique, with the highest affinity and selectivity for D<sub>3</sub> receptors of any second-generation antipsychotic. It has antipsychotic and mood-stabilizing effects, as well as possible antidepressant, procognitive, anti-abuse, and antihostility effects. Cariprazine has the potential to improve the cognitive and negative symptoms of schizophrenia, as shown in preclinical trials.

---

## References

---

- Actavis Inc: VRAYLAR™ (cariprazine) capsules, full prescribing information. Parsippany, NJ, Actavis Inc, 2015. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/204370lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204370lbl.pdf). Accessed May 15, 2016.
- Ahuja S, Bose A, Lu K, et al: A multicenter, randomized, double-blind trial to evaluate the effect of cariprazine in bipolar depression (no 23).. Poster presented at the International Society for CNS Clinical Trials and Methodology (ISCTM) 2011 Autumn Conference, Amelia Island, FL, October 3-4, 2011. Available at: [https://isctm.org/public\\_access/Oct\\_2011/PosterAbstracts.pdf](https://isctm.org/public_access/Oct_2011/PosterAbstracts.pdf). Accessed May 14, 2016.
- Bantick RA, Deakin JF, Grasby PM: The 5-HT<sub>1A</sub> receptor in schizophrenia: a promising target for novel atypical neuroleptics? *J Psychopharmacol* 15(1):37-46, 2001 11277607
- Blier P, Ward NM: Is there a role for 5-HT<sub>1A</sub> agonists in the treatment of depression? *Biol Psychiatry* 53(3):193-203, 2003 12559651
- Calabrese JR, Keck PE Jr, Starace A, et al: Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry* 76(3):284-292, 2015 25562205
- Citrome L: Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. *Adv Ther* 30(2):114-126, 2013a 23361833
- Citrome L: Cariprazine: chemistry, pharmacodynamics, pharmacokinetics, and metabolism, clinical efficacy, safety, and tolerability. *Expert Opin Drug Metab Toxicol* 9(2):193-206, 2013b 23320989
- Citrome L: The ABC's of dopamine receptor partial agonists—aripiprazole, brexpiprazole and cariprazine: the 15-min challenge to sort these agents out. *Int J Clin Pract* 69(11):1211-1220, 2015 26477545
- Citrome L, Durgam S, Lu K, et al: The effect of cariprazine on hostility associated with schizophrenia: post hoc analyses from 3 randomized controlled trials. *J Clin Psychiatry* 77(1):109-115, 2016 26845266
- Crocq MA, Mant R, Asherson P, et al: Association between schizophrenia and homozygosity at the dopamine D<sub>3</sub> receptor gene. *J Med Genet* 29(12):858-860, 1992 1362221
- Durgam S, Starace A, Li D, et al: An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. *Schizophr Res* 152(2-3):450-457, 2014 24412468
- Durgam S, Starace A, Li D, et al: The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *Bipolar Disord* 17(1):63-75, 2015 25056368
- Durgam S, Earley W, Lipschitz A, et al: An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. *Am J Psychiatry* 173(3):271-281, 2016a 26541814

- Durgam S, Litman RE, Papadakis K, et al: Cariprazine in the treatment of schizophrenia: a proof-of-concept trial. *Int Clin Psychopharmacol* 31(2):61-68, 2016b 26655732
- Forest Laboratories: Forest Laboratories submits new drug application for cariprazine for the treatment of both schizophrenia and manic or mixed episodes associated with bipolar I disorder. Press Release, November 28, 2012. Available at: <http://news.frx.com/press-release/corporate-news/forest-laboratories-submits-new-drug-application-cariprazine-treatment->. Accessed May 15, 2016.
- Girgis RR, Slifstein M, D'Souza D, et al: referential binding to dopamine D3 over D2 receptors by cariprazine in patients with schizophrenia using PET with the D3/D2 receptor ligand [(11)C]-(+)-PHNO. *Psychopharmacology (Berl)* 233(19-20):3503-3512, 2016 27525990
- Gross G, Drescher K: The role of dopamine D(3) receptors in antipsychotic activity and cognitive functions. *Handb Exp Pharmacol* (213):167-210, 2012 23027416
- Gyertyán I, Kiss B, Sághy K, et al: Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. *Neurochem Int* 59(6):925-935, 2011 21767587
- Hellstrand M, Danielsen EA, Steen VM, et al: The ser9gly SNP in the dopamine D3 receptor causes a shift from cAMP related to PGE2 related signal transduction mechanisms in transfected CHO cells. *J Med Genet* 41(11):867-871, 2004 15520413
- Jeanneteau F, Funalot B, Jankovic J, et al: A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. *Proc Natl Acad Sci U S A* 103(28):10753-10758, 2006 16809426
- Kane JM, Zukin S, Wang Y, et al: Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. *J Clin Psychopharmacol* 35(4):367-373, 2015 26075487
- Kapás M, Mészáros GP, Yu B, et al: P.3.c.051 Comparison of the pharmacokinetic behaviour of RGH-188 in schizophrenic patients and healthy volunteers (abstract). *Eur Neuropsychopharmacol* 18 (suppl 4):S433, 2008
- Ketter M, Sachs GS, Lu K, et al: Long-term safety and tolerability of open-label cariprazine in patients with bipolar I disorder. Paper presented at the 10th International Conference on Bipolar Disorder, Miami Beach, FL, June 13-16, 2013
- Kiss B, Horváth A, Némethy Z, et al: Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. *J Pharmacol Exp Ther* 333(1): 328-340, 2010 20093397
- Laszlovszky I, Lu K, Debelle M, et al: EPA-0870—Efficacy and safety of cariprazine in patients with acute exacerbation of schizophrenia: results

- of two phase III trials (abstract). *Eur Psychiatry* 29 (suppl 1): S1, 2014
- Lundstrom K, Turpin MP: Proposed schizophrenia-related gene polymorphism: expression of the Ser9Gly mutant human dopamine D3 receptor with the Semliki Forest virus system. *Biochem Biophys Res Commun* 225(3):1068-1072, 1996 8780735
- Ma G, He Z, Fang W, et al: The Ser9Gly polymorphism of the dopamine D3 receptor gene and risk of schizophrenia: an association study and a large meta-analysis. *Schizophr Res* 101(1-3):26-35, 2008 18295456
- Mattingly G, Anderson R: Cariprazine for schizophrenia and bipolar I disorder. *Current Psychiatry* 15(2):34-39, 2016
- McCormack PL: Cariprazine: first global approval. *Drugs* 75(17):2035-2043, 2015 26510944
- Mészáros GP, Bolf ET, Gemesi L: P.3.d.015 Pharmacokinetics of RGH-188, a novel dopamine D3/D2 antagonist/partial agonist atypical antipsychotic, in rats and dogs (abstract). *Eur Neuropsychopharmacol* 18 (suppl 4):S456-S457, 2008
- Nakamura T, Kubota T, Iwakaji A, et al: Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). *Drug Des Devel Ther* 10:327-338, 2016 26834462
- Nasrallah HA, Cutler AJ, Wang Y, et al: P.3.d.025 Safety and tolerability of cariprazine in long-term treatment of schizophrenia: integrated summary of safety data (poster & abstract). *Eur Neuropsychopharmacol* 24 (suppl 2):S536, 2014
- Román V, Gyertyán I, Sághy K, et al: Cariprazine (RGH-188), a D3-preferring dopamine D3/D2 receptor partial agonist antipsychotic candidate demonstrates anti-abuse potential in rats. *Psychopharmacology (Berl)* 226(2):285-293, 2013 23138433
- Sachs GS, Greenberg WM, Starace A, et al: Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord* 174:296-302, 2015 25532076
- Seneca N, Finnema SJ, Laszlovszky I, et al: Occupancy of dopamine D2 and D3 and serotonin 5-HT1A receptors by the novel antipsychotic drug candidate, cariprazine (RGH-188), in monkey brain measured using positron emission tomography. *Psychopharmacology (Berl)* 218(3):579-587, 2011 21625907
- Tadori Y, Forbes RA, McQuade RD, Kikuchi T: Functional potencies of dopamine agonists and antagonists at human dopamine D2 and D3 receptors. *Eur J Pharmacol* 666(1-3):43-52, 2011a 21658377
- Tadori Y, Forbes RA, McQuade RD, Kikuchi T: In vitro pharmacology of aripiprazole, its metabolite and experimental dopamine partial agonists at human dopamine D2 and D3 receptors. *Eur J Pharmacol* 668(3):355-365, 2011b 21816144
- Veselinovic T, Paulzen M, Gründer G: Cariprazine, a new, orally active dopamine D2/3 receptor partial agonist for the treatment of



schizophrenia, bipolar mania and depression. Expert Rev Neurother  
13(11): 1141-1159, 2013 24175719

## CHAPTER 35

# Drugs to Treat Extrapyrarnidal Side Effects

Joseph K. Stanilla, M.D.  
George M. Simpson, M.D.

---

## Extrapyrarnidal Side Effects

---

### History

The discovery of the therapeutic properties of chlorpromazine (Delay and Deniker 1952; Laborit et al. 1952) was soon followed by the description of its tendency to produce extrapyramidal side effects (EPS) that were indistinguishable from the symptoms of classic Parkinson's disease. A debate soon arose regarding the relationship between EPS and therapeutic efficacy, with some investigators suggesting that EPS were necessary for efficacy (Flügel 1953; Haase 1954).

Brooks (1956), on the other hand, suggested that "signs of parkinsonism heralded the particular effect being sought" (p. 1122) but that "the therapeutic effects were not dependent on extrapyramidal dysfunction. On the contrary, alleviation of such dysfunction, as soon as it occurred, sped the progress of recovery" (p. 1122).

### Types

Four types of EPS have been delineated, and the treatment of each type should be individualized. *Acute dystonic reactions* (ADRs) are generally the first EPS to appear and are often the most dramatic (Angus and Simpson 1970b). *Dystonias* are involuntary sustained or spasmodic muscle contractions that cause abnormal twisting or rhythmical movements and/or postures. ADRs tend to occur suddenly and generally involve muscles of the head and neck (as in torticollis, facial grimacing, or oculogyric crisis). Nearly 90% of all ADRs occur within 4 days of antipsychotic initiation or dosage increase, and virtually 100% of all ADRs occur by day 10 (Singh et al. 1990; Sramek et al. 1986). Although tardive dystonia can occur after this

period, movements occurring beyond this time frame are much less likely to be ADRs. Instead, other conditions, including seizures, need to be considered.

*Akathisia* is the second type of EPS to appear. Akathisia, meaning “inability to sit,” consists of both an objective restless movement and a subjective feeling of restlessness that the patient experiences as the need to move. It may be difficult for a patient to explain the sensation of akathisia, and the diagnosis can be missed. At times, patients may display the classic movements of akathisia but without the subjective distress, a condition that has been termed *pseudoakathisia*, which may be a type of tardive syndrome ([Barnes 1990](#)).

The third type of EPS, *pseudoparkinsonism*, is virtually indistinguishable from classic Parkinson’s disease. Symptoms of pseudoparkinsonism include a generalized slowing of movement (akinesia), masked facies, rigidity (including cogwheeling rigidity), resting tremor, and hypersalivation. Parkinson-like symptoms generally appear after a few weeks or more of antipsychotic treatment. Akinesia needs to be differentiated from both primary depression and the blunted affect of schizophrenia ([Rifkin et al. 1975](#)).

*Tardive syndromes* make up the fourth group of EPS. Tardive dyskinesia (TD), although clearly associated with the use of antipsychotic medications, was actually described prior to the advent of antipsychotics ([Simpson 2000](#)). TD consists of irregular stereotypical movements of the mouth, face, and tongue and choreoathetoid movements of the fingers, arms, legs, and trunk. It tends to appear after months to years of use of antipsychotic medications. Patients frequently have no awareness of the abnormal movements. The lack of awareness may be related to frontal lobe dysfunction ([Sandyk et al. 1993](#)).

Tardive dystonia, a variant of TD, also generally emerges months to years after treatment with antipsychotics ([Burke et al. 1982](#)). Unlike in ADRs, the movements associated with tardive dystonia tend to be persistent and more resistant to medical treatment ([Kang et al. 1988](#)).

---

## Agents Used to Treat Extrapyramidal Side Effects

---

### Antiparkinsonian Agents for Neuroleptic-Induced Parkinsonism and Acute Dystonic Reactions

Antiparkinsonian medications primarily have been used to treat EPS and include anticholinergic, antihistaminic, and dopaminergic agents ([Table 35-1](#)).

---

**TABLE 35-1. Pharmacological agents for the treatment of neuroleptic-induced parkinsonism and acute dystonic reactions**

---

Compound	Relative equivalence (mg) <sup>a</sup>	Route	Availability	Dosing	Dosage range (mg/day)
Anticholinergics					
Trihexyphenidyl (Artane)	2	Oral	Tablets: 2, 5 mg Elixir: 2 mg/mL	qd-bid	2-30
Benztropine (Cogentin)	1	Oral	Tablets: 0.5, 1, 2 mg	qd-bid	1-12
		Injectable	Ampules: 1 mg/mL (2 mL)	Every 30 minutes (until symptom relief)	2-8
Biperiden (Akineton) <sup>b</sup>	2	Oral	Tablets: 2 mg	qd-bid	2-24
		Injectable	Ampules: 5 mg/mL (1 mL) <sup>b</sup>	Every 30 minutes (until symptom relief)	2-8
Procyclidine (Kemadrin)	2	Oral	Tablets: 5 mg (scored)	bid-tid	5-20
Antihistaminics					
Diphenhydramine (Benadryl)	50	Oral	Tablets: 25, 50 mg	bid-qd	50-200
		Injectable	Ampules: 50 mg/mL (1 mL, 10 mL)		
			Syringe (prefilled): 1 mL		
Dopaminergics					
Amantadine (Symmetrel)	N/A	Oral	Tablets: 100 mg Syrup: 50 mg/5 mL	qd-bid	100-300

*Note.* bid=twice daily; N/A=not applicable; qd=once daily; tid=three times daily.

<sup>a</sup>Adapted from [Klett and Caffey 1972](#).

<sup>b</sup>No longer available as an injectable in the United States.

## Anticholinergic Medications

### Trihexyphenidyl.

*History and discovery.* Trihexyphenidyl, a synthetic analog of atropine, was introduced as benzhexol hydrochloride in 1949. It was found to be effective in the treatment of Parkinson's disease in a study of 411 patients ([Doshay et al. 1954](#)). Thereafter, it was also used to treat neuroleptic-induced parkinsonism (NIP) ([Rashkis and Smarr 1957](#)). (The term *neuroleptic*, derived from Greek and meaning "to clasp the neuron," was introduced to describe chlorpromazine and the extrapyramidal effects that it produced [[Delay et al. 1952](#)].)

*Structure-activity relations.* Trihexyphenidyl, a tertiary-amine analog of atropine, is a competitive antagonist of acetylcholine and other muscarinic agonists that compete for a common binding site on muscarinic receptors ([Yamamura and Snyder 1974](#)). It exerts little blockade at nicotinic receptors ([Timberlake et al. 1961](#)). Trihexyphenidyl and all drugs in this class are referred to as anticholinergic, antimuscarinic, or atropine-like drugs. As a tertiary amine, trihexyphenidyl readily crosses the blood-brain barrier ([Brown and Taylor 1996](#)).

*Pharmacological profile.* The pharmacological properties of trihexyphenidyl are qualitatively similar to those of atropine and other anticholinergic drugs, although trihexyphenidyl acts primarily centrally, with few peripheral effects and little sedation. In the eye, anticholinergic drugs block both the sphincter muscle of the iris, causing the pupil to dilate (mydriasis), and the ciliary muscle of the lens, preventing accommodation and causing cycloplegia. In the heart, anticholinergic drugs usually produce a mild tachycardia through vagal blockade at the sinoatrial node pacemaker, although a mild slowing can occur. In the gastrointestinal tract, anticholinergic drugs reduce gut motility and salivary and gastric secretions. Salivary secretion is particularly sensitive and can be completely abolished. In the respiratory system, anticholinergic agents reduce secretions and can produce mild bronchodilatation. Anticholinergics inhibit the activity of sweat glands and mildly decrease contractions in the urinary and biliary tracts ([Brown and Taylor 1996](#)).

*Pharmacokinetics and disposition.* Peak concentration for trihexyphenidyl is reached 1-2 hours after oral administration, and its half-life is 10-12 hours ([Cedarbaum and McDowell 1987](#)). As a tertiary amine, trihexyphenidyl crosses the blood-brain barrier to enter the central nervous system (CNS).

*Mechanism of action.* The presumed mechanism of action of trihexyphenidyl for treatment of EPS is the blockade of intrastriatal cholinergic activity, which is relatively increased, compared with nigrostriatal dopaminergic activity, which has become decreased by antipsychotic blockade. The blockade of cholinergic activity returns the system to its previous equilibrium.

*Indications.* Anticholinergic agents were reported to have been effective treatment for NIP from open empirical trials ([Medina et al. 1962](#); [Rashkis and Smarr 1957](#)).

Eventually, controlled trials were conducted, with most involving comparisons only with different anticholinergics and not with placebo. Despite the limited evidence of efficacy against placebo, anticholinergic agents became the mainstay of treatment for NIP, and they remain so today.

Trihexyphenidyl has U.S. Food and Drug Administration (FDA) approval for treatment of all forms of parkinsonism, including NIP. Daily dosages of 5–30 mg have been used in studies of trihexyphenidyl in the treatment of Parkinson's disease and NIP. Much higher dosages (up to 75 mg/day) have been used for the treatment of primary dystonia. However, the benefits of high dosages have been limited by the adverse effects on cognition and memory ([Jabbari et al. 1989](#); [Taylor et al. 1991](#)). Side effects correlate with blood levels, but efficacy does not ([Burke and Fahn 1985](#)). The individual therapeutic dosage must be determined empirically and can vary widely.

*Side effects and toxicology.* The *peripheral* side effects of trihexyphenidyl result from parasympathetic muscarinic blockade, and they occur in a consistent hierarchy among different organs. They are qualitatively similar to the side effects of atropine and other anticholinergic drugs, but they are quantitatively less because of the reduced peripheral activity of trihexyphenidyl ([Brown 1990](#)).

Anticholinergic drugs initially depress salivary and bronchial secretions and sweat production. Reduced salivation leads to dry mouth and contributes to the high incidence of dental caries found among patients with chronic psychiatric problems ([Winer and Bahn 1967](#)). Treatment for this condition is unsatisfactory; relief obtained from chewing sugar-free gum or sucking on hard candy is limited by the need for constant use. Reduced sweating can contribute to heat prostration and heatstroke, particularly in warmer ambient temperatures.

The next physiological effects occur in the eyes and heart. Pupillary dilatation and inhibition of accommodation in the eye lead to photophobia and blurred vision. Attacks of acute glaucoma can occur in susceptible subjects with narrow-angle glaucoma, although this is relatively uncommon. Vagus nerve blockade leads to increased heart rate and is more apparent in patients with high vagal tone (usually younger men).

The next effects are inhibition of urinary bladder function and bowel motility, which can produce urinary retention, constipation, and obstipation. Sufficiently high dosages of anticholinergics will inhibit gastric secretion and motility ([Brown and Taylor 1996](#)).

Memory disturbance is the most common *central* side effect of anticholinergic medications because memory is dependent on the cholinergic system ([Drachman 1977](#)). Patients with underlying brain pathology are more susceptible to memory disturbance ([Fayen et al. 1988](#)). Patients with chronic psychiatric conditions often have a decreased ability to express themselves, making evaluation of memory more difficult; therefore, subtle memory changes can be missed or attributed to the underlying illness. Memory disturbances have been identified in patients with Parkinson's disease treated with anticholinergics ([Yahr and Duvoisin 1968](#)), even in some patients receiving only small dosages ([Stephens 1967](#)). Patients receiving an

antipsychotic and benztropine had significantly increased overall scores on the Wechsler Memory Scale when benztropine was withdrawn (Baker et al. 1983).

Anticholinergic toxicity produces restlessness, irritability, disorientation, hallucinations, and delirium. Elderly patients are at increased risk for both memory loss and toxic delirium, even at very low dosages, because of the natural loss of cholinergic neurons with aging (Perry et al. 1977). Toxic dosages can produce a clinical situation identical to atropine poisoning, manifesting as fixed dilated pupils, flushed face, sinus tachycardia, urinary retention, dry mouth, and fever. This condition can proceed to coma, cardiorespiratory collapse, and death.

*Drug-drug interactions.* There may be increased anticholinergic effects, including side effects, when trihexyphenidyl or any anticholinergic is combined with amantadine. Anticholinergic side effects are also much more likely to occur when drugs with anticholinergic properties are combined.

Some investigators have suggested that anticholinergic medications can affect antipsychotic blood levels. However, a review of this subject suggests that the available data are too limited to reach a definite conclusion on this matter. The best studies indicate that anticholinergic drugs do not affect antipsychotic blood levels or, at most, that they lower these levels only transiently (McEvoy 1983).

Haase and Janssen (1965) reported from open studies that when anticholinergic medications are added to antipsychotic medications given at dosages that reach the neuroleptic threshold, rigidity, hypokinesia, and therapeutic effects disappear, but psychopathology worsens. (Haase [1954] postulated that the neuroleptic dosage that produced minimal subclinical rigidity and hypokinesia [i.e., the “neuroleptic threshold”] was the minimum neuroleptic dosage necessary for therapeutic antipsychotic effect and that it was manifested by micrographic handwriting changes.) Other studies have reported no change or an improvement in scores of psychopathology with the addition of anticholinergics (Hanlon et al. 1966; Simpson et al. 1980).

*Anticholinergic abuse.* Anticholinergic drugs may be abused for their euphoriant and hallucinogenic effects, and they may be combined with street drugs for enhanced effect (Crawshaw and Mullen 1984). Patients with a history of substance abuse are more likely to abuse anticholinergics (Wells et al. 1989). Cases of abuse have been reported with all anticholinergics, but trihexyphenidyl apparently is the anticholinergic most likely to be abused (Macvicar 1977). Theoretically, one anticholinergic should be as effective as another, although an idiosyncratic response is possible. The potential for abuse needs to be considered, particularly in patients with a history of substance abuse.

## **Benztropine.**

*History and discovery.* Benztropine was synthesized by uniting the tropine portion of atropine with the benzhydryl portion of diphenhydramine hydrochloride. Benztropine was found to be effective in the treatment of 302 patients with Parkinson’s disease (Doshay 1956). The best results in the control of rigidity, contracture, and tremor were obtained at dosages of 1–4 mg once daily for older

patients and 2–8 mg once daily for younger ones. Dosages of 15–30 mg once daily caused excessive flaccidity in some patients, who became unable to lift their arms or raise their heads off the bed. Subsequently, benztropine was found to be effective for the treatment of NIP ([Karn and Kasper 1959](#)).

*Structure-activity relations.* Benztropine is a tertiary amine with activity similar to that of trihexyphenidyl. As a tertiary amine, benztropine enters the CNS.

*Pharmacological profile.* Benztropine has the pharmacological properties of an anticholinergic and an antihistaminic; however, it produces less sedation (in experimental animals) than does diphenhydramine.

*Pharmacokinetics and disposition.* Little is known about the pharmacokinetics of benztropine. A correlation between serum anticholinergic levels and the presence of EPS has been documented ([Tune and Coyle 1980](#)). There is little correlation between the total daily dosage of benztropine and the serum anticholinergic level, with the serum activity for a given dosage varying 100-fold between subjects. When treated with higher dosages of anticholinergics, patients with EPS show increased serum anticholinergic activity and decreased EPS. Relatively small increments in the oral dosage of an anticholinergic drug can result in significant nonlinear increases in serum anticholinergic activity levels. Benztropine has a long-acting effect and can be given once or twice a day.

*Mechanism of action, side effects, and drug-drug interactions.* The mechanism of action and the drug interactions for benztropine are similar to those of trihexyphenidyl. The side effects of these two drugs are also similar, but the degree of sedation produced by benztropine may be less ([Doshay 1956](#)). Although not yet confirmed in double-blind studies, this reported difference in sedation might account for the fact that trihexyphenidyl is reportedly the anticholinergic drug more likely to be abused.

*Indications.* Benztropine has FDA approval for the treatment of all forms of parkinsonism, including NIP. Total daily dosages of 1–8 mg generally have been used to treat NIP.

**Biperiden.** Biperiden is an analog of trihexyphenidyl that has greater peripheral anticholinergic activity than trihexyphenidyl and greater activity against nicotinic receptors ([Timberlake et al. 1961](#)). Biperiden is well absorbed from the gastrointestinal tract. Its metabolism, although not completely understood, involves hydroxylation in the liver. Its activity, pharmacological profile, and side effects are similar to those of other anticholinergics. It has FDA approval for use in the treatment of all forms of parkinsonism, including NIP. Total daily dosages of 2–24 mg have been used in studies of biperiden for the treatment of parkinsonism and NIP.

**Procyclidine.** Procyclidine is an analog of trihexyphenidyl ([Schwab and Chafetz 1955](#)). Its activity, pharmacology, and side effects are similar to those of other anticholinergics. There is little information about its pharmacokinetics. Procyclidine has FDA approval for use in treating all forms of parkinsonism, including NIP. Total



daily dosages of 5–30 mg have been used in studies of procyclidine for the treatment of parkinsonism and NIP.

## Antihistaminic Medications

### Diphenhydramine.

*History and discovery.* Antihistaminic agents have been used for the treatment of Parkinson's disease. Diphenhydramine, one of the first antihistamines developed and used clinically (Bovet 1950), has been the primary antihistamine studied in the treatment of EPS. Although some antihistamines may be effective, other antihistamines have not been systematically studied for the treatment of EPS.

*Structure-activity relations.* All drugs referred to as antihistamines are reversible competitive inhibitors of histamine at the histamine-1 ( $H_1$ ) receptor. Some antihistamines also inhibit the action of acetylcholine at the muscarinic receptor. It is believed that central muscarinic blockade, rather than histaminic blockade, is responsible for the therapeutic effect of antihistamines for EPS. Ethanolamine antihistamines (diphenhydramine, dimenhydrinate, and carbinoxamine maleate) have the greatest anticholinergic activity, and ethylenediamine antihistamines have the least anticholinergic activity. Antihistamines such as terfenadine and astemizole have no anticholinergic activity, whereas many of the remaining antihistamines have very mild anticholinergic activity (Babe and Serafin 1996).

*Pharmacological profile.* Antihistamines inhibit the constrictor action of histamine on respiratory smooth muscle. They restrict the vasoconstrictor and vasodilatory effects of histamine on vascular smooth muscle and block histamine-induced capillary permeability. Antihistamines with CNS activity are depressants, producing diminished alertness, slowed reaction times, and somnolence. They can also block motion sickness. Antihistaminic drugs with anticholinergic activity also possess mild antimuscarinic pharmacological properties similar to those of other atropine-like drugs (Babe and Serafin 1996).

*Pharmacokinetics and disposition.* Diphenhydramine is well absorbed from the gastrointestinal tract. Peak concentrations occur 2–3 hours after oral administration. Its therapeutic effects usually last 4–6 hours, and it has a half-life of 3–9 hours. Diphenhydramine is widely distributed throughout the body, and as a tertiary amine, it enters the CNS. Age does not affect its pharmacokinetics. It undergoes demethylations in the liver and is then oxidized to carboxylic acid (Paton and Webster 1985).

*Mechanism of action.* Diphenhydramine possesses some anticholinergic activity, which is believed to be the basis for its effect in diminishing EPS.

*Indications.* Diphenhydramine has FDA approval for treatment of parkinsonism, including NIP, in the elderly and for mild cases of parkinsonism in other age groups. It is probably not as efficacious for treating EPS as are pure anticholinergic drugs,

but it may be better tolerated in patients bothered by anticholinergic side effects, such as geriatric patients. Diphenhydramine also tends to be more sedating than anticholinergics, which can be beneficial for some patients. The dosage generally ranges from 50 to 400 mg/day, given in divided doses.

Diphenhydramine also has indications for multiple other conditions that are unrelated to EPS.

*Side effects and toxicology.* The primary side effect of diphenhydramine is sedation. Although other antihistamines may cause gastrointestinal distress, diphenhydramine has a low incidence of such an effect. Drying of the mouth and respiratory passages can occur. In general, the toxic effects are similar to those of trihexyphenidyl and of other anticholinergics.

*Drug-drug interactions.* Diphenhydramine has no reported interactions with other drugs, but it has an additive depressant effect when used in combination with alcohol or with other CNS depressants.

## Dopaminergic Medications

### Amantadine.

*History and discovery.* Anticholinergic side effects and inadequate treatment response eventually led to the investigation of other agents to treat EPS. Initially, both methylphenidate and intravenous caffeine were investigated as treatments for NIP. Neither agent achieved general use, despite apparent efficacy (Brooks 1956; Freyhan 1959).

Amantadine is an antiviral agent that is effective against A2 (Asian) influenza (Wingfield et al. 1969). It was unexpectedly found to produce symptomatic improvement in patients with Parkinson's disease (Parkes et al. 1970; Schwab et al. 1969), and soon thereafter, it was reported to be effective for NIP (Kelly and Abuzzahab 1971).

*Structure-activity relations.* Amantadine is a water-soluble tricyclic amine. It binds to the M2 protein, a membrane protein that functions as an ion channel on the influenza A virus (Hay 1992). Its activity in reducing EPS is not known, although it has been shown to have activity at glutamate receptors (Stoof et al. 1992).

*Pharmacological profile.* Amantadine is effective in preventing and treating illness from influenza A virus. It also reduces the symptoms of parkinsonism.

*Pharmacokinetics and disposition.* In young healthy subjects, amantadine is slowly and well absorbed from the gastrointestinal tract, with unchanged oral bioavailability over a dosage range of 50–300 mg/day. It reaches steady state in 4–7 days. Plasma concentrations (0.12–1.12 µg/mL) may have some correlation with improvement in EPS (Greenblatt et al. 1977; Pacifici et al. 1976). Amantadine has relatively constant blood levels and a long duration of action (Aoki et al. 1979) and is excreted unchanged by the kidneys. Its half-life for elimination is about 16 hours,

which is prolonged in elderly patients and in patients with impaired renal function ([Hayden et al. 1985](#)).

*Mechanism of action.* Amantadine inhibits viral replication by binding to the M2 protein on the viral membrane and inhibiting replication ([Hay 1992](#)). Its mechanism of action as an antiparkinsonian agent is less clear. It has no anticholinergic activity in tests on animals, being only 1/209,000th as potent as atropine ([Grelak et al. 1970](#)). It appears to cause the release of dopamine and other catecholamines from intraneuronal storage sites via an amphetamine-like mechanism. It has also been shown to have activity at glutamate receptors, which may contribute to its antiparkinsonian effect ([Stoof et al. 1992](#)). Amantadine has preferential selectivity for central catecholamine neurons ([Grelak et al. 1970](#); [Strömberg et al. 1970](#)).

*Indications.* Amantadine has undergone more extensive investigation than have anticholinergic agents with regard to the efficacy for EPS. Most studies, although not all, found amantadine to be equal in efficacy to benztropine or biperiden in the treatment of parkinsonism ([DiMascio et al. 1976](#); [Fann and Lake 1976](#); [König et al. 1996](#); [Silver et al. 1995](#); [Stenson et al. 1976](#)). Some studies found amantadine to be more effective than benztropine ([Merrick and Schmitt 1973](#)) or effective for EPS that are refractory to benztropine ([Gelenberg 1978](#)). However, other studies found that amantadine was inferior to benztropine ([Kelly et al. 1974](#)), no more effective than placebo ([Mindham et al. 1972](#)), or unable to control EPS when used to replace an anticholinergic agent ([McEvoy et al. 1987](#)). The varying results can be attributed to differing methodologies and patient populations.

The conclusion that can be drawn from these studies is that amantadine is an effective drug for treating parkinsonism but that no clear data support its use prior to using anticholinergic agents. Most of the studies were of short duration, and in patients with Parkinson's disease, amantadine appears to lose efficacy after several weeks ([Mawdsley et al. 1972](#); [Schwab et al. 1972](#)). Similar studies evaluating the long-term efficacy of amantadine have not been conducted for EPS.

Amantadine also has been evaluated for the treatment of akathisia, but in only a small number of patients. The conclusion from these studies is that amantadine is probably not effective for treating akathisia ([Fleischhacker et al. 1990](#)).

Amantadine has FDA approval for the treatment of NIP and Parkinson's disease, as well as for the treatment and prophylaxis of influenza A respiratory illness. Dosages of 100–300 mg/day are used for the treatment of NIP, and plasma concentrations may have some correlation with improvement.

*Side effects and toxicology.* At dosages of 100–300 mg/day, amantadine does not produce adverse effects as readily as do anticholinergic medications. Side effects of amantadine result from CNS stimulation, with symptoms including irritability, tremor, dysarthria, ataxia, vertigo, agitation, reduced concentration, hallucinations, and delirium ([Postma and Van Tilburg 1975](#)). Hallucinations are often visual. Side effects are more likely to occur in elderly patients and in patients with reduced renal function ([Borison 1979](#); [Ing et al. 1979](#)). Toxic effects are directly related to elevated amantadine serum levels (>1.5 µg/mL). Resolution of toxic symptoms is dependent

on renal clearance and may require dialysis in extreme cases, although less than 5% of amantadine is removed through dialysis.

Patients with congestive heart failure or peripheral edema should be monitored because of amantadine's ability to increase the availability of catecholamines. Long-term use of amantadine may produce livedo reticularis in the lower extremities from the local release of catecholamines and resulting vasoconstriction ([Cedarbaum and Schleifer 1990](#)). Amantadine should be used with caution in patients with seizures because of possible increased seizure activity. Amantadine is embryotoxic and teratogenic in animals, but there are no well-controlled studies in women regarding teratogenicity.

*Drug-drug interactions.* There are no reported interactions between amantadine and other drugs. There may be increased anticholinergic side effects when amantadine is used in combination with an anticholinergic agent.

## Beta-Adrenergic Receptor Antagonists

**History and discovery.** Propranolol was reported to be effective for the treatment of restless legs syndrome (Ekbom syndrome; [Ekbom 1965](#)), which resembles the physical movements of akathisia ([Strang 1967](#)). Later it was reported to be effective in the treatment of medication-induced akathisia ([Kulik and Wilbur 1983](#); [Lipinski et al. 1983](#)). Subsequently, other  $\beta$ -blockers have been investigated for the treatment of akathisia.

**Structure-activity relations.** Competitive  $\beta$ -adrenergic receptor antagonism is a property common to all  $\beta$ -blockers.  $\beta$ -Blockers are distinguished by the additional properties of their relative affinity for  $\beta_1$  and  $\beta_2$  receptors (selectivity), lipid solubility, intrinsic  $\beta$ -adrenergic receptor *agonist* activity, blockade of receptors, capacity to induce vasodilation, and general pharmacokinetic properties (Hoffman and Lefkowitz [1996](#)).  $\beta$ -Blockers with high lipid solubility readily cross the blood-brain barrier.

**Pharmacological profile.** The major pharmacological effects of  $\beta$ -blockers involve the cardiovascular system.  $\beta$ -Blockers slow the heart rate and decrease cardiac contractility; however, these effects are modest in a normal heart. In the lung, they can cause bronchospasm, although, again, there is little effect in normal lungs. They block glycogenolysis, preventing production of glucose during hypoglycemia ([Hoffman and Lefkowitz 1996](#)).  $\beta$ -Blockers affect lipid metabolism by preventing release of free fatty acids while elevating triglycerides ([Miller 1987](#)). In the CNS, they produce fatigue, sleep disturbance (insomnia and nightmares), and CNS depression (see [Drayer 1987](#); [Gengo et al. 1987](#)).

**Pharmacokinetics and disposition.** All  $\beta$ -blockers, except atenolol and nadolol, are well absorbed from the gastrointestinal tract ([McDevitt 1987](#)). All  $\beta$ -blockers undergo metabolism in the liver. Propranolol and metoprolol undergo significant first-pass effect, with bioavailability as low as 25%. Large interindividual variation (as much as 20-fold) leads to wide variation in clinically therapeutic

dosages (Hoffman and Lefkowitz 1996). Metabolites appear to have limited  $\beta$ -receptor antagonistic activity. The degree to which a particular  $\beta$ -blocker enters the CNS is related directly to its lipid solubility (Table 35-2).

**TABLE 35-2. Characteristics of  $\beta$ -blockers investigated in the treatment of akathisia**

Compound	$\beta_1$ blockade	$\beta_2$ blockade	Lipid solubility	Effective for EPS	Dosage range (mg/day)
Propranolol (Inderal)	++	++	++++	Yes	20-120
Nadolol (Corgard)	++	++	+	Yes	40-80
Metoprolol (Lopressor)	++	0 at low dosages; + at high dosages	++	Yes	~300
Pindolol (Visken)	++	++	++	Yes	5
Atenolol (Tenormin)	++	0	0	No	50-100
Betaxolol (Kerlone)	++	0	+++	Yes	5-20
Sotalol (Betapace, Sorine)	++	++	0	No	40-80

*Note.* EPS=extrapyramidal side effects; 0=insignificant; +=low; ++=moderate; +++=high; ++++=very high.

*Source.* Adapted from Hoffman and Lefkowitz 1996.

**Mechanism of action.** The exact mechanism of action of  $\beta$ -blockers in the treatment of EPS is unclear. The existence of a noradrenergic pathway from the locus coeruleus to the limbic system has been proposed as a modulator involved in symptoms of TD, akathisia, and tremor (Wilbur et al. 1988). It appears that lipid solubility and the corresponding ability to enter the CNS are the most important factors determining the efficacy of a  $\beta$ -blocker in treating akathisia and perhaps other types of EPS (Adler et al. 1991).

**Indications.**  $\beta$ -Blockers have FDA approval primarily for cardiovascular indications, and propranolol is also indicated for familial essential tremor, but there are no FDA-approved indications for the treatment of any type of EPS.

$\beta$ -Blockers have been studied primarily for the treatment of akathisia. Both nonselective ( $\beta_1$  and  $\beta_2$  antagonism) and selective ( $\beta_1$  antagonism)  $\beta$ -blockers have been reported to be efficacious. The studies generally have been for short periods of

time, involving small numbers of patients who were often receiving varying combinations of additional antiparkinsonian agents or benzodiazepines to which  $\beta$ -blockers had been added (Fleischhacker et al. 1990). From these studies, it is difficult to draw any firm conclusions, but  $\beta$ -blockers probably have some efficacy in the treatment of akathisia. The maximum benefit for propranolol occurred at 5 days (Fleischhacker et al. 1990). Betaxolol may be the  $\beta$ -blocker of choice in patients with lung disease and smokers because of its  $\beta_1$  selectivity at lower dosages (5–10 mg/day).

In addition to essential tremor,  $\beta$ -blockers have been reported to be beneficial for the tremor of Parkinson's disease (Foster et al. 1984) and lithium-induced tremor (Gelenberg and Jefferson 1995). However, for neuroleptic-induced tremor, propranolol was found to be not any better than placebo (Metzer et al. 1993), which could be an indication of a difference in etiologies for the different tremors.

**Side effects and toxicology.** The side effects of  $\beta$ -blockers result from  $\beta$ -receptor blockade.  $\beta_2$  blockade of bronchial smooth muscle produces bronchospasm. Individuals with normal lung function are unlikely to be affected, but smokers and others with lung disease can develop serious breathing difficulties.  $\beta$ -Blockers can contribute to heart failure in susceptible individuals, such as those with compensated heart failure, acute myocardial infarction, or cardiomegaly. Abrupt cessation of  $\beta$ -blockers can also exacerbate coronary heart disease in susceptible patients, producing angina or, potentially, myocardial infarction (see Hoffman and Lefkowitz 1996 for details).

In individuals with normal heart function, bradycardia produced by  $\beta$ -blockers is insignificant; however, in patients with conduction defects or when combined with other drugs that impair cardiac conduction,  $\beta$ -blockers can contribute to serious conduction problems.

$\beta$ -Blockers can block the tachycardia associated with hypoglycemia, eliminating this warning sign in patients with diabetes.  $\beta_2$  blockade also can inhibit glycogenolysis and glucose mobilization, interfering with recovery from hypoglycemia (Hoffman and Lefkowitz 1996).

$\beta$ -Blockers can impair exercise performance and produce fatigue, insomnia, and major depressive disorder. However, the development of major depressive disorder probably only occurs in individuals with a predisposition to developing depression.

**Drug-drug interactions.**  $\beta$ -Blockers can have significant interactions with other drugs. Chlorpromazine in combination with propranolol may increase the blood levels of both drugs. Additive effects on cardiac conduction and blood pressure can occur when  $\beta$ -blockers are combined with drugs having similar effects (e.g., calcium channel blockers). Phenytoin, phenobarbital, and rifampin increase the clearance of propranolol. Cimetidine increases propranolol blood levels by decreasing hepatic metabolism. Theophylline clearance is reduced by propranolol. Aluminum salts (antacids), cholestyramine, and colestipol may reduce the absorption of  $\beta$ -blockers (Hoffman and Lefkowitz 1996).



# Benzodiazepines for Medication-Induced Dystonia

## History and Discovery

Diazepam was initially shown to be effective in the treatment of restless legs syndrome (Ekbom syndrome), which resembles the physical movements of akathisia (Ekbom 1965). Subsequently, diazepam, lorazepam, and clonazepam were reported to be beneficial for medication-induced akathisia (Adler et al. 1985; Donlon 1973; Kutcher et al. 1987). Clonazepam also has been reported to be beneficial for drug-induced dystonia (O'Flanagan 1975) and TD (Thaker et al. 1987).

## Mechanism of Action

All benzodiazepines promote the binding of  $\gamma$ -aminobutyric acid (GABA) to GABA<sub>A</sub> receptors, magnifying the effects of GABA. The mechanism of action regarding improvement of EPS is unknown, but it may be related to augmentation of the inhibitory GABAergic effect (Hobbs et al. 1996). For a complete discussion of the properties of benzodiazepines, see Chapter 22 in this volume, "Benzodiazepines," by Sheehan.

## Indications

Benzodiazepines have FDA approval for use in treatment of anxiety disorders, agoraphobia, insomnia, and seizure disorders; management of alcohol withdrawal; anesthetic premedication; and skeletal muscle relaxation; however, they are not approved for use in treating any type of EPS. As noted earlier, a few initial reports have indicated that benzodiazepines are beneficial for the treatment of akathisia. Other studies also have reported similar benefit (Bartels et al. 1987; Braude et al. 1983; Gagrut et al. 1978; Horiguchi and Nishimatsu 1992; Kutcher et al. 1989; Pujalte et al. 1994).

Clonazepam has been reported to be effective in the treatment of TD (Bobruff et al. 1981; Thaker et al. 1990). Dosages of 1–10 mg/day were used in the first study, although the optimal dosage was found to be 4 mg/day, with many patients unable to tolerate higher dosages. In the second study, dosages of 2–4.5 mg/day were used, and tolerance developed after 5–8 months.

Although some of the studies were limited by short duration and by the small number of subjects also receiving other antiparkinsonian agents, the overall conclusion was that benzodiazepines probably have some efficacy in the treatment of akathisia and TD. However, the potential problems associated with the chronic use of benzodiazepines (i.e., tolerance and abuse) need to be kept in mind.

Lorazepam (intermediate-acting) and clonazepam (long-acting) are the two primary benzodiazepines that have been studied in the treatment of EPS. Because of its long duration of action, clonazepam often can be given once a day. Lorazepam has the advantage of having no active metabolites, which eliminates potential side effects and toxicity.

# Botulinum Toxin for Medication-Induced Dystonia

## History and Discovery

Botulinum toxin, produced by *Clostridium botulinum*, causes botulism when ingested. The first clinical use of the toxin was in the treatment of childhood strabismus (Scott 1980). The first focal dystonia treated was blepharospasm (Elston 1988). Botulinum toxin has been subsequently used to treat several other conditions associated with excessive muscle activity, including medication-induced dystonias (Hughes 1994).

## Structure-Activity Relations

There are seven immunologically distinct botulinum toxins (Simpson 1981). Type A is the primary type used clinically (Hambleton 1992). Type F and possibly type B also have clinical utility, but they have much shorter durations of action ( $\leq 3$  weeks, compared with  $\geq 3$  months for type A) (Borodic et al. 1996). The toxin is quantified by bioassay and is expressed as mouse units, which refers to the dose that is lethal to 50% of animals following intraperitoneal injection (Quinn and Hallet 1989).

## Pharmacological Profile

Botulinum toxin binds to cholinergic motor nerve terminals, preventing release of acetylcholine and producing a functionally denervated muscle. The prevention of acetylcholine release occurs within a few hours, but the clinical effect does not occur for 1–3 days. The innervation gradually becomes restored, although the number or size of active muscle fibers is reduced (Odergren et al. 1994).

## Pharmacokinetics and Disposition

After binding to the presynaptic nerve terminal, the toxin is taken into the nerve cell and is metabolized. When antibodies are present, the toxin is metabolized by immunological processes.

## Mechanism of Action

Botulinum toxin acts presynaptically to prevent the release of acetylcholine at the neuromuscular junction. This produces a functional chemical denervation and paralysis of the muscle. When botulinum toxin is used clinically, the aim is to reduce the excessive muscle activity without producing significant weakness (Hughes 1994).

## Indications

The FDA has approved the use of botulinum toxin for strabismus, blepharospasm, and other facial nerve disorders (see Jankovic and Brin 1991). Botulinum toxin has been used to treat focal neuroleptic-induced dystonias that may occur as part of TD, including laryngeal dystonia (Blitzer and Brin 1991) and refractory torticollis (Kaufman 1994). For laryngeal dystonia, the toxin is injected percutaneously through the cricothyroid membrane into the thyroarytenoid muscle bilaterally. The response rate is 80%–90%, and the effect lasts 3–4 months and sometimes longer. Botulinum treatment of tardive cervical dystonia has been found to be effective; the observed improvement is similar to the improvement seen in the treatment of idiopathic



cervical dystonia, although patients with tardive cervical dystonia required higher doses ([Brashear et al. 1998](#)).

### Side Effects and Toxicology

The major potential side effect of botulinum toxin is focal weakness in the muscle group injected, an effect that is usually dose dependent. This effect is generally temporary, given the mechanism of action. Transient weakness can occur through diffusion of the toxin into surrounding noninjected muscles ([Hughes 1994](#)).

Antibodies to the toxin can occur and thus can prevent a therapeutic response, particularly during subsequent treatments. The two main factors that apparently contribute to the development of antibodies are early age at first treatment with the toxin and total cumulative dose ([Jankovic and Schwartz 1995](#)). Some patients with antibodies will respond to other botulinum serotypes, such as type F ([Greene and Fahn 1993](#)). Local skin reactions also can occur. Some degree of muscle atrophy is apparent in injected muscles ([Hughes 1994](#)). Reinnervation usually takes place over the course of 3–4 months ([Odergren et al. 1994](#)).

Botulinum toxin has no known contraindications. Because the effect on the fetus is unknown, use of the toxin is not recommended during pregnancy. In conditions in which there are neuromuscular junction disorders, such as myasthenia gravis, patients could theoretically experience increased weakness. The long-term effects are unknown ([Hughes 1994](#)).

### Drug-Drug Interactions

Botulinum toxin has no known interactions with other drugs.

## Vitamin E (Alpha-Tocopherol) for Tardive Dyskinesia

### History and Discovery

Vitamin E was proposed as a treatment for TD after it was noted that a neurotoxin in rats induced an irreversible movement disorder and axonal damage similar to that caused by vitamin E deficiency. It was proposed that chronic antipsychotic use might produce free radicals, which would contribute to neurological damage and TD, and that the antioxidant effect of vitamin E could attenuate the damage ([Cadet et al. 1986](#)).

### Indications

The only known indication for vitamin E is treatment of vitamin E deficiency, which almost always results from malabsorption syndromes or abnormal transport, such as with abetalipoproteinemia ([Bieri and Farrell 1976](#)).

Early studies of vitamin E treatment of TD reported a range of results from general benefit ([Adler et al. 1993](#); [Dabiri et al. 1994](#); [Lohr et al. 1988](#)) to benefit only in subjects with TD of less than 5 years' duration ([Egan et al. 1992](#); [Lohr and Caligiuri 1996](#)) to no benefit ([Schmidt et al. 1991](#); [Shrqui et al. 1992](#)). Subsequently, a major double-blind study comparing vitamin E with placebo found that vitamin E was no more beneficial than placebo ([Adler et al. 1999](#)). There were no significant

effects of vitamin E on total scores or subscale scores for the Abnormal Involuntary Movement Scale (AIMS; [Guy 1976](#)), on electromechanical measures of dyskinesia, or on scores for four other scales measuring dyskinesia. The authors concluded that there was no evidence for efficacy of vitamin E in the treatment of TD ([Adler et al. 1999](#)).

The use of vitamin E supplementation is not without risk. A meta-analysis of high-dosage vitamin E supplementation trials showed a statistically significant association between vitamin E dosage and all-cause mortality, with increased risk for dosages greater than 150 IU/day (E.R. [Miller et al. 2005](#)). Given the lack of data showing consistent effectiveness for TD, we do not recommend that vitamin E be used for this purpose.

### Side Effects and Toxicology

Side effects are minimal when vitamin E is given orally. High levels of vitamin E can exacerbate bleeding abnormalities that are associated with vitamin K deficiency. Dosages of up to 3,200 mg/day in studies for other conditions have been used without significant adverse effects ([Kappus and Diplock 1992](#)). The only known drug interactions are with vitamin K (when it is being given for a deficiency) and bleeding abnormalities and possibly with oral anticoagulants. High dosages of vitamin E can exacerbate the coagulation abnormalities in both cases and therefore are contraindicated ([Kappus and Diplock 1992](#)).

---

## Antipsychotic Dopamine-Receptor Blockade and EPS

---

No drug with antipsychotic activity has been identified that does not have significant affinity for D<sub>2</sub> dopamine receptors. D<sub>2</sub> receptor blockade is the pharmacodynamic property of all antipsychotics, and without this property, a drug will not show any antipsychotic effects. This is true for both typical (first-generation) and atypical (second-generation) antipsychotics. The antipsychotic effects of typical antipsychotics are directly related to the degree of D<sub>2</sub> receptor blockade. The antipsychotic effects of atypical antipsychotics, however, are more complicated ([Meltzer 2002](#)).

All of the atypical antipsychotics are potent serotonin type 2A (5-HT<sub>2A</sub>) receptor antagonists and relatively weak D<sub>2</sub> receptor antagonists compared with the typical antipsychotics (except for cariprazine, which has relatively weak blockade of 5-HT<sub>2A</sub> receptors compared with the other atypical antipsychotics [[Gyertyán et al. 2011](#)]). The high ratio of 5-HT<sub>2A</sub> receptor blockade to striatal D<sub>2</sub> receptor blockade that characterizes clozapine is thought to contribute to its lack of EPS ([Meltzer et al. 1989](#)).

Blockade of 5-HT<sub>2A</sub> and dopamine receptors was first labeled in 1989 as a pharmacodynamic mechanism that differentiated conventional from second-generation antipsychotics ([Meltzer 1989](#)). [Meltzer \(2002\)](#) defined atypical

antipsychotics as drugs showing a higher affinity for 5-HT<sub>2A</sub> receptors than for D<sub>2</sub> receptors and a lower affinity for D<sub>2</sub> receptors than that seen with conventional antipsychotics. For the nigrostriatal dopaminergic pathway, one proposed model suggested that blockade of 5-HT<sub>2A</sub> receptors would lead to increased output of dopaminergic neurons into the striatum, causing an antipsychotic drug to be displaced from its binding to D<sub>2</sub> receptors. It was theorized that this displacement could decrease the risk of EPS development ([Horacek et al. 2006](#)).

---

## Treatment Approaches to Specific Types of EPS

---

### Acute Dystonic Reactions

Intramuscular anticholinergics are the treatment of choice for ADRs. Benztropine 2 mg or diphenhydramine 50–100 mg generally will produce complete resolution within 20–30 minutes, with a second dose repeated after 30 minutes if complete recovery does not occur. Benztropine has been shown to resolve ADRs in less time than diphenhydramine ([Lee 1979](#)). Starting a standing dose of an antiparkinsonian agent afterward is generally not necessary. ADRs do not recur, unless large dosages of high-potency antipsychotics are being used or unless the dosage is increased. A more complete discussion of prophylaxis is provided in the section “Prophylactic Use of Antiparkinsonian Agents” later in this chapter.

### Parkinsonism and Akathisia

The initial steps in treatment of parkinsonism ([Table 35-3](#)) and of akathisia (also referred to here as EPS) are identical: evaluating the dosage and type of antipsychotic. It has been shown that an increase in dosage beyond the neuroleptic threshold will not produce any greater therapeutic benefit but will increase EPS ([Angus and Simpson 1970a](#); [Baldessarini et al. 1988](#); [McEvoy et al. 1991](#)). It also has been found that EPS frequently can be eliminated with a reduction in dosage or a change to a lower-potency antipsychotic ([Braude et al. 1983](#); [Stratas et al. 1963](#)).

---

**TABLE 35-3. Treatment of parkinsonism**

---

Step	Action
1	Reduce dosage of antipsychotic, if clinically possible.
2	Substitute a lower-potency antipsychotic, or carry out step 8.
3	Add an anticholinergic agent.
4	Titrate anticholinergic to maximum dosage tolerated.

Step	Action
5	Add amantadine in combination with anticholinergic or as a single agent.
6	Add a benzodiazepine or a $\beta$ -blocker.
7	In severe cases of extrapyramidal side effects, stop antipsychotic temporarily and repeat process, beginning with step 3.
8	Substitute antipsychotic with atypical antipsychotic or clozapine.

If this approach does not resolve EPS, or if a lower-potency antipsychotic cannot be substituted, the addition of an anticholinergic drug is the next step. Maximum therapeutic response occurs in 3–10 days, with more severe EPS taking a longer time to respond (DiMascio et al. 1976; Fann and Lake 1976). The anticholinergic dose should be increased until EPS are alleviated or until an unacceptable degree of anticholinergic side effects is obtained. Akathisia frequently does not respond as well to anticholinergic medications and amantadine as do parkinsonism and ADRs (DiMascio et al. 1976). Akathisia is more likely to be responsive to anticholinergic agents if symptoms of parkinsonism are also present (Fleischhacker et al. 1990).

If EPS remain uncontrolled, amantadine can be either added to the regimen or substituted as a single agent. The next step would be the addition of a benzodiazepine or a  $\beta$ -blocker, although fewer data support both of these treatments.

In the case of severe EPS, the antipsychotic should be temporarily stopped, because severe EPS may be a risk factor for the development of neuroleptic malignant syndrome (Levinson and Simpson 1986).

Additional drugs have been studied or suggested as treatments for akathisia. The data supporting the use of amantadine for the treatment of akathisia are limited. Clonidine has been studied in a small number of patients, but its benefit was limited by sedation and hypotension (Fleischhacker et al. 1990). Sodium valproate was reported to have had no significant effect on akathisia and was found to increase parkinsonism (Friis et al. 1983).

### Atypical Antipsychotics and Risk of Parkinsonism and Akathisia

As experience with the use of atypical antipsychotics has increased, further data have been obtained about the risk of EPS. A review of studies involving atypical antipsychotics in which EPS were assessed found that EPS, especially akathisia, did occur with atypical antipsychotics, although the frequency was not as high as with typical antipsychotics. Risk factors include the use of high dosages of medication, high-potency atypical antipsychotics, combinations of atypical antipsychotics with other psychotropics, bipolar depression, palliative care settings, and substance abuse with psychosis (Kumar and Sachdev 2009).

Gao et al. (2008) conducted a review of studies of patients with schizophrenia or bipolar disorder. The studies included both typical and atypical antipsychotics. Haloperidol significantly increased the risk for akathisia, overall EPS, and anticholinergic use in both mania and schizophrenia, with a larger magnitude in mania. Among atypical antipsychotics, only ziprasidone significantly increased the

risk for overall EPS and anticholinergic use in both mania and schizophrenia, again with larger differences in mania. Patients with mania treated with risperidone had a significantly increased risk for overall EPS and anticholinergic use. Patients taking aripiprazole for bipolar mania and bipolar depression had increased risk for akathisia. Patients with bipolar depression treated with quetiapine had an increased risk for overall EPS. The authors concluded that bipolar depressed patients are at the greatest risk for acute antipsychotic-induced movement disorders.

Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies showed no clinically significant difference in the incidence of parkinsonian symptoms and akathisia between the atypical agents and a moderate-potency typical agent, perphenazine. Although a statistically significantly greater number of patients taking perphenazine than patients taking atypical antipsychotics discontinued treatment because of EPS (8% vs. 2%–4%), the EPS incidence was low and of limited clinical significance (D.D. [Miller et al. 2005](#)).

In the past, if a patient receiving a typical antipsychotic developed severe parkinsonism or akathisia and did not respond to antiparkinsonian treatment, the recommended strategy was to switch to an atypical antipsychotic. Now the recommendation can be made to consider the use of a less potent typical antipsychotic as one of the options for treatment, along with possibly changing to an atypical agent.

For severe refractory EPS that have not responded to standard treatments, the use of clozapine specifically to treat the EPS is indicated ([Casey 1989](#)). This is particularly true for akathisia, given its significant negative correlation with the outcome of schizophrenia. This is also true for patients who do not have any psychotic symptoms, if the EPS are judged to be severe enough to be disabling or potentially life-threatening, such as laryngeal dystonia.

**Clozapine.** Patients taking clozapine (FDA approved in 1989) were found to have significantly less parkinsonism compared with patients taking a combination of chlorpromazine and an antiparkinsonian agent (benztropine) ([Kane et al. 1988](#)). The prevalence and incidence of akathisia also were shown to be lower in patients taking clozapine than in patients taking other first- or second-generation antipsychotics ([Chengappa et al. 1994](#); [Chouinard et al. 1993](#); [Kurz et al. 1995](#); [Stanilla et al. 1995](#)). Clozapine is covered in detail elsewhere in this volume (see [Chapter 25](#), “Clozapine,” by [Marder and Yang](#)).

**Other atypical antipsychotics.** The atypical antipsychotics approved for use in the United States after clozapine were also shown either to produce EPS at rates similar to those seen with haloperidol (risperidone, olanzapine, quetiapine, ziprasidone, asenapine, and iloperidone) or to produce EPS at rates comparable to those seen with placebo (aripiprazole, paliperidone, cariprazine, and brexpiprazole).

*Risperidone.* Risperidone (approved in 1993) was the first atypical antipsychotic to become available after clozapine ([Claus et al. 1992](#)). At lower dosages (4–6 mg/day), risperidone usually does not produce significant parkinsonism, but unlike clozapine, it can produce significant parkinsonism at higher dosages ([Chouinard et al. 1993](#)). In initial studies comparing risperidone with haloperidol, the extrapyramidal scores for

patients receiving risperidone (6 mg once daily) were not significantly different from the scores of patients receiving placebo. Risperidone can cause ADRs, and patients with severe EPS at baseline were more likely to develop EPS when taking risperidone ([Simpson and Lindenmayer 1997](#)). Risperidone is covered in detail elsewhere in this volume (see [Chapter 28, "Risperidone and Paliperidone,"](#) by [Hill and Goff](#)).

*Olanzapine.* Olanzapine (approved in 1996) has been shown to have an antipsychotic effect comparable to that of haloperidol while producing less dystonia, parkinsonism, and akathisia ([Tollefson et al. 1997](#)). The reduced incidence of EPS was observed across the entire therapeutic dosage range of 5–24 mg/day. Olanzapine is covered in detail elsewhere in this volume (see [Chapter 26, "Olanzapine,"](#) by [Silberschmidt et al.](#)).

*Quetiapine.* Quetiapine (approved in 1997) has been found to have antipsychotic activity comparable to that of haloperidol at dosages ranging from 150 to 750 mg/day while producing parkinsonism at a level similar to that produced by placebo across the entire dosage range ([Arvanitis and Miller 1997](#); [Small et al. 1997](#)). Most patients had no significant changes in AIMS scores from baseline to the end of a 6-week period of treatment. Quetiapine is covered in detail elsewhere in this volume (see [Chapter 27, "Quetiapine,"](#) by [Buckley et al.](#)).

*Ziprasidone.* Ziprasidone (approved in 2001) was compared with haloperidol in a double-blind, dose-ranging trial and found to have comparable antipsychotic effect at higher dosages. Benzotropine use at any time during the study was less frequent with the highest dosage of ziprasidone (160 mg/day) than with haloperidol (15% vs. 53%) ([Goff et al. 1998](#)). Studies of ziprasidone found no significant differences in baseline-to-endpoint mean changes on Simpson-Angus Scale ([Simpson and Angus 1970](#)) and AIMS scores between placebo and ziprasidone (40–160 mg/day) ([Keck et al. 2001](#)). Ziprasidone is covered in detail elsewhere in this volume (see [Chapter 30, "Ziprasidone,"](#) by [Newcomer et al.](#)).

*Aripiprazole.* Aripiprazole (approved in 2002) was found to be comparable to risperidone in antipsychotic effect while producing EPS comparable to those seen with placebo ([Kane et al. 2002](#); [Potkin et al. 2003](#)). Aripiprazole is covered in detail elsewhere in this volume (see [Chapter 29, "Aripiprazole and Brexpiprazole,"](#) by [Gonzalez and Strassnig](#)).

*Paliperidone.* Extended-release paliperidone (approved in 2006) was found to have an incidence of EPS nearly comparable to that of placebo (7% vs. 3%) at a dosage range of 3–15 mg/day ([Kramer et al. 2007](#)). Paliperidone is covered in detail elsewhere in this volume (see [Chapter 28, "Risperidone and Paliperidone,"](#) by [Hill and Goff](#)).

*Asenapine.* Asenapine (approved in 2009) was evaluated in a 6-week double-blind, placebo- and active-controlled (haloperidol) trial of 458 patients with acute schizophrenia. Patients were given asenapine (5 mg or 10 mg twice a day),



haloperidol (4 mg twice a day), or placebo. The incidence of EPS for asenapine was 15% for 5 mg twice a day and 18% for 10 mg twice a day, 34% for haloperidol, and 10% for placebo ([Kane et al. 2010](#)).

In a study of 488 patients with manic or mixed episodes of bipolar disorder, patients receiving asenapine (5–10 mg twice a day) were compared with those receiving olanzapine (5–20 mg/day) or placebo. The incidence of EPS was found to be 10.3% for asenapine, 6.8% for olanzapine, and 3.1% for placebo ([McIntyre et al. 2010](#)).

Asenapine is covered in detail elsewhere in this volume (see [Chapter 31](#), “Asenapine,” by Citrome).

*Lurasidone.* Lurasidone (approved in 2009) was compared with placebo in a 6-week double-blind study of 180 patients with acute schizophrenia. Patients receiving lurasidone 80 mg/day were found to have no clinically significant differences in the incidence of EPS compared with patients receiving placebo ([Nakamura et al. 2009](#)). Lurasidone is covered in detail elsewhere in this volume (see [Chapter 33](#), “Lurasidone,” by Harvey).

*Iloperidone.* Iloperidone (approved in 2009) was evaluated from the pooled results of three double-blind studies of 1,912 patients with schizophrenia. Patients received iloperidone (4–24 mg/day), haloperidol (15 mg/day), risperidone (4–8 mg/day), or placebo. The incidences of akathisia and EPS were lower with iloperidone than with risperidone and haloperidol and generally were similar to the incidences with placebo ([Potkin et al. 2008](#)). Iloperidone is covered in detail elsewhere in this volume (see [Chapter 32](#), “Iloperidone,” by Buckley et al.).

*Brexpiprazole.* Brexpiprazole was approved in 2015 for the treatment of schizophrenia. A double-blind study compared brexpiprazole (daily dosages of 0.25, 2, or 4 mg) with placebo in patients with acute schizophrenia. The incidence of akathisia was relatively low for both placebo (2%) and brexpiprazole 0.25 mg (0%), 2 mg (7%), and 4 mg (7%) ([Correll et al. 2015](#)). Brexpiprazole is covered in detail elsewhere in this volume (see [Chapter 29](#), “Aripiprazole and Brexpiprazole,” by Gonzalez and Strassnig).

*Cariprazine.* Cariprazine was approved in 2015 for the treatment of schizophrenia and bipolar disorder in adults ([Sachs et al. 2015](#)). Cariprazine was evaluated in a 6-week double-blind, placebo- and active-controlled (aripiprazole) study in patients with acute schizophrenia. Patients were assigned to cariprazine 3 or 6 mg/day, aripiprazole 10 mg/day, or placebo. The only treatment-emergent adverse event that occurred in more than 5% of the patients was akathisia in the 6 mg/day cariprazine group (15%). The incidence was significantly greater than the incidence with placebo (4.6%;  $P=0.0034$ ). The incidence for the 3 mg/day group was 7%. The incidence for aripiprazole was 7% ([Durgam et al. 2015](#)). Cariprazine is covered in detail elsewhere in this volume (see [Chapter 34](#), “Cariprazine,” by Albrahim et al.).

## Tardive Dyskinesia and Tardive Dystonia

Historically, TD has been refractory to treatment, which explains the large number of drugs used in attempts to alleviate the condition. Treatments investigated have included, but are not limited to, noradrenergic antagonists (propranolol and clonidine), antagonists of dopamine and other catecholamines, dopamine agonists, catecholamine-depleting drugs (reserpine and tetrabenazine), GABAergic drugs, cholinergic drugs (deanol, choline, and lecithin), catecholaminergic drugs ([Kane et al. 1992](#)), calcium channel blockers ([Cates et al. 1993](#)), and selective monoamine oxidase inhibitors (selegiline) ([Goff et al. 1993](#)). Based on the investigations of these drugs, the American Psychiatric Association Task Force on Tardive Dyskinesia concluded that there is no consistently effective treatment for TD ([Kane et al. 1992](#)).

Evaluating the effects of any treatment for TD has inherent difficulties. These include the variability of clinical raters ([Bergen et al. 1984](#)), the variability of placebo response ([Sommer et al. 1994](#)), and the diurnal and longitudinal variability of TD ([Hyde et al. 1995](#); [Stanilla et al. 1996](#)). The degree of improvement needs to be greater than the sum of such variations to show an actual benefit.

The first step in evaluating TD is to determine the type of antipsychotic agent that is being used. If a typical antipsychotic is necessary, it is important to use the lowest dosage possible ([Simpson 2000](#)). Second, if anticholinergic antiparkinsonian medications are being used, the patient should be gradually weaned from these medications and the medications then discontinued. In contrast to their effect on other extrapyramidal movements, anticholinergic medications will make TD movements worse (see [Greil et al. 1984](#); [Jeste and Wyatt 1982](#)).

Some drugs have been shown to have some benefit in the treatment of TD, but they have limitations. Clonazepam has been reported to reduce the movements of TD for up to 9 months, although tolerance to the benefits developed ([Thaker et al. 1990](#)). Additional limitations are the inherent problems associated with chronic use of a benzodiazepine. Botulinum toxin is beneficial for treating localized tardive dystonias, particularly laryngeal and cervical dystonias ([Hughes 1994](#)). The injections need to be repeated every 3–6 months, and botulinum toxin is not a general treatment for TD. Vitamin E has not consistently been shown to be beneficial in all studies, and a large long-term double-blind study found no benefit for vitamin E compared with placebo ([Adler et al. 1999](#)).

Valbenazine (NBI-98854) is a vesicular monoamine transporter inhibitor that is actively being studied in the treatment of TD. Tetrabenazine, the original agent in this class, is effective in treating movement disorders but has important dosing and safety limitations. In a recent report of a Phase II study in 102 patients, valbenazine was highly statistically significantly more effective than placebo in improving TD ([O'Brien et al. 2016](#)), with apparently better safety and tolerability and greater ease of administration relative to tetrabenazine. Valbenazine is currently being investigated in pivotal Phase III trials and has been granted a Breakthrough Therapy designation by the FDA ([Müller 2015](#)).

Tardive dystonia also tends to be resistant to treatment; however, unlike TD, it may respond to anticholinergic medications ([Wojcik et al. 1991](#)) and to reserpine ([Kang et al. 1988](#)).

## **Atypical Antipsychotics and Risk of Tardive Syndromes**



Clozapine has been shown to decrease the symptoms of TD ([Simpson and Varga 1974](#); [Simpson et al. 1978](#)), with the greatest improvement occurring in cases of severe TD and tardive dystonia ([Lieberman et al. 1991](#)). These findings have been replicated and suggest that clozapine is unlikely to cause TD ([Chengappa et al. 1994](#); [Kane et al. 1993](#)). The disadvantages to clozapine are the potential side effects of agranulocytosis and seizures and the need for regular blood monitoring.

More data indicating the potential benefit of the other novel antipsychotics in the prevention and treatment of TD are being reported.

In a prospective double-blind study of patients with schizophrenia receiving treatment with either olanzapine or haloperidol and followed for up to 2.6 years, the risk for the development of TD with olanzapine was significantly decreased. The 1-year risk was 0.52% for olanzapine and 7.45% for haloperidol ([Beasley et al. 1999](#)).

A prospective study examined the incidence of emergent dyskinesia in middle-aged to elderly patients (mean age=66 years) taking haloperidol or low-dosage risperidone (mean total daily dosage for both medications=1 mg/day). Compared with the patients taking haloperidol, those taking risperidone were significantly less likely to develop TD ([Jeste et al. 1999](#)). A double-blind prospective study comparing 397 patients with schizophrenia on stable dosages of antipsychotics who were randomly assigned to switch to either risperidone or haloperidol and followed up for at least a year found that only 1 of the patients receiving risperidone developed dyskinetic movements, compared with 5 of the patients receiving haloperidol ([Csernansky et al. 2002](#)).

The data regarding the long-term effect of atypical antipsychotics in causing TD are more limited; however, any drug that is less likely to produce EPS is probably less likely to produce TD.

The best treatment for TD is prevention. Of the 1,460 subjects involved in the CATIE study, D.D. [Miller et al. \(2005\)](#) found 212 to have probable TD by Schooler-Kane criteria. They found that subjects with TD were older, had a longer duration of receiving antipsychotic medications, and were more likely to have been receiving a typical antipsychotic and an anticholinergic agent. They also found that substance abuse significantly predicted TD, as well as subjects with higher ratings of psychopathology, parkinsonian symptoms, and akathisia (D.D. [Miller et al. 2005](#)).

Patients with TD who are taking typical antipsychotics are candidates for switching to an atypical antipsychotic. In the case of severe TD or dystonia that has been unresponsive to other treatment, the use of clozapine is indicated ([Simpson 2000](#)).

---

## Prophylactic Use of Antiparkinsonian Agents

---

### Indications and Efficacy

Prophylactic use of antiparkinsonian agents to prevent EPS is a common but not completely accepted practice. Most controlled prospective studies regarding prophylactic use of antiparkinsonian medication have shown that prophylaxis can be beneficial for certain patients who are at high risk for developing ADRs but that it is

not beneficial in routine use across all patient groups ([Hanlon et al. 1966](#); [Sramek et al. 1986](#)). Several retrospective studies also have found that the need for prophylaxis of EPS is limited ([Swett et al. 1977](#)). The retrospective studies that identified a greater benefit from prophylaxis involved the use of high antipsychotic dosages ([Keepers et al. 1983](#); [Stern and Anderson 1979](#)).

[Table 35-4](#) summarizes the risk factors for developing ADRs, which include younger age (<35 years), higher dosages of antipsychotic, higher potency of antipsychotic, intramuscular route of delivery, (possibly) male sex ([Sramek et al. 1986](#)), and a history of ADRs from a similar antipsychotic ([Keepers and Casey 1991](#)). The use of cocaine also has been suggested as a possible risk factor ([van Harten et al. 1998](#)).

<b>TABLE 35-4. Risk factors for acute dystonic reactions</b>
High-potency antipsychotics
Haloperidol
Fluphenazine
Trifluoperazine
High dosages
Younger age (<35 years) <sup>a</sup>
Intramuscular route of delivery
Previous dystonic reaction to similar antipsychotic and dosage
Male sex (?)

<sup>a</sup>Approaches 100% at age <20 years.

## Withdrawal of Prophylactic Agents

Studies examining withdrawal of antiparkinsonian agents have found that not all subjects redevelop EPS when these agents are discontinued. In the first study to report this serendipitous finding ([Cahan and Parrish 1960](#)), patients were being withdrawn from benztropine in preparation for a trial of a new antiparkinsonian agent. The discovery that only 20% of the patients developed recurrent parkinsonian symptoms following withdrawal led the study authors to suggest that antiparkinsonian agents should be withdrawn after 2 months and that their use should be resumed only in patients who re-develop EPS ([Cahan and Parrish 1960](#)).

Other withdrawal studies have reported wide-ranging rates of EPS recurrence. Differences in rates of recurrence are related to the varying methodologies involved in the studies, including methods of rating and the initial reason for treatment with anticholinergics—prophylaxis or active treatment ([Ananth et al. 1970](#)). The types, dosages, and combinations of antipsychotics used—the same factors that contribute to the initial development of EPS—also have been major factors in determining recurrence rates ([Baker et al. 1983](#); [McClelland et al. 1974](#)).

Almost all anticholinergic withdrawal studies have involved abrupt withdrawal of the anticholinergic medications. Abrupt, compared with gradual, withdrawal is more

likely to result in a return of EPS. Gradual withdrawal studies have found that a large percentage (up to 90%) of patients can be completely withdrawn from anticholinergic medications without developing EPS, and the remaining patients can have their EPS controlled with a considerably reduced dosage ([Double et al. 1993](#); [Ungvari et al. 1999](#)).

Patients are more likely to develop EPS on withdrawal of antiparkinsonian agents if the risk factors for developing EPS are present. If these risk factors are minimized, the rate of EPS recurrence is lowered.

Among patients who experience a recurrence of EPS, the EPS generally reappear within 2 weeks, and control is easily reestablished ([Klett and Caffey 1972](#)). Patients respond rapidly and often require smaller dosages of antiparkinsonian medications for control while continuing to take the same antipsychotic dosage ([McClelland et al. 1974](#)).

---

## Conclusion

---

The unique properties of chlorpromazine and other similarly active agents in ameliorating psychotic symptoms and producing parkinsonian side effects were described in the early 1950s by French psychiatrists. Theories soon arose regarding the relationship between these two properties. Recognition of the benefits of reducing parkinsonian side effects led to investigations of methods to reduce EPS and to the development of instruments to measure EPS.

The debate regarding the routine and prophylactic use of antiparkinsonian agents has continued since that time. It appears that prophylactic antiparkinsonian agents need to be used in some situations, but probably with less frequency and for briefer periods of time than has generally been the practice. The trend toward the use of lower dosages of antipsychotics should also lead to a decreased need for the use of antiparkinsonian agents.

Finally, the advent of atypical antipsychotic agents has opened a new chapter in both the treatment and the prevention of EPS and suggests that in the future, EPS will be less of a problem than they have been in the past.

A summary of an American Psychiatric Association Task Force report on TD suggested that a “deliberate and sustained effort must be made to maintain patients on the lowest effective amount of drug and to keep the treatment regimen as simple as possible” ([Baldessarini et al. 1980](#), p. 1168), and that anticholinergic drugs should be discontinued as soon as possible. Apart from a greater emphasis on avoiding the initial use of antiparkinsonian agents, this statement remains valid.

---

## References

---

- Adler L, Angrist B, Peselow E, et al: Efficacy of propranolol in neuroleptic-induced akathisia. *J Clin Psychopharmacol* 5(3): 164-166, 1985 2860136
- Adler LA, Angrist B, Weinreb H, et al: Studies on the time course and efficacy of beta-blockers in neuroleptic-induced akathisia and the akathisia of idiopathic

- Parkinson's disease. *Psychopharmacol Bull* 27(2):107-111, 1991 1681561
- Adler LA, Peselow E, Rotrosen J, et al: Vitamin E treatment of tardive dyskinesia. *Am J Psychiatry* 150(9):1405-1407, 1993 8102511
- Adler LA, Rotrosen J, Edson R, et al: Vitamin E treatment for tardive dyskinesia. Veterans Affairs Cooperative Study #394 Study Group. *Arch Gen Psychiatry* 56(9):836-841, 1999 12892048
- Ananth JV, Horodesky S, Lehmann HE, et al: Effect of withdrawal of antiparkinsonian medication on chronically hospitalized psychiatric patients. *Laval Med* 41(7):934-938, 1970 5509491
- Angus JW, Simpson GM: Handwriting changes and response to drugs—a controlled study. *Acta Psychiatr Scand Suppl* 212:28-37, 1970a 4917969
- Angus JW, Simpson GM: Hysteria and drug-induced dystonia. *Acta Psychiatr Scand Suppl* 212:52-58, 1970b 5272365
- Aoki FY, Sitar DS, Ogilvie RI: Amantadine kinetics in healthy young subjects after long-term dosing. *Clin Pharmacol Ther* 26(6):729-736, 1979 498714
- Arvanitis LA, Miller BG: Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry* 42(4):233-246, 1997 9270900
- Babe KS, Serafin WE: Histamine, bradykinin, and their antagonists, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th Edition. Edited by Hardman JG, Limbird LE, Molinoff PB, et al. New York, McGraw-Hill, 1996, pp 581-600
- Baker LA, Cheng LY, Amara IB: The withdrawal of benztropine mesylate in chronic schizophrenic patients. *Br J Psychiatry* 143:584-590, 1983 6362765
- Baldessarini RJ, Cole JO, Davis JM, et al: Tardive dyskinesia: summary of a task force report of the American Psychiatric Association. *Am J Psychiatry* 137(10):1163-1172, 1980 6106389
- Baldessarini RJ, Cohen BM, Teicher MH: Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 45(1):79-91, 1988 2892478
- Barnes TR: Movement disorder associated with antipsychotic drugs: the tardive syndromes. *International Review of Psychiatry* 2(3-4):355-366, 1990
- Bartels M, Heide K, Mann K, et al: Treatment of akathisia with lorazepam: an open clinical trial. *Pharmacopsychiatry* 20(2):51-53, 1987 2884681
- Beasley CM, Dellva MA, Tamura RN, et al: Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. *Br J Psychiatry* 174:23-30, 1999 10211147
- Bergen JA, Griffiths DA, Rey JM, et al: Tardive dyskinesia: fluctuating patient or fluctuating rater. *Br J Psychiatry* 144:498-502, 1984 6733374
- Bieri JG, Farrell PM: Vitamin E. *Vitam Horm* 34:31-75, 1976 828356
- Blitzer A, Brin MF: Laryngeal dystonia: a series with botulinum toxin therapy. *Ann Otol Rhinol Laryngol* 100(2):85-89, 1991 1992905
- Bobruff A, Gardos G, Tarsy D, et al: Clonazepam and phenobarbital in tardive dyskinesia. *Am J Psychiatry* 138(2):189-193, 1981 6109454
- Borison RL: Amantadine-induced psychosis in a geriatric patient with renal disease. *Am J Psychiatry* 136(1):111-112, 1979 758814
- Borodic G, Johnson E, Goodnough M, et al: Botulinum toxin therapy, immunologic resistance, and problems with available materials. *Neurology* 46(1):26-29, 1996

8559392

- Bovet D: Introduction to antihistamine agents and antergan derivative. *Ann N Y Acad Sci* 50(9):1089-1126, 1950 15413927
- Brashear A, Ambrosius WT, Eckert GJ, et al: Comparison of treatment of tardive dystonia and idiopathic cervical dystonia with botulinum toxin type A. *Mov Disord* 13(1):158-161, 1998 9452343
- Braude WM, Barnes TR, Gore SM: Clinical characteristics of akathisia: a systematic investigation of acute psychiatric inpatient admissions. *Br J Psychiatry* 143:139-150, 1983 6137254
- Brooks GW: Experience with the use of chlorpromazine and reserpine in psychiatry, with special reference to the significance and management of extrapyramidal dysfunction. *N Engl J Med* 254(24):1119-1123, 1956 13322223
- Brown JH: Atropine, scopolamine, and related antimuscarinic drugs, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 8th Edition. Edited by Gilman AG, Rall TW, Nies AS, et al. New York, Pergamon, 1990, pp 150-165
- Brown JH, Taylor P: Muscarinic receptor agonists and antagonists, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th Edition. Edited by Hardman JG, Limbird LE, Molinoff PB, et al. New York, McGraw-Hill, 1996, pp 141-160
- Burke RE, Fahn S: Serum trihexyphenidyl levels in the treatment of torsion dystonia. *Neurology* 35(7):1066-1069, 1985 4010950
- Burke RE, Fahn S, Jankovic J, et al: Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. *Neurology* 32(12):1335-1346, 1982 6128697
- Cadet JL, Lohr JB, Jeste DV: Free radicals and tardive dyskinesia (letter). *Trends Neurosci* 9:107-108, 1986
- Cahan RB, Parrish DD: Reversibility of drug-induced parkinsonism. *Am J Psychiatry* 116:1022-1023, 1960 13806781
- Casey DE: Clozapine: neuroleptic-induced EPS and tardive dyskinesia. *Psychopharmacology (Berl)* 99 (suppl):S47-S53, 1989 2682732
- Cates M, Lusk K, Wells BG: Are calcium-channel blockers effective in the treatment of tardive dyskinesia? *Ann Pharmacother* 27(2):191-196, 1993 7679936
- Cedarbaum JM, McDowell FH: Sixteen-year follow-up of 100 patients begun on levodopa in 1968: emerging problems, in *Advances in Neurology*, Vol 45: Parkinson's Disease. Edited by Yahr MD, Bergmann KJ. New York, Raven, 1987, pp 469-472
- Cedarbaum JM, Schleifer LS: Drugs for Parkinson's disease, spasticity, and acute muscle spasms, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 8th Edition. Edited by Gilman AG, Rall TW, Nies AS, et al. New York, Pergamon, 1990, pp 463-484
- Chengappa KN, Shelton MD, Baker RW, et al: The prevalence of akathisia in patients receiving stable doses of clozapine. *J Clin Psychiatry* 55(4):142-145, 1994 7915271
- Chouinard G, Jones B, Remington G, et al: A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 13(1):25-40, 1993 7683702
- Claus A, Bollen J, De Cuyper H, et al: Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. *Acta Psychiatr Scand* 85(4):295-305, 1992 1375801

- Correll CU, Skuban A, Ouyang J, et al: Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 172(9):870-880, 2015 25882325
- Crawshaw JA, Mullen PE: A study of benzhexol abuse. *Br J Psychiatry* 145:300-303, 1984 6478124
- Csernansky JG, Mahmoud R, Brenner R; Risperidone-USA-79 Study Group: A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 346(1):16-22, 2002 11777998
- Dabiri LM, Pasta D, Darby JK, et al: Effectiveness of vitamin E for treatment of long-term tardive dyskinesia. *Am J Psychiatry* 151(6):925-926, 1994 8185007
- Delay J, Deniker P: [Thirty-eight cases of psychoses treated with a long and continued course of 4560 RP. The Congress of the French Language for Alienists and Neurologists, Luxembourg, 21-27 July 1952.] Paris, Masson et Cie, 1952, pp 503-513
- Delay J, Deniker P, Harl JM: [Therapeutic method derived from hiberno-therapy in excitation and agitation states]. *Annales Medico-Psychologiques (Paris)* 110(2):267-273, 1952 13008201
- DiMascio A, Bernardo DL, Greenblatt DJ, et al: A controlled trial of amantadine in drug-induced extrapyramidal disorders. *Arch Gen Psychiatry* 33(5):599-602, 1976 5066
- Donlon PT: The therapeutic use of diazepam for akathisia. *Psychosomatics* 14(4):222-225, 1973 4795129
- Doshay LJ: Five-year study of benztropine (cogentin) methanesulfonate; outcome in three hundred two cases of paralysis agitans. *J Am Med Assoc* 162(11):1031-1034, 1956 13366700
- Doshay LJ, Constable K, Zier A: Five year follow-up of treatment with trihexyphenidyl (artane); outcome in four hundred eleven cases of paralysis agitans. *J Am Med Assoc* 154(16):1334-1336, 1954 13151847
- Double DB, Warren GC, Evans M, et al: Efficacy of maintenance use of anticholinergic agents. *Acta Psychiatr Scand* 88(5):381-384, 1993 7905226
- Drachman DA: Memory and cognitive function in man: does the cholinergic system have a specific role? *Neurology* 27(8):783-790, 1977 560649
- Drayer DE: Lipophilicity, hydrophilicity, and the central nervous system side effects of beta blockers. *Pharmacotherapy* 7(4):87-91, 1987 2891122
- Durgam S, Cutler AJ, Lu K, et al: Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry* 76(12):e1574-e1582, 2015 26717533
- Egan MF, Hyde TM, Albers GW, et al: Treatment of tardive dyskinesia with vitamin E. *Am J Psychiatry* 149(6):773-777, 1992 1350428
- Ekbom KA: [Restless legs] [Article in Swedish]. *Swed Med J* 62(31):2376-2378, 1965 5869584
- Elston J: Botulinum toxin treatment of blepharospasm. *Adv Neurol* 50:579-581, 1988 3400511
- Fann WE, Lake CR: Amantadine versus trihexyphenidyl in the treatment of neuroleptic-induced parkinsonism. *Am J Psychiatry* 133(8):940-943, 1976 782262
- Fayen M, Goldman MB, Moulthrop MA, et al: Differential memory function with dopaminergic versus anticholinergic treatment of drug-induced extrapyramidal symptoms. *Am J Psychiatry* 145(4):483-486, 1988 2894780
- Fleischhacker WW, Roth SD, Kane JM: The pharmacologic treatment of neuroleptic-induced akathisia. *J Clin Psychopharmacol* 10(1):12-21, 1990 1968470

- Flügel F: [Clinical observations on the effect of phenothiazine derivative megaphen on the psychic disorders in children]. *Med Klin* 48(29):1027-1029, 1953 13086364
- Foster NL, Newman RP, LeWitt PA, et al: Peripheral beta-adrenergic blockade treatment of parkinsonian tremor. *Ann Neurol* 16(4):505-508, 1984 6149724
- Freyhan FA: Therapeutic implications of differential effects of new phenothiazine compounds. *Am J Psychiatry* 115(7):577-585, 1959 13617475
- Friis T, Christensen TR, Gerlach J: Sodium valproate and biperiden in neuroleptic-induced akathisia, parkinsonism and hyperkinesia: a double-blind cross-over study with placebo. *Acta Psychiatr Scand* 67(3):178-187, 1983 6134430
- Gagrat D, Hamilton J, Belmaker RH: Intravenous diazepam in the treatment of neuroleptic-induced acute dystonia and akathisia. *Am J Psychiatry* 135(10):1232-1233, 1978 29498
- Gao K, Kemp DE, Ganocy SJ, et al: Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *J Clin Psychopharmacol* 28(2):203-209, 2008 18344731
- Gelenberg AJ: Amantadine in the treatment of benztropine refractory extrapyramidal disorders induced by antipsychotic drugs. *Curr Ther Res Clin Exp* 23:375-380, 1978
- Gelenberg AJ, Jefferson JW: Lithium tremor. *J Clin Psychiatry* 56(7):283-287, 1995 7615481
- Gengo FM, Huntoon L, McHugh WB: Lipid-soluble and water-soluble beta-blockers: comparison of the central nervous system depressant effect. *Arch Intern Med* 147(1):39-43, 1987 3541824
- Goff DC, Renshaw PF, Sarid-Segal O, et al: A placebo-controlled trial of selegiline (L-deprenyl) in the treatment of tardive dyskinesia. *Biol Psychiatry* 33(10):700-706, 1993 8102552
- Goff DC, Posever T, Herz L, et al: An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 18(4):296-304, 1998 9690695
- Greenblatt DJ, DiMascio A, Harmatz JS, et al: Pharmacokinetics and clinical effects of amantadine in drug-induced extrapyramidal symptoms. *J Clin Pharmacol* 17(11-12):704-708, 1977 336651
- Greene PE, Fahn S: Use of botulinum toxin type F injections to treat torticollis in patients with immunity to botulinum toxin type A. *Mov Disord* 8(4):479-483, 1993 8232357
- Greil W, Haag H, Rossnagl G, et al: Effect of anticholinergics on tardive dyskinesia: a controlled discontinuation study. *Br J Psychiatry* 145:304-310, 1984 6148119
- Grelak RP, Clark R, Stump JM, et al: Amantadine-dopamine interaction: possible mode of action in Parkinsonism. *Science* 169(3941):203-204, 1970 5427356
- Guy W: ECDEU Assessment Manual for Psychopharmacology, Revised Edition. Washington, DC, U.S. Department of Health, Education, and Welfare, 1976
- Gyertyán I, Kiss B, Sággy K, et al: Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. *Neurochem Int* 59(6):925-935, 2011 21767587
- Haase HJ: [Occurrence and interpretation of psychomotor parkinsonism in megaphen or largactil prolonged therapy]. *Nervenarzt* 25(12):486-492, 1954 14356297

- Haase HJ, Janssen PAJ: The Action of Neuroleptic Drugs. Chicago, IL, Year Book Medical, 1965
- Hambleton P: Clostridium botulinum toxins: a general review of involvement in disease, structure, mode of action and preparation for clinical use. J Neurol 239(1):16-20, 1992 1311751
- Hanlon TE, Schoenrich C, Freinek W, et al: Perphenazine-benzotropine mesylate treatment of newly admitted psychiatric patients. Psychopharmacology (Berl) 9(4):328-339, 1966 4874349
- Hay AJ: The action of amantadine against influenza A viruses: inhibition of the M2 ion channel protein. Semin Virol 3:21-30, 1992
- Hayden FG, Minocha A, Spyker DA, et al: Comparative single-dose pharmacokinetics of amantadine hydrochloride and rimantadine hydrochloride in young and elderly adults. Antimicrob Agents Chemother 28(2):216-221, 1985 3834831
- Hobbs WR, Rall TW, Verdoorn TA: Hypnotics and sedatives; ethanol, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th Edition. Edited by Hardman JG, Limbird LE, Molinoff PB, et al. New York, McGraw-Hill, 1996, pp 361-396
- Hoffman BB, Lefkowitz RJ: Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th Edition. Edited by Hardman JG, Limbird LE, Molinoff PB, et al. New York, McGraw-Hill, 1996, pp 199-248
- Horacek J, Bubenikova-Valesova V, Kopecek M, et al: Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. CNS Drugs 20(5):389-409, 2006 16696579
- Horiguchi J, Nishimatsu O: Usefulness of antiparkinsonian drugs during neuroleptic treatment and the effect of clonazepam on akathisia and parkinsonism occurred after antiparkinsonian drug withdrawal: a double-blind study. Jpn J Psychiatry Neurol 46(3):733-739, 1992 1362592
- Hughes AJ: Botulinum toxin in clinical practice. Drugs 48(6):888-893, 1994 7533696
- Hyde TM, Egan MF, Brown RJ, et al: Diurnal variation in tardive dyskinesia. Psychiatry Res 56(1):53-57, 1995 7792342
- Ing TS, Daugirdas JT, Soung LS, et al: Toxic effects of amantadine in patients with renal failure. Can Med Assoc J 120(6):695-698, 1979 436051
- Jabbari B, Scherokman B, Gunderson CH, et al: Treatment of movement disorders with trihexyphenidyl. Mov Disord 4(3):202-212, 1989 2779591
- Jankovic J, Brin MF: Therapeutic uses of botulinum toxin. N Engl J Med 324(17):1186-1194, 1991 2011163
- Jankovic J, Schwartz K: Response and immunoresistance to botulinum toxin injections. Neurology 45(9):1743-1746, 1995 7675238
- Jeste DV, Wyatt RJ: Therapeutic strategies against tardive dyskinesia: two decades of experience. Arch Gen Psychiatry 39(7): 803-816, 1982 6131655
- Jeste DV, Lacro JP, Bailey A, et al: Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. J Am Geriatr Soc 47(6):716-719, 1999 10366172
- Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45(9): 789-796, 1988 3046553
- Kane JM, Jeste DV, Barnes TR, et al: Treatment of tardive dyskinesia, in Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. Washington, DC, American Psychiatric Association, 1992, pp 103-120



- Kane JM, Woerner MG, Pollack S, et al: Does clozapine cause tardive dyskinesia? *J Clin Psychiatry* 54(9):327-330, 1993 8104929
- Kane JM, Carson WH, Saha AR, et al: Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 63(9):763-771, 2002 12363115
- Kane JM, Cohen M, Zhao J, et al: Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol* 30(2):106-115, 2010 20520283
- Kang UJ, Burke RE, Fahn S: Tardive dystonia. *Adv Neurol* 50:415-429, 1988 3400500
- Kappus H, Diplock AT: Tolerance and safety of vitamin E: a toxicological position report. *Free Radic Biol Med* 13(1):55-74, 1992 1628854
- Karn WN Jr, Kasper S: Pharmacologically induced Parkinson-like signs as index of the therapeutic potential. *Dis Nerv Syst* 20(3):119-122, 1959 13639829
- Kaufman DM: Use of botulinum toxin injections for spasmodic torticollis of tardive dystonia. *J Neuropsychiatry Clin Neurosci* 6(1):50-53, 1994 8148637
- Keck PE Jr, Reeves KR, Harrigan EP; Ziprasidone Study Group: Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. *J Clin Psychopharmacol* 21(1):27-35, 2001 11199944
- Keepers GA, Casey DE: Use of neuroleptic-induced extrapyramidal symptoms to predict future vulnerability to side effects. *Am J Psychiatry* 148(1):85-89, 1991 1670616
- Keepers GA, Clappison VJ, Casey DE: Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. *Arch Gen Psychiatry* 40(10):1113-1117, 1983 6138011
- Kelly JT, Abuzzahab FS Sr: The antiparkinson properties of amantadine in drug-induced parkinsonism. *J Clin Pharmacol New Drugs* 11(3):211-214, 1971 5211353
- Kelly JT, Zimmermann RL, Abuzzahab FS Sr, et al: A double-blind study of amantadine hydrochloride versus bztropine mesylate in drug-induced parkinsonism. *Pharmacology* 12(2):65-73, 1974 4610599
- Klett CJ, Caffey E Jr: Evaluating the long-term need for antiparkinson drugs by chronic schizophrenics. *Arch Gen Psychiatry* 26(4):374-379, 1972 4552131
- König P, Chwatal K, Havelec L, et al: Amantadine vs. biperiden: a double-blind study of treatment efficacy in neuroleptic extrapyramidal movement disorders. *Neuropsychobiology* 33(2):80-84, 1996 8927233
- Kramer M, Simpson G, Maciulis V, et al: Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 27(1):6-14, 2007 17224706
- Kulik AV, Wilbur R: Case report of propranolol (Inderal) pharmacotherapy for neuroleptic-induced akathisia and tremor. *Prog Neuropsychopharmacol Biol Psychiatry* 7(2-3):223-225, 1983 6137028
- Kumar R, Sachdev PS: Akathisia and second-generation antipsychotic drugs. *Curr Opin Psychiatry* 22(3):293-299, 2009 19378382
- Kurz M, Hummer M, Oberbauer H, et al: Extrapyramidal side effects of clozapine and haloperidol. *Psychopharmacology (Berl)* 118(1):52-56, 1995 7597122
- Kutcher SP, Mackenzie S, Galarraga W, et al: Clonazepam treatment of adolescents with neuroleptic-induced akathisia (letter). *Am J Psychiatry* 144(6):823-824, 1987

2884890

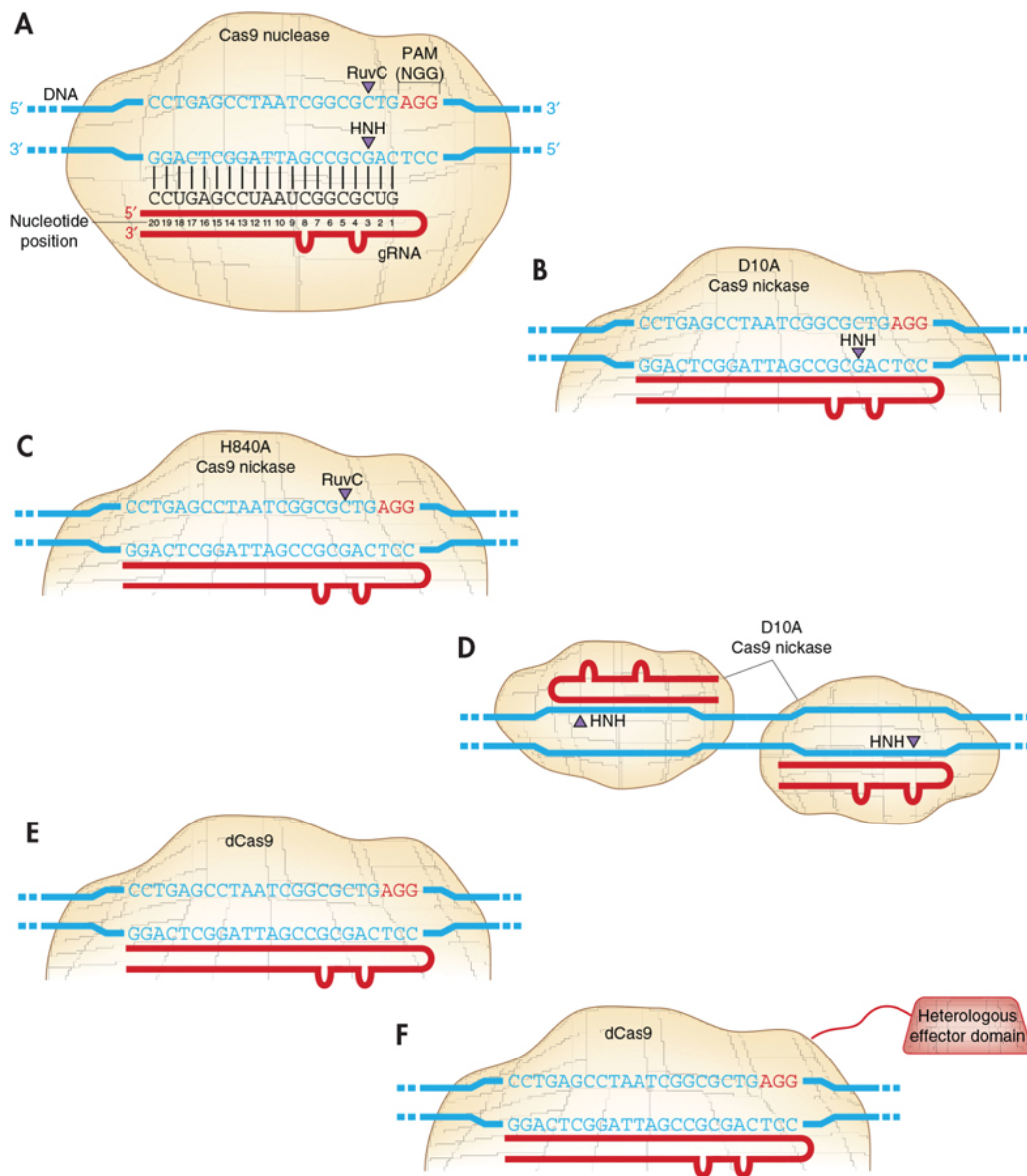
- Kutcher S, Williamson P, MacKenzie S, et al: Successful clonazepam treatment of neuroleptic-induced akathisia in older adolescents and young adults: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 9(6):403-406, 1989 2574191
- Laborit H, Huguenard P, Alluaume R: [A new vegetative stabilizer; 4560 R.P.]. *Presse Med* 60(10):206-208, 1952 14957790
- Lee AS: Treatment of drug-induced dystonic reactions. *JACEP* 8(11):453-457, 1979 502106
- Levinson DF, Simpson GM: Neuroleptic-induced extrapyramidal symptoms with fever. Heterogeneity of the "neuroleptic malignant syndrome". *Arch Gen Psychiatry* 43(9):839-848, 1986 2875701
- Lieberman JA, Saltz BL, Johns CA, et al: The effects of clozapine on tardive dyskinesia. *Br J Psychiatry* 158:503-510, 1991 1675900
- Lipinski JF, Zubenko GS, Barreira P, et al: Propranolol in the treatment of neuroleptic-induced akathisia. *Lancet* 1(8326 Pt 1):685-686, 1983 6132044
- Lohr JB, Caligiuri MP: A double-blind placebo-controlled study of vitamin E treatment of tardive dyskinesia. *J Clin Psychiatry* 57(4):167-173, 1996 8601552
- Lohr JB, Cadet JL, Lohr MA, et al: Vitamin E in the treatment of tardive dyskinesia: the possible involvement of free radical mechanisms. *Schizophr Bull* 14(2):291-296, 1988 2904696
- Macvicar K: Abuse of antiparkinsonian drugs by psychiatric patients. *Am J Psychiatry* 134(7):809-811, 1977 869063
- Mawdsley C, Williams IR, Pullar IA, et al: Treatment of parkinsonism by amantadine and levodopa. *Clin Pharmacol Ther* 13(4):575-583, 1972 4557584
- McClelland HA, Blessed G, Bhate S, et al: The abrupt withdrawal of antiparkinsonian drugs in schizophrenic patients. *Br J Psychiatry* 124(579):151-159, 1974 4596671
- McDevitt DG: Comparison of pharmacokinetic properties of beta-adrenoceptor blocking drugs. *Eur Heart J* 8 (suppl M): 9-14, 1987 2897304
- McEvoy JP: The clinical use of anticholinergic drugs as treatment for extrapyramidal side effects of neuroleptic drugs. *J Clin Psychopharmacol* 3(5):288-302, 1983 6138370
- McEvoy JP, McCue M, Freter S: Replacement of chronically administered anticholinergic drugs by amantadine in outpatient management of chronic schizophrenia. *Clin Ther* 9(4):429-433, 1987 2886223
- McEvoy JP, Hogarty GE, Steingard S: Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry* 48(8):739-745, 1991 1883257
- McIntyre RS, Cohen M, Zhao J, et al: Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 122(1-2):27-38, 2010 20096936
- McIntyre RS, Filteau MJ, Martin L, et al: Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord* 156(1):1-7, 2014 24314926
- Medina C, Kramer MD, Kurland AA: Biperiden in the treatment of phenothiazine-induced extrapyramidal reactions. *JAMA* 182:1127-1129, 1962 13934374
- Meltzer HY: Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. *Psychopharmacology (Berl)* 99 (suppl):S18-S27, 1989 2682729

- Meltzer HY: Commentary on "clinical studies on the mechanism of action of clozapine; the dopamine-serotonin hypothesis of schizophrenia." *Psychopharmacology* (1989) 99:S18-S27. *Psychopharmacology (Berl)* 163(1):1-3, 2002 12185394
- Meltzer HY, Matsubara S, Lee JC: Classification of typical and atypical antipsychotic drugs on the basis of dopamine D1, D2 and serotonin2 pKi values. *J Pharmacol Exp Ther* 251(1):238-246, 1989 2571717
- Merrick EM, Schmitt PP: A controlled study of the clinical effects of amantadine hydrochloride (Symmetrel). *Curr Ther Res Clin Exp* 15(8):552-558, 1973 4200529
- Metzer WS, Paige SR, Newton JE: Inefficacy of propranolol in attenuation of drug-induced parkinsonian tremor. *Mov Disord* 8(1):43-46, 1993 8093548
- Miller DD, McEvoy JP, Davis SM, et al: Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. *Schizophr Res* 80(1):33-43, 2005 16171976
- Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al: Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 142(1):37-46, 2005 15537682
- Miller NE: Effects of adrenoceptor-blocking drugs on plasma lipoprotein concentrations. *Am J Cardiol* 60(9):17E-23E, 1987 2889350
- Mindham RHS, Gaiend R, Anstee BH, et al: Comparison of amantadine, orphenadrine, and placebo in the control of phenothiazine-induced Parkinsonism. *Psychol Med* 2(4):406-413, 1972 4571143
- Müller T: Valbenazine granted breakthrough drug status for treating tardive dyskinesia. *Expert Opin Investig Drugs* 24(6):737-742, 2015 25809133
- Nakamura M, Ogasa M, Guarino J, et al: Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 70(6):829-836, 2009 19497249
- O'Brien CF, Jimenez R, Hauser RA, et al: NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: A randomized, double-blind, placebo-controlled study. *Mov Disord* 30(12):1681-1687, 2016 26346941
- Odergren T, Tollbäck A, Borg J: Electromyographic single motor unit potentials after repeated botulinum toxin treatments in cervical dystonia. *Electroencephalogr Clin Neurophysiol* 93(5):325-329, 1994 7525239
- O'Flanagan PM: Letter: Clonazepam in the treatment of drug-induced dyskinesia. *BMJ* 1(5952):269-270, 1975 1111773
- Pacifici GM, Nardini M, Ferrari P, et al: Effect of amantadine on drug-induced parkinsonism: relationship between plasma levels and effect. *Br J Clin Pharmacol* 3(5):883-889, 1976 788761
- Parkes JD, Calver DM, Zilkha KJ, et al: Controlled trial of amantadine hydrochloride in Parkinson's disease. *Lancet* 1(7641): 259-262, 1970 4189290
- Paton DM, Webster DR: Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 10(6):477-497, 1985 2866055
- Perry EK, Perry RH, Blessed G, et al: Necropsy evidence of central cholinergic deficits in senile dementia (letter). *Lancet* 1(8004):189, 1977 64712
- Postma JU, Van Tilburg W: Visual hallucinations and delirium during treatment with amantadine (Symmetrel). *J Am Geriatr Soc* 23(5):212-215, 1975 123540
- Potkin SG, Saha AR, Kujawa MJ, et al: Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 60(7):681-690, 2003 12860772

- Potkin SG, Litman RE, Torres R, et al: Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. *J Clin Psychopharmacol* 28 (2 suppl 1):S4-S11, 2008 18334911
- Pujalte D, Bottai T, Huë B, et al: A double-blind comparison of clonazepam and placebo in the treatment of neuroleptic-induced akathisia. *Clin Neuropharmacol* 17(3):236-242, 1994 9316669
- Quinn N, Hallet M: Dose standardization of botulinum toxin (letter) (erratum appears in *Lancet* 1[8646]:1092, 1989). *Lancet* 1(8644):964, 1989 2565459
- Rashkis HA, Smarr ER: Protection against reserpine-induced Parkinsonism (clinical note). *Am J Psychiatry* 113(12):1116, 1957 13424739
- Rifkin A, Quitkin F, Klein DF: Akinesia. A poorly recognized drug-induced extrapyramidal behavioral disorder. *Arch Gen Psychiatry* 32(5):672-674, 1975
- Sachs GS, Greenberg WM, Starace A, et al: Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord* 174:296-302, 2015 25532076
- Sandyk R, Kay SR, Awerbuch GI: Subjective awareness of abnormal involuntary movements in schizophrenia. *Int J Neurosci* 69(1-4):1-20, 1993 7916006
- Schmidt M, Meister P, Baumann P: Treatment of tardive dyskinesias with vitamin E. *Eur Psychiatry* 6(4):201-207, 1991
- Schwab RS, Chafetz ME: Kemadrin in the treatment of parkinsonism. *Neurology* 5(4):273-277, 1955 14370378
- Schwab RS, England AC, Poskanzer DC, et al: Amantadine in the treatment of Parkinson's disease. *JAMA* 208(7):1160-1170, 1969 5818715
- Schwab RS, Poskanzer DC, England AC Jr, et al: Amantadine in Parkinson's disease: review of more than two years' experience. *JAMA* 222(7):792-795, 1972 4677928
- Scott AB: Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 87(10):1044-1049, 1980 7243198
- Shriqui CL, Bradwejn J, Annable L, et al: Vitamin E in the treatment of tardive dyskinesia: a double-blind placebo-controlled study. *Am J Psychiatry* 149(3):391-393, 1992 1346951
- Silver H, Geraisy N, Schwartz M: No difference in the effect of biperiden and amantadine on parkinsonian- and tardive dyskinesia-type involuntary movements: a double-blind crossover, placebo-controlled study in medicated chronic schizophrenic patients. *J Clin Psychiatry* 56(4): 167-170, 1995 7713856
- Simpson GM: The treatment of tardive dyskinesia and tardive dystonia. *J Clin Psychiatry* 61 (suppl 4):39-44, 2000 10739330
- Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 212:11-19, 1970 4917967
- Simpson GM, Lindenmayer JP: Extrapyramidal symptoms in patients treated with risperidone. *J Clin Psychopharmacol* 17(3):194-201, 1997 9169965
- Simpson GM, Varga E: Clozapine—a new antipsychotic agent. *Curr Ther Res Clin Exp* 16(7):679-686, 1974 4210457
- Simpson GM, Lee JH, Shrivastava RK: Clozapine in tardive dyskinesia. *Psychopharmacology (Berl)* 56(1):75-80, 1978 415329
- Simpson GM, Cooper TB, Bark N, et al: Effect of antiparkinsonian medication on plasma levels of chlorpromazine. *Arch Gen Psychiatry* 37(2):205-208, 1980 7352851
- Simpson LL: The origin, structure, and pharmacological activity of botulinum toxin. *Pharmacol Rev* 33(3):155-188, 1981 6119708

- Singh H, Levinson DF, Simpson GM, et al: Acute dystonia during fixed-dose neuroleptic treatment. *J Clin Psychopharmacol* 10(6):389-396, 1990 2286708
- Small JG, Hirsch SR, Arvanitis LA, et al; Seroquel Study Group: Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry* 54(6):549-557, 1997 9193196
- Sommer BR, Cohen BM, Satlin A, et al: Changes in tardive dyskinesia symptoms in elderly patients treated with ganglioside GM1 or placebo. *J Geriatr Psychiatry Neurol* 7(4):234-237, 1994 7826493
- Sramek JJ, Simpson GM, Morrison RL, et al: Anticholinergic agents for prophylaxis of neuroleptic-induced dystonic reactions: a prospective study. *J Clin Psychiatry* 47(6):305-309, 1986 2872206
- Stanilla JK, Nair C, de Leon J, et al: Clozapine does not produce akathisia or parkinsonism. Poster presented at the 34th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 11-15, 1995
- Stanilla JK, Büchel C, Alarcon J, et al: Diurnal and weekly variation of tardive dyskinesia measured by digital image processing. *Psychopharmacology (Berl)* 124(4):373-376, 1996 8739553
- Stenson RL, Donion PT, Meyer JE: Comparison of benztropine mesylate and amantadine HCl in neuroleptic-induced extrapyramidal symptoms. *Compr Psychiatry* 17(6):763-768, 1976 791573
- Stephens DA: Psychotoxic effects of benzhexol hydrochloride (Artane). *Br J Psychiatry* 113(495):213-218, 1967 6032482
- Stern TA, Anderson WH: Benztropine prophylaxis of dystonic reactions. *Psychopharmacology (Berl)* 61(3):261-262, 1979 36644
- Stoof JC, Booij J, Drukarch B: Amantadine as N-methyl-D-aspartic acid receptor antagonist: new possibilities for therapeutic applications? *Clin Neurol Neurosurg* 94 (suppl):S4-S6, 1992 1320514
- Strang RR: The symptom of restless legs. *Med J Aust* 1(24):1211-1213, 1967 6028353
- Stratas NE, Phillips RD, Walker PA, et al: A study of drug-induced parkinsonism. *Dis Nerv Syst* 24:180, 1963 13978774
- Strömberg U, Svensson TH, Waldeck B: On the mode of action of amantadine. *J Pharm Pharmacol* 22(12):959-962, 1970 4395528
- Swett C Jr, Cole JO, Shapiro S, et al: Extrapyramidal side effects in chlorpromazine recipients: emergence according to benztropine prophylaxis. *Arch Gen Psychiatry* 34(8):942-943, 1977 889418
- Taylor AE, Lang AE, Saint-Cyr JA, et al: Cognitive processes in idiopathic dystonia treated with high-dose anticholinergic therapy: implications for treatment strategies. *Clin Neuropharmacol* 14(1):62-77, 1991 2029694
- Thaker GK, Tamminga CA, Alphs LD, et al: Brain gamma-aminobutyric acid abnormality in tardive dyskinesia: reduction in cerebrospinal fluid GABA levels and therapeutic response to GABA agonist treatment. *Arch Gen Psychiatry* 44(6):522-529, 1987 3034188
- Thaker GK, Nguyen JA, Strauss ME, et al: Clonazepam treatment of tardive dyskinesia: a practical GABA-mimetic strategy. *Am J Psychiatry* 147(4):445-451, 1990 1969244
- Timberlake WH, Schwab RS, England AC Jr: Biperiden (Akineton) in parkinsonism. *Arch Neurol* 5:560-564, 1961 13921278

- Tollefson GD, Beasley CM Jr, Tran PV, et al: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 154(4):457-465, 1997 9090331
- Tune L, Coyle JT: Serum levels of anticholinergic drugs in treatment of acute extrapyramidal side effects. *Arch Gen Psychiatry* 37(3):293-297, 1980 6102457
- Ungvari GS, Chiu HF, Lam LC, et al: Gradual withdrawal of long-term anticholinergic antiparkinson medication in Chinese patients with chronic schizophrenia. *J Clin Psychopharmacol* 19(2):141-148, 1999 10211915
- van Harten PN, van Trier JC, Horwitz EH, et al: Cocaine as a risk factor for neuroleptic-induced acute dystonia. *J Clin Psychiatry* 59(3):128-130, 1998 9541156
- Wells BG, Marken PA, Rickman LA, et al: Characterizing anticholinergic abuse in community mental health. *J Clin Psychopharmacol* 9(6):431-435, 1989 2592590
- Wilbur R, Kulik FA, Kulik AV: Noradrenergic effects in tardive dyskinesia, akathisia and pseudoparkinsonism via the limbic system and basal ganglia. *Prog Neuropsychopharmacol Biol Psychiatry* 12(6):849-864, 1988 2907387
- Winer JA, Bahn S: Loss of teeth with antidepressant drug therapy. *Arch Gen Psychiatry* 16(2):239-240, 1967 6019340
- Wingfield WL, Pollack D, Grunert RR: Therapeutic efficacy of amantadine HCl and rimantadine HCl in naturally occurring influenza A2 respiratory illness in man. *N Engl J Med* 281(11):579-584, 1969 4897137
- Wojcik JD, Falk WE, Fink JS, et al: A review of 32 cases of tardive dystonia. *Am J Psychiatry* 148(8):1055-1059, 1991 1677236
- Yahr MD, Duvoisin RC: Medical therapy of Parkinsonism. *Mod Treat* 5(2):283-300, 1968 5655945
- Yamamura HI, Snyder SH: Muscarinic cholinergic receptor binding in the longitudinal muscle of the guinea pig ileum with [3H]quinuclidinyl benzilate. *Mol Pharmacol* 10(6):861-867, 1974



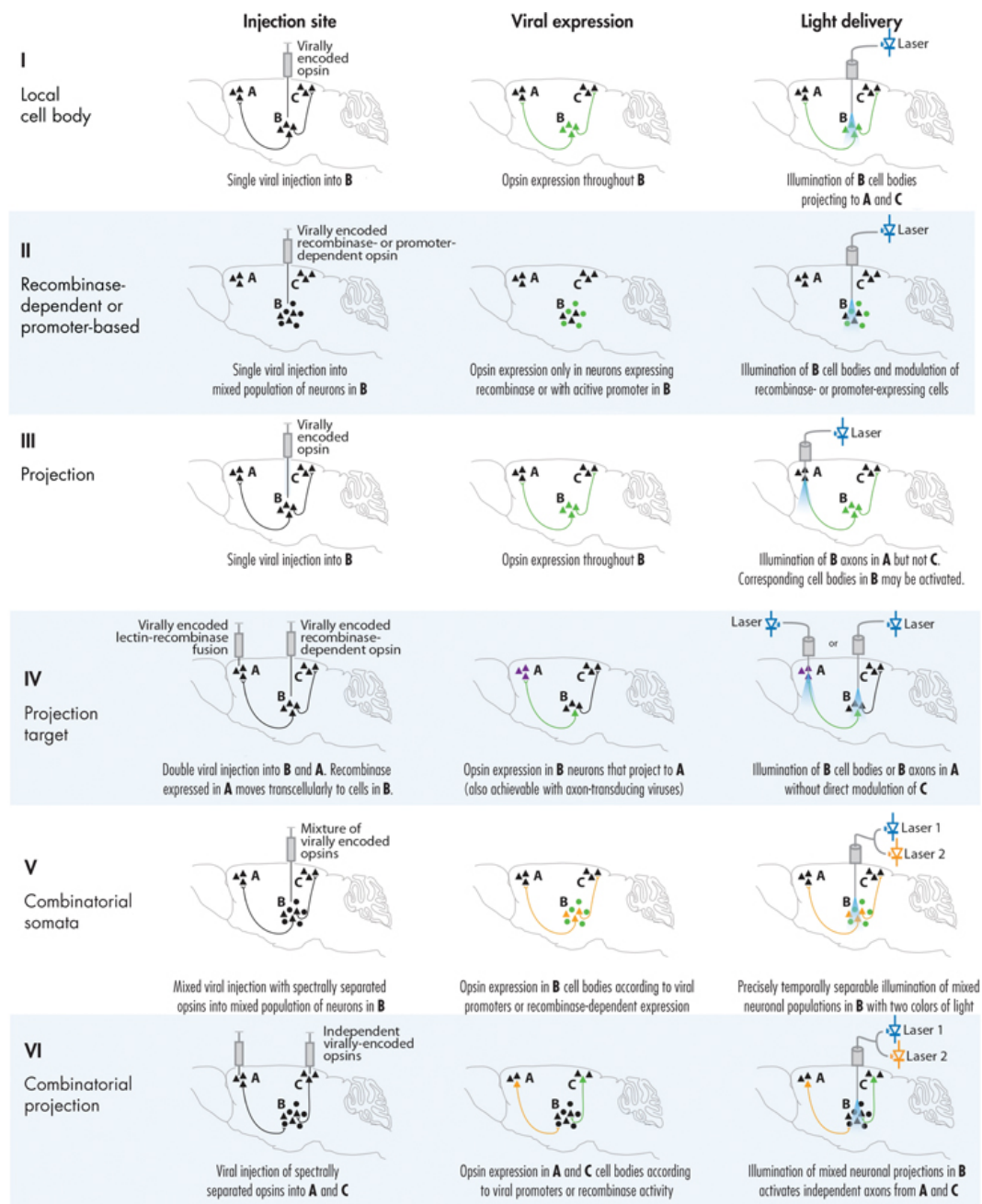
**PLATE 1.** (Figure 1-7) Cas9-based systems for altering gene sequence or expression.

(A) Cas9 nuclease creates double-strand breaks at DNA target sites with complementarity to the 5' end of a gRNA. (B) Cas9 nickase created by mutation of the RuvC nuclease domain with a D10A mutation. This nickase cleaves only the DNA strand that is complementary to and recognized by the gRNA. (C) Cas9 nickase created by mutation of the HNH nuclease domain with an H840A

mutation. This nickase cleaves only the DNA strand that does not interact with the small RNA. **(D)** Paired nickase strategy for improving Cas9 specificity. D10A Cas9 nickase directed by a pair of appropriately oriented gRNAs leads to induction of two nicks that, if introduced simultaneously, would be expected to generate a 5' overhang. **(E)** Catalytically inactive or "dead" Cas9 (dCas9) that can be recruited by a gRNA without cleaving the target DNA site. **(F)** Catalytically inactive dCas9-bearing dual D10A/H840A mutations fused to a heterologous effector domain. Cas9=CRISPR-associated protein 9 nuclease from *Streptococcus pyogenes*; CRISPR=clustered, regularly interspaced, short palindromic repeat; gRNA=guide RNA; PAM (NGG)=protospacer adjacent motif (sequence 5'-NGG-3', where "N" is any nucleobase followed by two guanine ("G") nucleobases).

*Source.* Reprinted from Sander JD, Joung JK: "CRISPR-Cas Systems for Editing, Regulating and Targeting Genomes." *Nature Biotechnology* 32(4):347-355, 2014. Copyright 2014, Nature Publishing Group. Used with permission.



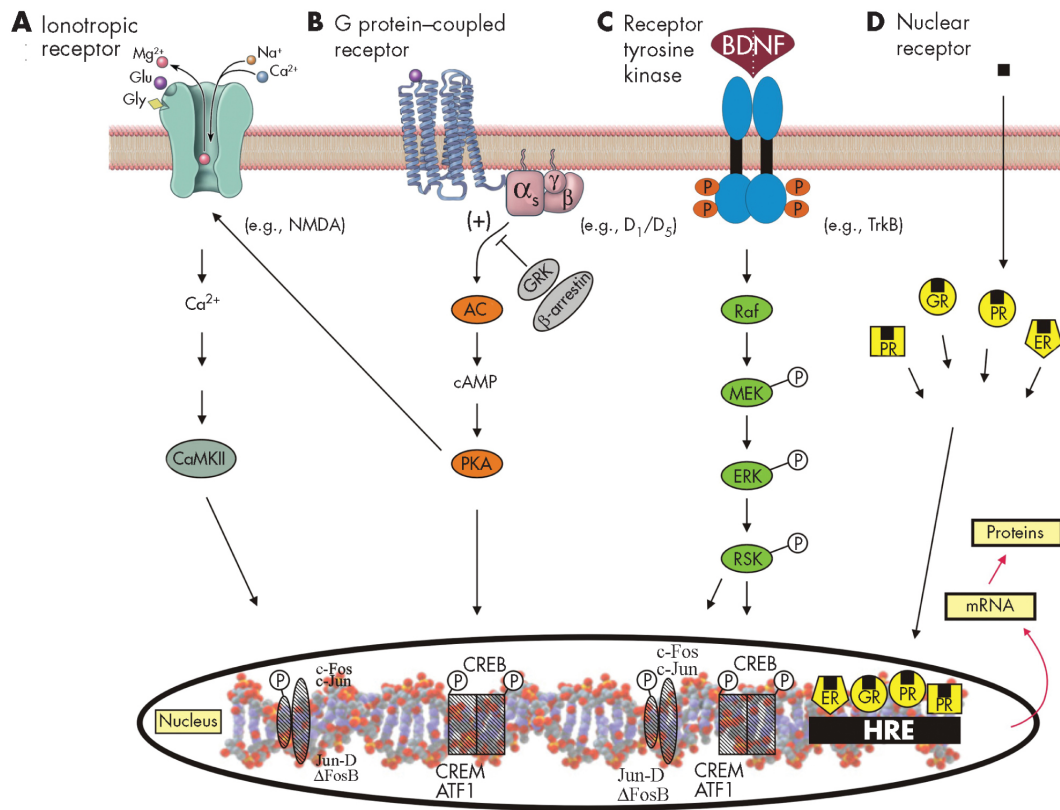


## PLATES 2 AND 3. (Figure 1–9) Optogenetic manipulation of neural circuits.

**(I)** Direct stimulation of neuronal cell bodies is achieved by injecting virus at the target region and then implanting a light-delivery device above the injected region. Even this simple experiment can provide specificity with viruses that will not

transduce afferent axons and fibers of passage. **(II)** Additional cell-type specificity is attained either by cell-type-specific promoters in the viral vector or via a recombinase-dependent virus, injected in a transgenic animal expressing a recombinase such as Cre in specific cells, leading to specific expression of the transgene only in defined cell types. **(III)** Projection (axonal) targeting is achieved by viral injection at the region harboring cell bodies, followed by implantation of a light-delivery device above the target region containing neuronal processes from the virally transduced region; in this way, cell types are targeted by virtue of their projections. **(IV)** Projection termination labeling is a more refined version of projection targeting, in which cells are targeted by virtue of synaptic connectivity to the target region, with likely exclusion of cells whose axons simply pass through the region. Transcellular labeling using a recombinase-dependent system is shown. Viruses expressing Cre fused to a transneuronal tracer (lectin) are delivered at the synaptic target site, and a Cre-dependent virus is injected into the region with cell bodies. Cells that project to the Cre-injected area express the Cre-dependent virus and become light sensitive. This can also be achieved with axon terminal-transducing viruses, although without control over the postsynaptic cell type. **(V)** Expression of two opsins with different characteristics in one brain region using a combination of promoter- or Cre-based approaches. Light delivery to the somata is performed using two different wavelengths designed to minimize cross-activation. **(VI)** Projections from two different brain regions are differentially stimulated with two wavelengths matched to the respective opsins expressed upstream.

*Source.* Reprinted from Yizhar O, Fenno LE, Davidson TJ, et al.: "Optogenetics in Neural Systems." *Neuron* 71(1):9-34, 2011. Copyright 2011, Elsevier, Inc. Used with permission.



**PLATE 4.** (*Figure 2-1*) Major receptor subtypes in the central nervous system.

This figure depicts the four major classes of receptors in the CNS.

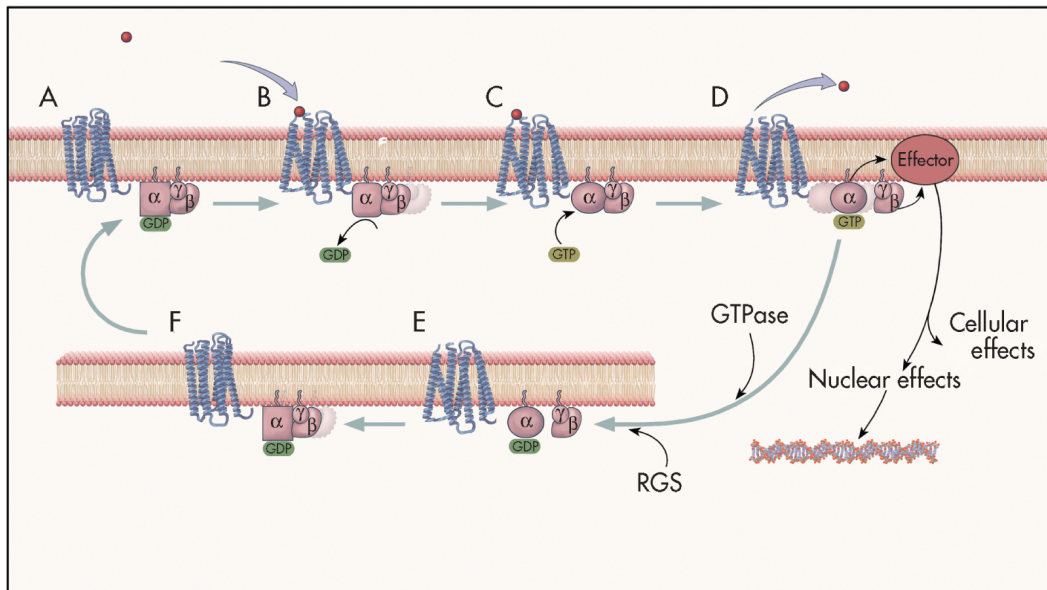
**(A) Ionotropic receptors.** These receptors comprise multiple protein subunits that are combined in such a way as to create a central membrane pore through this complex, allowing the flow of ions. This type of receptor has a very rapid response time (milliseconds). The consequences of receptor stimulation (i.e., excitatory or inhibitory) depend on the types of ions that the receptor specifically allows to enter the cell. Thus, for example,  $\text{Na}^+$  entry through the NMDA (*N*-methyl-D-aspartate) receptor depolarizes the neuron and brings about an excitatory response, whereas  $\text{Cl}^-$  efflux through the  $\gamma$ -aminobutyric acid type A ( $\text{GABA}_A$ ) receptor hyperpolarizes the neuron and brings about an inhibitory response. Illustrated here is the NMDA receptor regulating a channel permeable to  $\text{Ca}^{2+}$ ,  $\text{Na}^+$ , and  $\text{K}^+$  ions. The NMDA receptors also have binding sites for

glycine,  $\text{Zn}^{2+}$ , phencyclidine, MK801/ketamine, and  $\text{Mg}^{2+}$ ; these molecules are able to regulate the function of this receptor. **(B) *G protein-coupled receptors*** (GPCRs). The majority of neurotransmitters, hormones, and even sensory signals mediate their effects via seven transmembrane domain-spanning receptors that are G protein-coupled. The amino terminus of the G protein is on the outside of the cell and plays an important role in the recognition of specific ligands; the third intracellular loop and carboxy terminus of the receptor play an important role in coupling to G proteins and are sites of regulation of receptor function (e.g., by phosphorylation). All G proteins are heterotrimers (consisting of  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits). The G proteins are attached to the membrane by isoprenoid moieties (fatty acid) via their  $\gamma$  subunits. Compared with the ionotropic receptors, GPCRs mediate a slower response (on the order of seconds). Detailed depiction of the activation of G protein-coupled receptors is given in [Figure 2-2](#). Here we depict a receptor coupled to the G protein  $G_s$  (the *s* stands for stimulatory to the enzyme adenylyl cyclase [AC]). Activation of such a receptor produces activation of AC and increases in cyclic adenosine monophosphate (cAMP) levels. G protein-coupled pathways exhibit major amplification properties, and, for example, in model systems researchers have demonstrated a 10,000-fold amplification of the original signal. The effects of cAMP are mediated largely by activation of protein kinase A (PKA). One major downstream target of PKA is CREB (cAMP response element-binding protein), which may be important to the mechanism of action of antidepressants.

**(C) *Receptor tyrosine kinases***. These receptors are activated by neurotrophic factors and are able to bring about acute changes in synaptic function, as well as long-term effects on neuronal growth and survival. These receptors contain intrinsic tyrosine kinase activity. Binding of the ligand triggers receptor dimerization and transphosphorylation of tyrosine residues in its cytoplasmic domain, which then recruits cytoplasmic signaling and scaffolding proteins.

The recruitment of effector molecules generally occurs via interaction of proteins with modular binding domains SH2 and SH3 (named after homology to the src oncogenes–src homology domains); SH2 domains are a stretch of about 100 amino acids that allow high-affinity interactions with certain phosphotyrosine motifs. The ability of multiple effectors to interact with phosphotyrosines is undoubtedly one of the keys to the pleiotropic effects that neurotrophins can exert. Shown here is a tyrosine kinase receptor type B (TrkB), which upon activation produces effects on the Raf, MEK (mitogen-activated protein kinase/ERK), extracellular response kinase (ERK), and ribosomal S6 kinase (RSK) signaling pathway. Some major downstream effects of RSK are CREB and stimulation of factors that bind to the AP-1 site (c-Fos and c-Jun). **(D) Nuclear receptors.** These receptors are transcription factors that regulate the expression of target genes in response to steroid hormones and other ligands. Many hormones (including glucocorticoids, gonadal steroids, and thyroid hormones) are able to rapidly penetrate into the lipid bilayer membrane, because of their lipophilic composition, and thereby directly interact with these cytoplasmic receptors inside the cell. Upon activation by a hormone, the nuclear receptor–ligand complex translocates to the nucleus, where it binds to specific DNA sequences, referred to as *hormone responsive elements* (HREs), and regulates gene transcription. Nuclear receptors often interact with a variety of coregulators that promote transcriptional activation when recruited (coactivators) and those that attenuate promoter activity (corepressors). However, nongenomic effects of neuroactive steroids have also been documented, with the majority of evidence suggesting modulation of ionotropic receptors. This figure illustrates both the genomic and the nongenomic effects. ATF1=activation transcription factor 1; BDNF=brain-derived neurotrophic factor; CaMKII= $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II; CREM=cyclic adenosine 5'-monophosphate response element

modulator; D<sub>1</sub>=dopamine<sub>1</sub> receptor; D<sub>5</sub>=dopamine<sub>5</sub> receptor; ER=estrogen receptor; GR=glucocorticoid receptor; GRK=G protein-coupled receptor kinase; P=phosphorylation; PR=progesterone receptor.

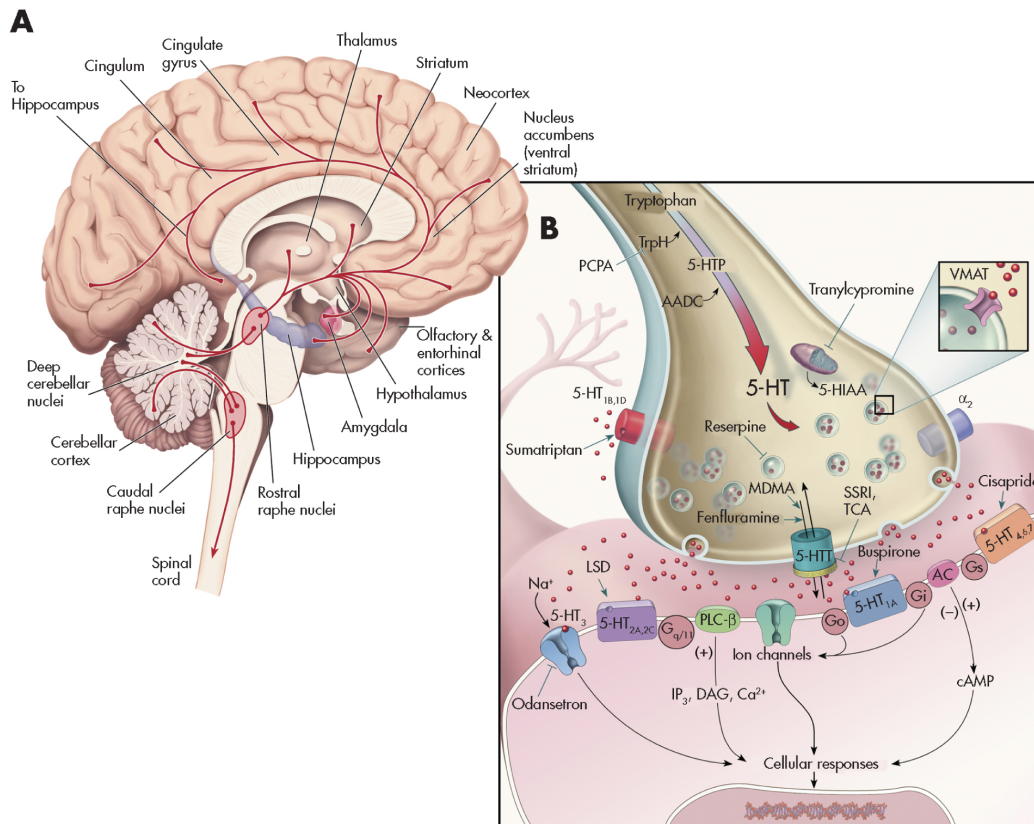


## PLATE 5. (Figure 2-2) G protein-coupled receptors and G protein activation.

All G proteins are heterotrimers consisting of  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits. The receptor shuttles between a low-affinity form that is not coupled to a G protein and a high-affinity form that is coupled to a G protein. **(A)** At rest, G proteins are largely in their inactive state, namely, as  $\alpha\beta\gamma$  heterotrimers, which have GDP (guanosine diphosphate) bound to the  $\alpha$  subunit. **(B)** When a receptor is activated by a neurotransmitter, it undergoes a conformational (shape) change, forming a transient state referred to as a *high-affinity ternary complex*, comprising the agonist, the receptor in a high-affinity state, and the G protein. A consequence of the receptor interaction with the G protein is that the GDP comes off the G protein  $\alpha$  subunit, leaving a very transient empty guanine nucleotide binding domain. **(C)** Guanine nucleotides (generally

GTP) quickly bind to this nucleotide binding domain; thus, one of the major consequences of active receptor-G protein interaction is to facilitate guanine nucleotide exchange—this is basically the “on switch” for the G protein cycle. **(D)** A family of GTPase-activating proteins for G protein-coupled receptors has been identified, and they are called regulators of G protein signaling (RGS) proteins. Since activating GTPase activity facilitates the “turn off” reaction, these RGS proteins are involved in dampening the signal. Binding of GTP to the  $\alpha$  subunit of G proteins results in subunit dissociation, whereby the  $\alpha$ -GTP dissociates from the  $\beta\gamma$  subunits. Although not covalently bound, the  $\beta$  and  $\gamma$  subunits remain tightly associated and generally function as dimers. The  $\alpha$ -GTP and  $\beta\gamma$  subunits are now able to activate multiple diverse effectors, thereby propagating the signal. While they are in their active states, the G protein subunits can activate multiple effector molecules in a “hit and run” manner; this results in major signal amplification (i.e., one active G protein subunit can activate multiple effector molecules). The activated G protein subunits also dissociate from the receptor, converting the receptor to a low-affinity conformation and facilitating the dissociation of the agonist from the receptor. The agonist can now activate another receptor, and this also results in signal amplification. Together, these processes have been estimated to produce a 10,000-fold amplification of the signal in certain models. **(E)** Interestingly, the  $\alpha$  subunit has intrinsic GTPase activity, which cleaves the third phosphate group from GTP (G-P-P-P) to GDP (G-P-P). Since  $\alpha$ -GDP is an inactive state, the GTPase activity serves as a built-in timing mechanism, and this is the “turn off” reaction. **(F)** The reassociation of  $\alpha$ -GDP with  $\beta\gamma$  is thermodynamically favored, and the reformation of the inactive heterotrimer ( $\alpha\beta\gamma$ ) completes the G protein cycle.





## PLATE 6. (Figure 2-3) The serotonergic system.

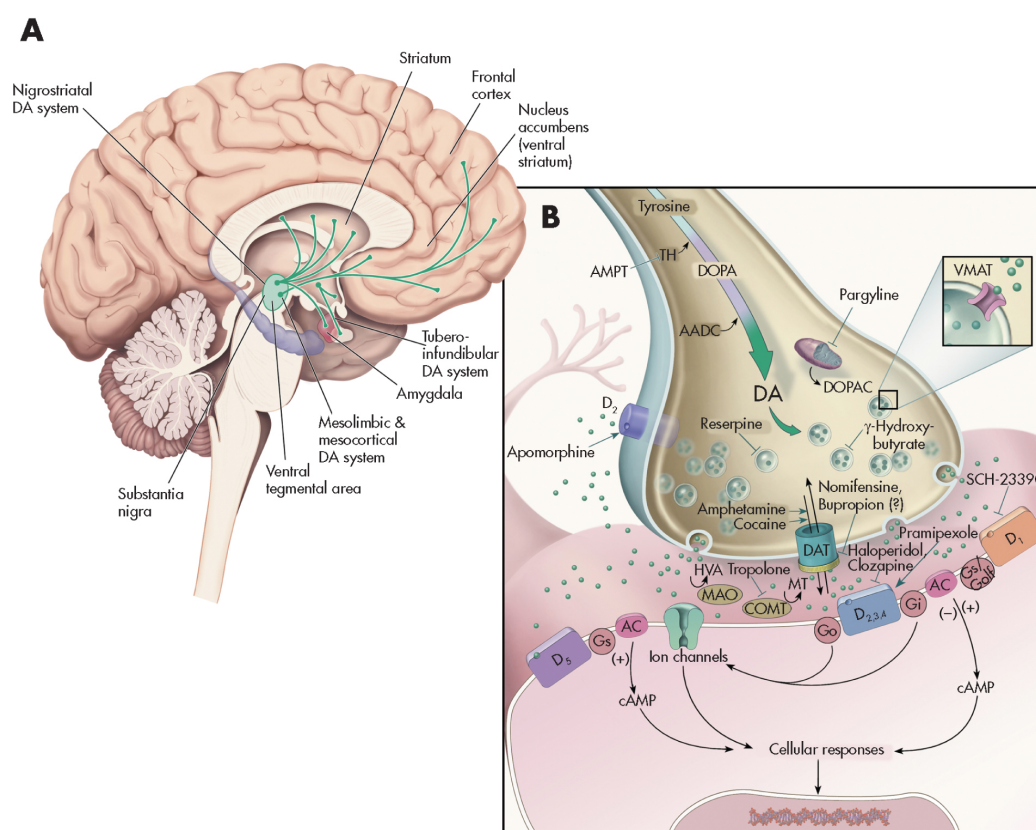
This figure depicts the location of the major serotonin (5-HT)-producing cells (raphe nuclei) innervating brain structures **(A)**, and various cellular regulatory processes involved in serotonergic neurotransmission **(B)**. 5-HT neurons project widely throughout the CNS and innervate virtually every part of the neuroaxis. L-Tryptophan, an amino acid actively transported into presynaptic 5-HT-containing terminals, is the precursor for 5-HT. It is converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme tryptophan hydroxylase (TrpH). This enzyme is effectively inhibited by the drug *p*-chlorophenylalanine (PCPA). Aromatic amino acid decarboxylase (AADC) converts 5-HTP to 5-HT. Once released from the presynaptic terminal, 5-HT can interact with a variety (15 different types) of presynaptic and postsynaptic receptors. Presynaptic regulation of 5-HT neuron firing activity and release



occurs through somatodendritic 5-HT<sub>1A</sub> (not shown) and 5-HT<sub>1B,1D</sub> autoreceptors, respectively, located on nerve terminals. Sumatriptan is a 5-HT<sub>1B,1D</sub> receptor agonist. (The antimigraine effects of this agent are likely mediated by local activation of this receptor subtype on blood vessels, which results in their constriction.) Buspirone is a partial 5-HT<sub>1A</sub> receptor agonist that activates both pre- and postsynaptic receptors. Cisapride is a preferential 5-HT<sub>4</sub> receptor agonist that is used to treat irritable bowel syndrome as well as nausea associated with antidepressants. The binding of 5-HT to G protein receptors (G<sub>o</sub>, G<sub>i</sub>, etc.) that are coupled to adenylyl cyclase (AC) and phospholipase C-β (PLC-β) will result in the production of a cascade of second-messenger and cellular effects. Lysergic acid diethylamide (LSD) likely interacts with numerous 5-HT receptors to mediate its effects. Pharmacologically this ligand is often used as a 5-HT<sub>2</sub> receptor agonist in receptor-binding experiments. Ondansetron is a 5-HT<sub>3</sub> receptor antagonist that is marketed as an antiemetic agent for chemotherapy patients but is also given to counteract side effects produced by antidepressants in some patients. 5-HT has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron through 5-HT transporters (5-HTTs). Once inside the neuron, it can either be repackaged into vesicles for reuse or undergo enzymatic catabolism. The selective 5-HT reuptake inhibitors (SSRIs) and older-generation tricyclic antidepressants (TCAs) are able to interfere/block the reuptake of 5-HT. 5-HT is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase (MAO), located on the outer membrane of mitochondria or sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). Reserpine causes a depletion of 5-HT in vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported with this agent). Tranylcypromine is an MAO inhibitor (MAOI) and an effective antidepressant. Fenfluramine (an anorectic agent) and 3,4-

methylenedioxymethamphetamine (MDMA; “Ecstasy”) are able to facilitate 5-HT release by altering 5-HTT function. cAMP=cyclic adenosine monophosphate; DAG=diacylglycerol; IP<sub>3</sub>=inositol-1,4,5-triphosphate.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Modified from Nestler et al. 2001.



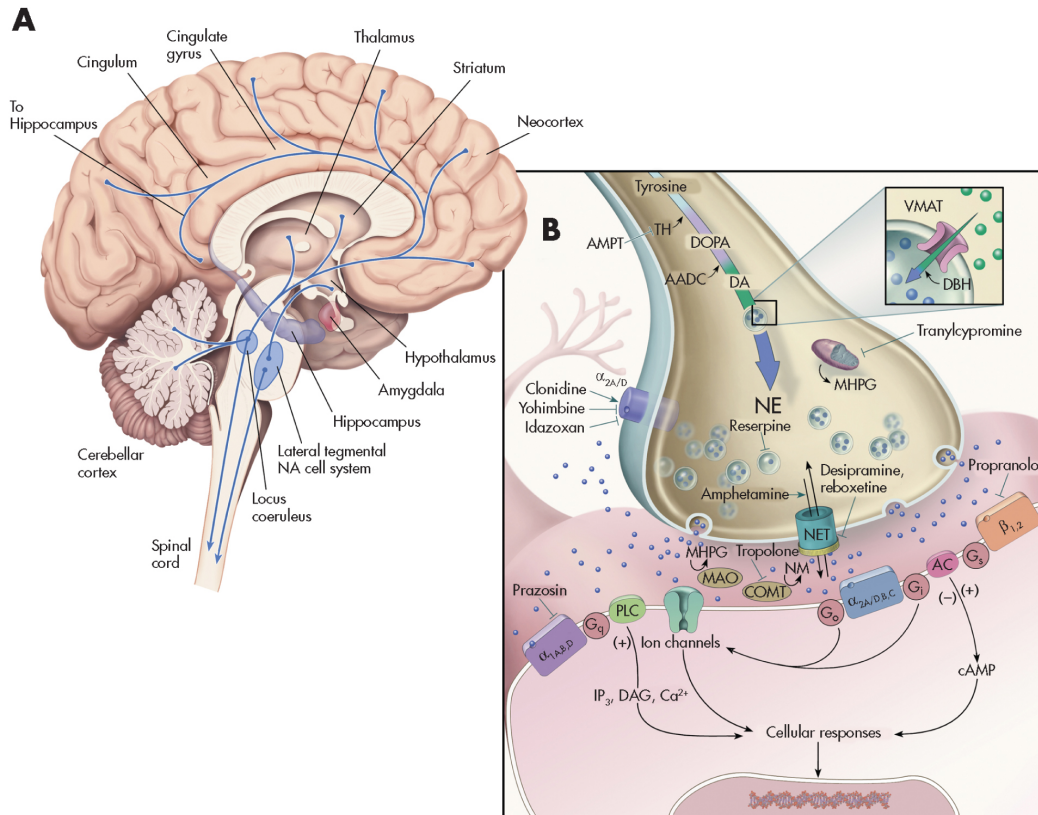
## PLATE 7. (Figure 2-4) The dopaminergic system.

This figure depicts the dopaminergic projections throughout the brain **(A)** and various regulatory processes involved in dopaminergic neurotransmission **(B)**. The amino acid L-tyrosine is

actively transported into presynaptic dopamine (DA) nerve terminals, where it is ultimately converted into DA. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase (TH).  $\alpha$ -Methyl-*p*-tyrosine (AMPT) is a competitive inhibitor of tyrosine hydroxylase and has been used to assess the impact of reduced catecholaminergic function in clinical studies. The production of DA requires that L-aromatic amino acid decarboxylase (AADC) act on L-dopa. Thus, the administration of L-dopa to patients with Parkinson's disease bypasses the rate-limiting step and is able to produce DA quite readily. DA has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron through DA transporters (DATs). DA is then metabolized to dihydroxyphenylalanine (DOPAC) by intraneuronal monoamine oxidase (MAO; preferentially by the MAO-B subtype) located on the outer membrane of mitochondria, or is sequestered and stored in secretory vesicles by vesicular monoamine transporters (VMATs). Reserpine causes a depletion of DA in vesicles by interfering and irreversibly damaging uptake and storage mechanisms.  $\gamma$ -Hydroxybutyrate inhibits the release of DA by blocking impulse propagation in DA neurons. Pargyline inhibits MAO and may have efficacy in treating parkinsonian symptoms by augmenting DA levels through inhibition of DA catabolism. Other clinically used inhibitors of MAO are nonselective and thus likely elevate the levels of DA, norepinephrine, and serotonin. Once released from the presynaptic terminal (because of an action potential and calcium influx), DA can interact with five different G protein-coupled receptors (D<sub>1</sub>-D<sub>5</sub>), which belong to either the D<sub>1</sub> or D<sub>2</sub> receptor family. Presynaptic regulation of DA neuron firing activity and release occurs through somatodendritic (not shown) and nerve terminal D<sub>2</sub> autoreceptors, respectively. Pramipexole is a D<sub>2</sub>/D<sub>3</sub> receptor agonist and has been documented to have efficacy as an augmentation strategy in cases of treatment-resistant depression

and in the management of Parkinson's disease. The binding of DA to G protein receptors ( $G_o$ ,  $G_i$ , etc.) positively or negatively coupled to adenylyl cyclase (AC) results in the activation or inhibition of this enzyme, respectively, and the production of a cascade of second-messenger and cellular effects (see diagram). Apomorphine is a  $D_1/D_2$  receptor agonist that has been used clinically to aid in the treatment of Parkinson's disease. (SKF-82958 is a pharmacologically selective  $D_1$  receptor agonist.) SCH-23390 is a  $D_1/D_5$  receptor antagonist. There are likely physiological differences between  $D_1$  and  $D_5$  receptors, but the current unavailability of selective pharmacological agents has precluded an adequate differentiation thus far. Haloperidol is a  $D_2$  receptor antagonist, and clozapine is a nonspecific  $D_2/D_4$  receptor antagonist (both are effective antipsychotic agents). Once inside the neuron, DA can either be repackaged into vesicles for reuse or undergo enzymatic catabolism. Nomifensine is able to interfere/block the reuptake of DA. The antidepressant bupropion has affinity for the dopaminergic system, but it is not known whether this agent mediates its effects through DA or possibly by augmenting other monoamines. DA can be degraded to homovanillic acid (HVA) through the sequential action of catechol-*O*-methyltransferase (COMT) and MAO. Tropolone is an inhibitor of COMT. Evidence suggests that the COMT gene may be linked to schizophrenia ([Akil et al. 2003](#)). cAMP=cyclic adenosine monophosphate; DOPA=dihydroxyphenylalanine; MT=methoxytyramine;

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.



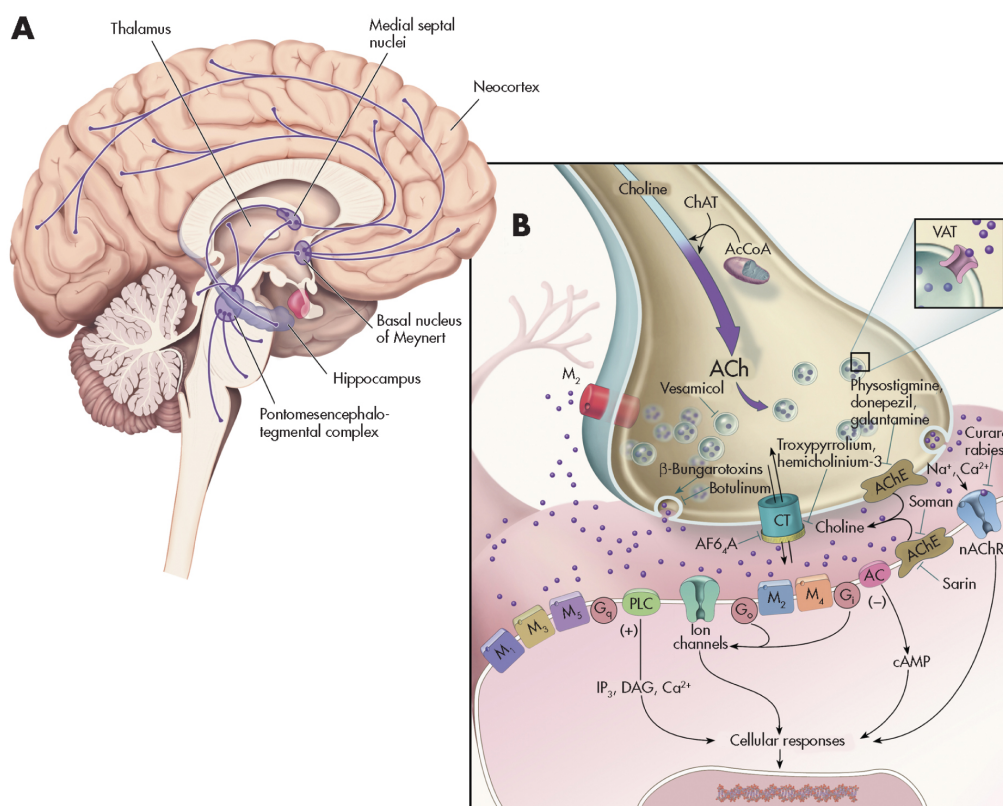
## PLATE 8. (Figure 2-5) The noradrenergic system.

This figure depicts the noradrenergic projections throughout the brain **(A)** and the various regulatory processes involved in norepinephrine (NE) neurotransmission **(B)**. NE neurons innervate nearly all parts of the neuroaxis, with neurons in the locus coeruleus being responsible for most of the NE in the brain (90% of NE in the forebrain and 70% of total NE in the brain). The amino acid L-tyrosine is actively transported into presynaptic NE nerve terminals, where it is ultimately converted into NE. The rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase (TH).  $\alpha$ -Methyl-*p*-tyrosine (AMPT) is a competitive inhibitor of tyrosine hydroxylase and has been used to assess the impact of reduced catecholaminergic function in clinical studies. Aromatic amino acid decarboxylase (AADC) converts L-dopa to dopamine (DA). L-dopa

then becomes decarboxylated by decarboxylase to form DA. DA is then taken up from the cytoplasm into vesicles, by vesicular monoamine transporters (VMATs), and hydroxylated by dopamine  $\beta$ -hydroxylase (DBH) in the presence of  $O_2$  and ascorbate to form NE. Normetanephrine (NM), which is formed by the action of catechol-*O*-methyltransferase (COMT) on NE, can be further metabolized by monoamine oxidase (MAO) and aldehyde reductase to 3-methoxy-4-hydroxyphenylglycol (MHPG). Reserpine causes a depletion of NE in vesicles by interfering with uptake and storage mechanisms (depressive-like symptoms have been reported with this hypertension). Once released from the presynaptic terminal, NE can interact with a variety of presynaptic and postsynaptic receptors. Presynaptic regulation of NE neuron firing activity and release occurs through somatodendritic (not shown) and nerve-terminal  $\alpha_2$  adrenoreceptors, respectively. Yohimbine potentiates NE neuronal firing and NE release by blocking these  $\alpha_2$  adrenoreceptors, thereby disinhibiting these neurons from a negative feedback influence. Conversely, clonidine attenuates NE neuron firing and release by activating these receptors. Idazoxan is a relatively selective  $\alpha_2$  adrenoreceptor antagonist primarily used for pharmacological purposes. The binding of NE to G protein receptors ( $G_o$ ,  $G_i$ , etc.) that are coupled to adenylyl cyclase (AC) and phospholipase C- $\beta$  (PLC- $\beta$ ) produces a cascade of second-messenger and cellular effects (see diagram and later sections of the text). NE has its action terminated in the synapse by rapidly being taken back into the presynaptic neuron via NE transporters (NETs). Once inside the neuron, it can either be repackaged into vesicles for reuse or undergo enzymatic degradation. The selective NE reuptake inhibitor and antidepressant reboxetine and older-generation tricyclic antidepressant desipramine are able to interfere/block the reuptake of NE. On the other hand, amphetamine is able to facilitate NE release by altering NET function. Green spheres represent DA neurotransmitters; blue

spheres represent NE neurotransmitters. cAMP=cyclic adenosine monophosphate;  
DAG=diacylglycerol;  
DOPA=dihydroxyphenylalanine; IP<sub>3</sub>=inositol-1,4,5-triphosphate;  
NA=nucleus accumbens.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Modified from Nestler et al. 2001.



## PLATE 9. (Figure 2-6) The cholinergic system.

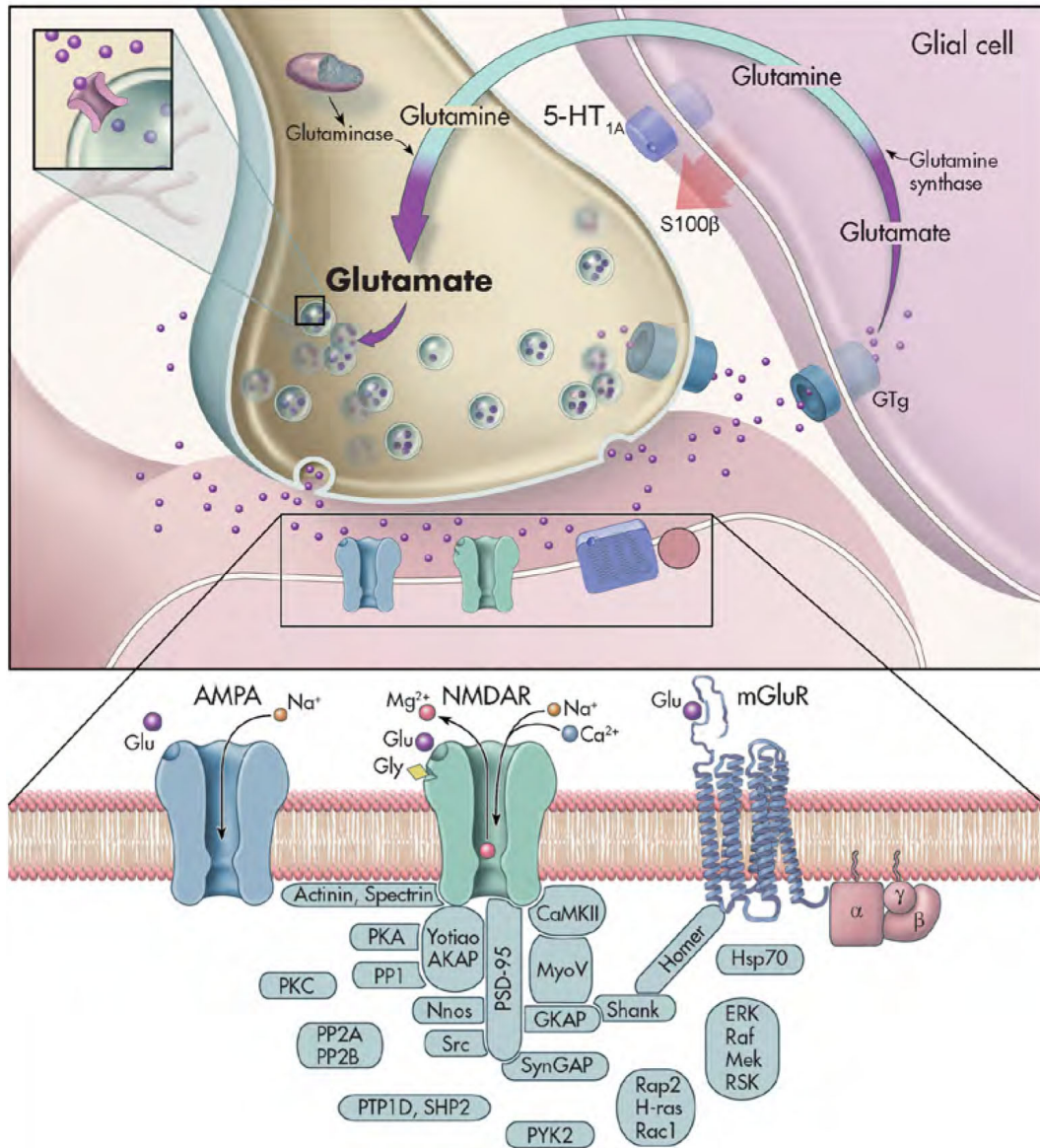
This figure depicts the cholinergic pathways in the brain **(A)** and various regulatory processes involved in cholinergic neurotransmission **(B)**. Choline crosses the blood-brain barrier to

enter the brain and is actively transported into cholinergic presynaptic terminals by an active uptake mechanism (requiring adenosine triphosphate [ATP]). This neurotransmitter is produced by a single enzymatic reaction in which acetyl coenzyme A (AcCoA) donates its acetyl group to choline by means of the enzyme choline acetyltransferase (ChAT). AcCoA is primarily synthesized in the mitochondria of neurons. Upon its formation, acetylcholine (ACh) is sequestered into secretory vesicles by vesicle ACh transporters (VATs), where it is stored. Vesamicol effectively blocks the transport of ACh into vesicles. An agent such as  $\beta$ -bungarotoxin or AF6<sub>4</sub>A is capable of increasing synaptic concentration of ACh by acting as a releaser or a noncompetitive reuptake inhibitor, respectively. In turn, agents such as botulinum toxin are able to attenuate ACh release from nerve terminals. Once released from the presynaptic terminals, ACh can interact with a variety of presynaptic and postsynaptic receptors. In contrast to many other monoaminergic neurotransmitters, the ACh signal is terminated primarily by degradation by the enzyme acetylcholinesterase (AChE) rather than by reuptake. Interestingly, AChE is present on both presynaptic and postsynaptic membranes and can be inhibited by physostigmine (reversible) and soman (irreversible). Currently, AChE inhibitors such as donepezil and galantamine are the only classes of agents that are FDA approved for the treatment of Alzheimer's disease. ACh receptors are of two types: muscarinic (G protein-coupled) and nicotinic (ionotropic). Presynaptic regulation of ACh neuron firing activity and release occurs through somatodendritic (not shown) and nerve terminal M2 autoreceptors, respectively. The binding of ACh to G protein-coupled muscarinic receptors that are negatively coupled to adenylyl cyclase (AC) or coupled to phosphoinositol hydrolysis produces a cascade of second-messenger and cellular effects (see diagram). ACh also activates ionotropic nicotinic acetylcholine (nACh) receptors. ACh has its action terminated in the synapse through rapid degradation by AChE, which liberates free



choline to be taken back into the presynaptic neuron through choline transporters (CTs). Once inside the neuron, it can be reused for the synthesis of ACh, can be repackaged into vesicles for reuse, or undergoes enzymatic degradation. There are some relatively new agents that selectively antagonize the muscarinic receptors, such as CI-1017 for M<sub>1</sub>, methoctramine for M<sub>2</sub>, 4-DAMP for M<sub>3</sub>, PD-102807 for M<sub>4</sub>, and scopolamine (hardly a new agent) for M<sub>5</sub> (although it also has affinity for the M<sub>3</sub> receptor). Nicotine receptors (or nACh receptors) are activated by nicotine and the specific alpha(4)beta(2\*) agonist metanicotine. Mecamylamine is an ACh receptor antagonist. cAMP=cyclic adenosine monophosphate; DAG=diacylglycerol; IP<sub>3</sub>=inositol-1,4,5-triphosphate; PLC=phospholipase C.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Modified from Nestler et al. 2001.



### Glutamate receptor subtypes: new classification

Ionotropic			Metabotropic		
NMDA	AMPA	Kainate	Group I	Group II	Group III
GluN1	GluA1	GluK1	mGlu1 a-b-c-d	mGlu2	mGlu4 a-b
GluN2A-B-C-D	GluA2	GluK2	mGlu5 a-b	mGlu3	mGlu6
GluN3A-B	GluA3	GluK3			mGlu7 a-b
	GluA4	GluK4			mGlu8 a-b
		GluK5			

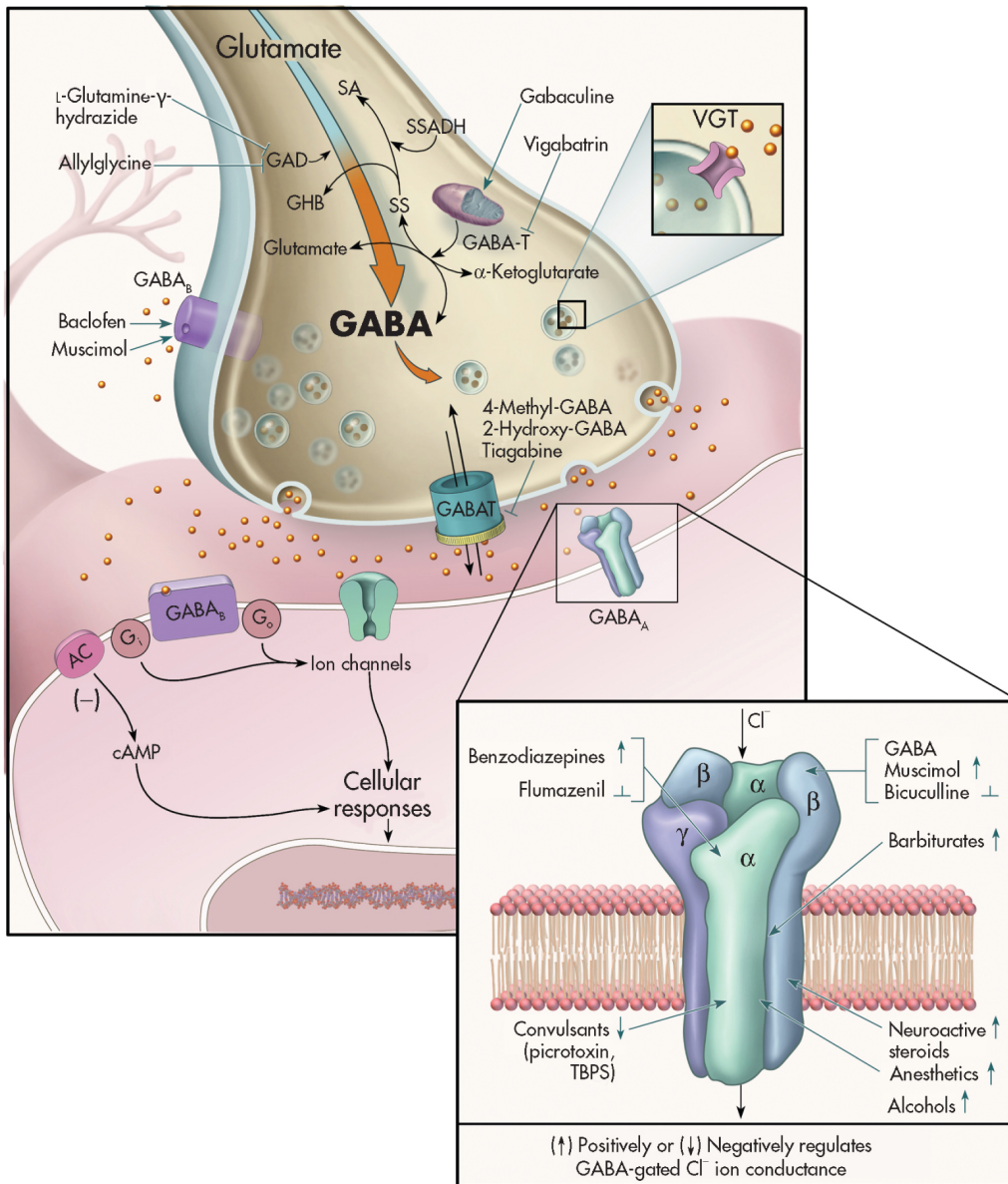
---

**PLATE 10.** (*Figure 2-7*) The glutamatergic system.

This figure depicts the various regulatory processes involved in glutamatergic neurotransmission. The biosynthetic pathway for glutamate involves synthesis from glucose and the transamination of  $\alpha$ -ketoglutarate; however, a small proportion of glutamate is formed more directly from glutamine by glutamine synthetase. The latter is actually synthesized in glia and, via an active process (requiring adenosine triphosphate [ATP]), is transported to neurons, where in the mitochondria glutaminase is able to convert this precursor to glutamate. Furthermore, in astrocytes glutamine can undergo oxidation to yield  $\alpha$ -ketoglutarate, which can also be transported to neurons and participate in glutamate synthesis. Glutamate is either metabolized or sequestered and stored in secretory vesicles by vesicle glutamate transporters (VGluTs). Glutamate can then be released by a calcium-dependent excitotoxic process. Once released from the presynaptic terminal, glutamate is able to bind to numerous excitatory amino acid (EAA) receptors, including both ionotropic (e.g., NMDA [*N*-methyl-D-aspartate]) and metabotropic (mGlu) receptors. Presynaptic regulation of glutamate release occurs through metabotropic glutamate receptors (mGlu2 and mGlu3), which subserve the function of autoreceptors; however, these receptors are also located on the postsynaptic element. Glutamate has its action terminated in the synapse by reuptake mechanisms utilizing distinct glutamate transporters that exist on not only presynaptic nerve terminals but also astrocytes; indeed, current data suggest that astrocytic glutamate uptake may be more important for clearing excess glutamate, raising the possibility that astrocytic loss (as has been documented in mood disorders) may contribute to deleterious glutamate signaling, but more so by astrocytes. It is now known that a number of important intracellular proteins are able to alter the function of glutamate receptors (see diagram). Also, growth factors such as glial-derived neurotrophic

factor (GDNF) and S100 $\beta$  secreted from glia have been demonstrated to exert a tremendous influence on glutamatergic neurons and synapse formation. Of note, serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) receptors have been documented to be regulated by antidepressant agents; this receptor is also able to modulate the release of S100 $\beta$ . AKAP=A kinase anchoring protein; AMPA= $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CaMKII=Ca<sup>2+</sup>/calmodulin-dependent protein kinase II; ERK=extracellular response kinase; H-ras=Harvey rat sarcoma proto-oncogene; GKAP=guanylate kinase-associated protein; Glu=glutamate; Gly=glycine; GTg=glutamate transporter glial; GTn=glutamate transporter neuronal; Hsp70=heat shock protein 70; MEK=mitogen-activated protein kinase/ERK; mGluR=metabotropic glutamate receptor; MyoV=myosin V; NMDAR=NMDA receptor; nNOS=neuronal nitric oxide synthase; PKA=phosphokinase A; PKC=phosphokinase C; PP1, PP2A, PP2B=protein phosphatases; PSD-95=an abundant postsynaptic density (PSD) protein that forms a two-dimensional lattice immediately under the postsynaptic membrane; PTP1D=a protein tyrosine phosphatase; PYK2=protein tyrosine kinase 2; Rac1=Ras-related C3 botulinum toxin substrate 1; Raf=Raf-1 proto-oncogene, serine/threonine kinase; Rap2=related to AP2 domain protein; RSK=ribosomal S6 kinase; SHP2=src homology 2 (SH2) domain-containing tyrosine phosphatase; Src=SRC proto-oncogene, non-receptor tyrosine kinase; SynGAP=synaptic Ras-GTPase activating protein.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc. Table modified from [Nestler et al. 2015](#).



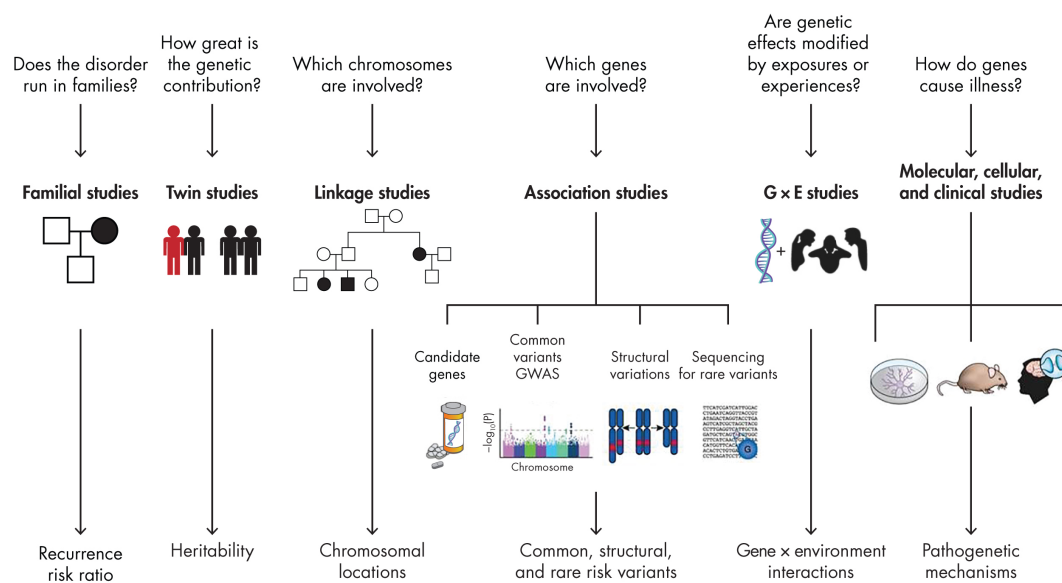
## PLATE 11. (Figure 2-8) The GABAergic system.

This figure depicts the various regulatory processes involved in GABAergic neurotransmission. The amino acid (and neurotransmitter) glutamate serves as the precursor for the biosynthesis of γ-aminobutyric acid (GABA). The rate-limiting enzyme for the process is glutamic acid decarboxylase (GAD), which utilizes pyridoxal phosphate as an important cofactor. Furthermore,

agents such as L-glutamine- $\gamma$ -hydrazide and allylglycine inhibit this enzyme and, thus, the production of GABA. Once released from the presynaptic terminal, GABA can interact with a variety of presynaptic and postsynaptic receptors. Presynaptic regulation of GABA neuron firing activity and release occurs through somatodendritic (not shown) and nerve-terminal GABA<sub>B</sub> receptors, respectively. Baclofen is a GABA<sub>B</sub> receptor agonist. The binding of GABA to ionotropic GABA<sub>A</sub> receptors and metabotropic GABA<sub>B</sub> receptors mediates the effects of this receptor. The GABA<sub>B</sub> receptors are thought to mediate their actions by being coupled to Ca<sup>2+</sup> or K<sup>+</sup> channels via second-messenger systems. Many agents are able to modulate GABA<sub>A</sub> receptor function. Benzodiazepines, such as diazepam, increase Cl<sup>-</sup> permeability, and there are numerous available antagonists directed against this site. There is also a distinctive barbiturate binding site on GABA<sub>A</sub> receptors, and many psychotropic agents are capable of influencing the function of this receptor (see blown-up diagram). GABA is taken back into presynaptic nerve endings by a high-affinity GABA uptake transporter (GABAT) similar to that of the monoamines. Once inside the neuron, GABA can be broken down by GABA transaminase (GABA-T), which is localized in the mitochondria; GABA that is not degraded is sequestered and stored in secretory vesicles by vesicular GABA transporters (VGATs), which differ from vesicular monoamine transporters (VMATs) in their bioenergetic dependence. The metabolic pathway that produces GABA, mostly from glucose, is referred to as the *GABA shunt*. The conversion of  $\alpha$ -ketoglutarate into glutamate by the action of GABA-T and GAD catalyzes the decarboxylation of glutamic acid to produce GABA. GABA can undergo numerous transformations, of which the simplest is the reduction of succinic semialdehyde (SS) to  $\gamma$ -hydroxybutyrate (GHB). On the other hand, when SS is oxidized by succinic semialdehyde dehydrogenase (SSADH), the production of succinic acid (SA) occurs. GHB has received attention because it regulates

narcoleptic episodes and may produce amnestic effects. The mood stabilizer and antiepileptic drug valproic acid is reported to inhibit SSADH and GABA-T. AC=adenylyl cyclase; TBPS=*t*-butylbicyclophosphorothionate.

*Source.* Adapted from Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, 8th Edition. New York, Oxford University Press, 2001. Copyright 1970, 1974, 1978, 1982, 1986, 1991, 1996, 2001 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

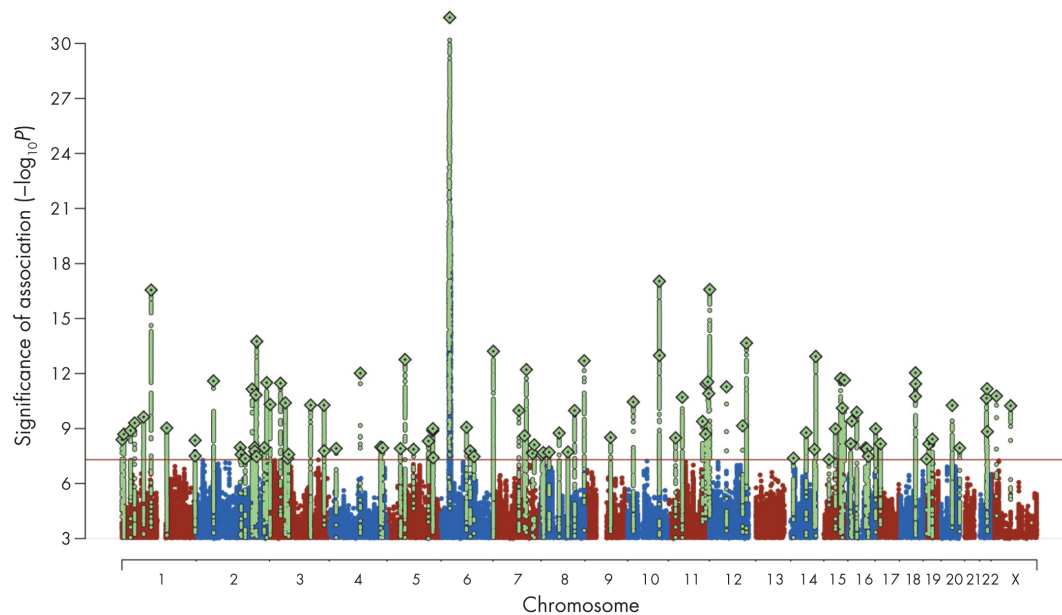


**PLATE 12.** (Figure 3-1) Overview of genetic methods available for psychiatry research.

G × E=genex environment; GWAS=genomewide association studies.

*Source.* Adapted from Smoller JW: "The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders." *Neuropsychopharmacology* 41(1):297-319, 2016. Copyright 2016, American College of Neuropsychopharmacology. Used with permission.





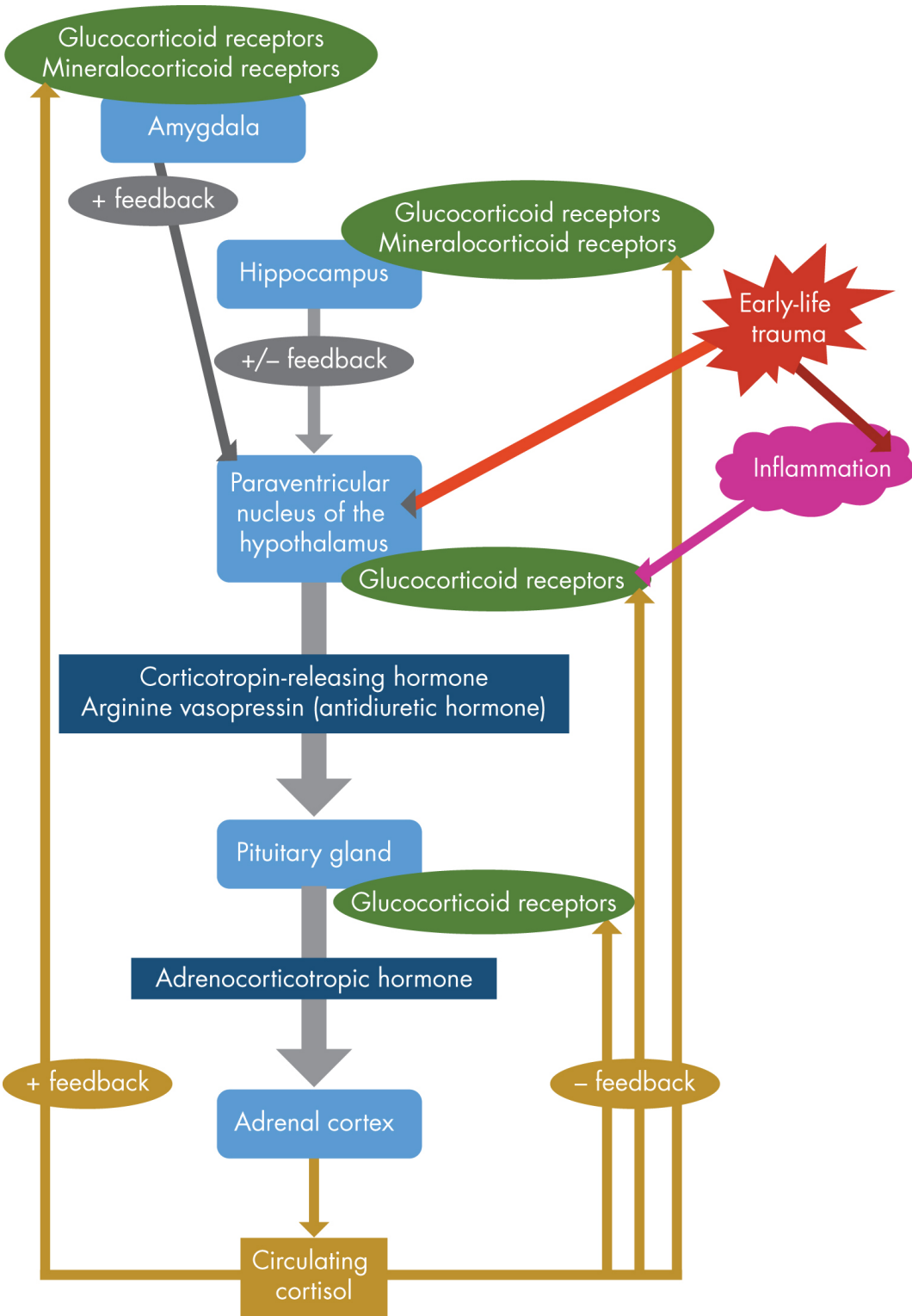
**PLATE 13.** (*Figure 3-3*) Manhattan plot showing schizophrenia associations.

Manhattan plot of the discovery genomewide association meta-analysis of 49 case-control samples (34,241 case participants and 45,604 control participants) and 3 family-based association studies (1,235 parent-affected offspring trios). The x axis is the chromosomal position (the *red* and *blue* blocks along the axis are provided to enhance visualization of the chromosome number), and the y axis is the significance ( $-\log_{10} P$ ) of association derived by logistic regression. The *red horizontal line* shows the threshold for genomewide significance ( $5 \times 10^{-8}$ ). Single nucleotide polymorphisms (SNPs) in *green* are in linkage disequilibrium with the index SNPs (*diamonds*) which represent independent genomewide significant associations. Schizophrenia was associated with 108 independent loci.

*Source.* Reprinted from Schizophrenia Working Group of the Psychiatric Genomics Consortium: "Biological Insights From 108 Schizophrenia-Associated Genetic Loci." *Nature* 511(7510):421-

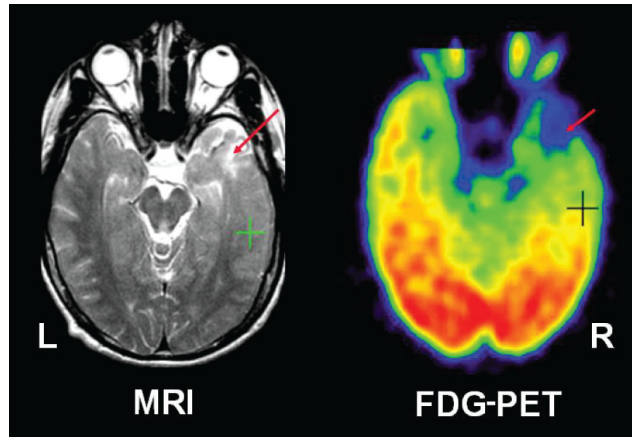


427, 2014. Copyright 2014, Nature Publishing Group. Used with permission.



**PLATE 14.** (*Figure 4-1*) Schematic diagram of the hypothalamic-pituitary-adrenal (HPA) axis.

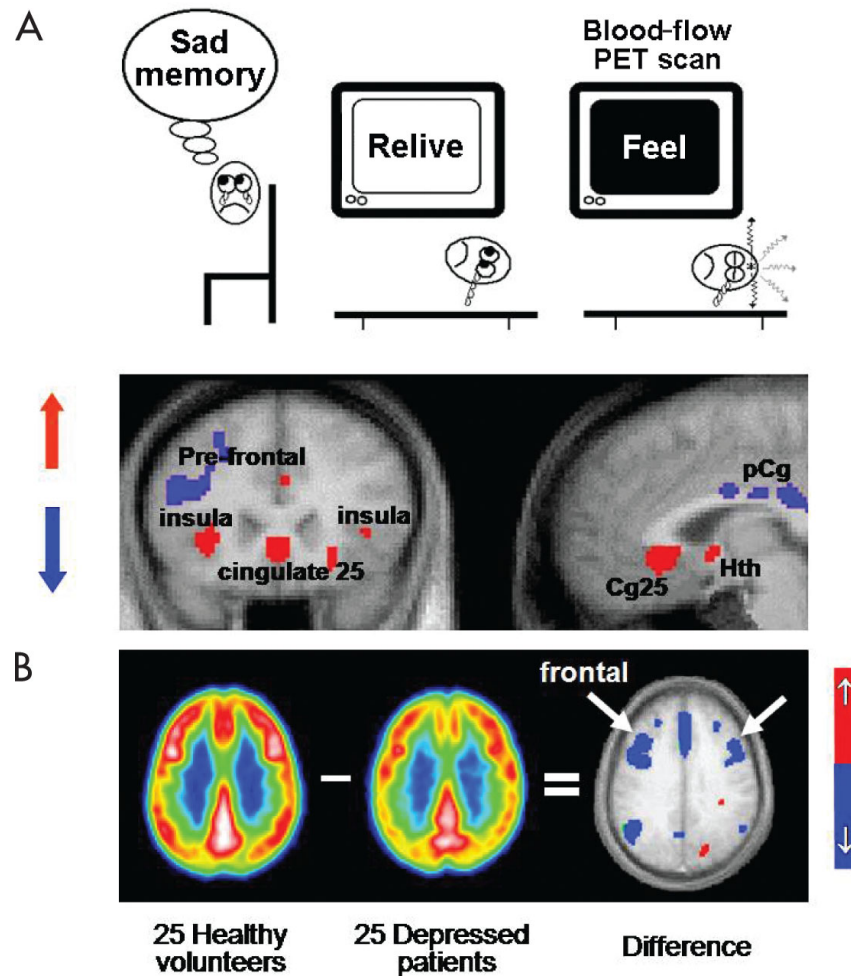
In response to a threat, the hypothalamus synthesizes corticotropin-releasing hormone (CRH), which stimulates pituitary secretion of adrenocorticotrophic hormone (ACTH), triggering adrenal glucocorticoid production in a feedforward cascade.



---

**PLATE 15.** (*Figure 7-1*) Functional localization of an epileptic focus in the right temporal lobe during presurgical workup using magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET).

*Source.* Image courtesy of Carolyn C. Meltzer, M.D.

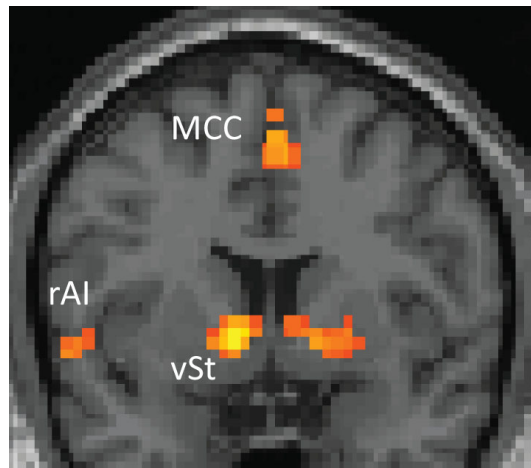


**PLATE 16.** (Figure 7-2) PET studies of regional functional activity in the brain.

**(A)** Task-induced increased cerebral blood flow using H<sub>2</sub>O-PET. **(B)** FDG-PET resting-state contrasts among depressed patients versus healthy control subjects. FDG=fluorodeoxyglucose; PET=positron emission tomography; Cg25=subgenual cingulate; pCg=posterior cingulate; Hth=hypothalamus.

*Source.* **(A)** Adapted from Mayberg HS, Liotti M, Brannan SK, et al.: "Reciprocal Limbic-Cortical Function and Negative Mood: Converging PET Findings in Depression and Normal Sadness." *American Journal of Psychiatry* 156:675-682, 1999. Copyright 1999,

American Psychiatric Association. Used with permission. **(B)** Image courtesy of Helen Mayberg, M.D.

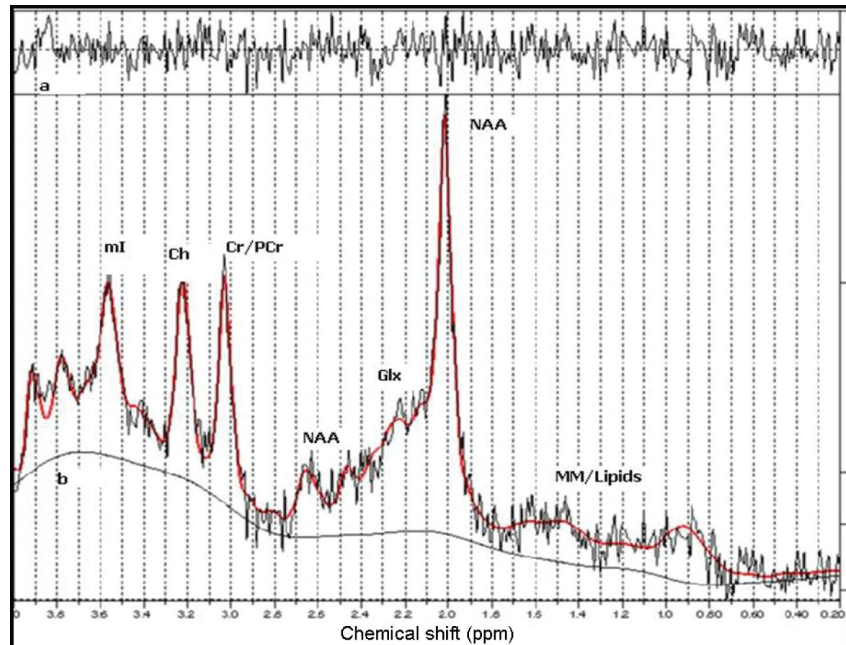


---

**PLATE 17.** (*Figure 7-5*) Activation of the ventral striatum (vSt), midcingulate cortex (MCC), and right anterior insula (rAI) during a monetary reward task, as visualized using functional magnetic resonance imaging.

*Note.* The activation pattern reflects changes in both salience and reward centers in the brain.

*Source.* Image courtesy of Helen Mayberg, M.D.



**PLATE 18.** (Figure 7-6) Proton magnetic resonance spectroscopy ( $[^1\text{H}]$ -MRS) spectrum from right dorsolateral prefrontal cortex voxel of a healthy individual.

MM=macromolecules;

NAA=N-acetylaspartate;

Glx=glutamate/glutamine;

Cr/PCr=creatine/phosphocreatine;

Ch=choline; mI=myo-inositol.

*Source.* Reprinted from Haroon E, Watari K, Thomas MA, et al.: "Prefrontal Myo-Inositol Concentration and Visuospatial Functioning Among Diabetic Depressed Patients." *Psychiatry Research: Neuroimaging* 171:10-19, 2009. Copyright 2009, Elsevier Ltd. Used with permission.

# **Drugs for Treatment of Bipolar Disorder**

# CHAPTER 36

## Lithium

Masoud Kamali, M.D.

Venkatesh Basappa Krishnamurthy, M.D.

Raman Baweja, M.D.

Erika F.H. Saunders, M.D.

Alan J. Gelenberg, M.D.

---

## History and Discovery

---

After noting the sedating properties of lithium in animals, Cade first described the successful treatment of mania with lithium salts ([Cade 1949](#)). The U.S. Food and Drug Administration (FDA) approved lithium for the treatment of acute mania in 1970 and for the maintenance treatment of bipolar disorder 4 years later ([Jefferson and Greist 1977](#)). However, lithium did not enter the market easily in the United States. Pharmaceutical companies were reluctant to produce this inexpensive drug that they could not patent ([Kline 1973](#)). Lithium is a highly cost-effective treatment for

bipolar disorder ([Chisholm et al. 2005](#)). A growing number of medications with proven efficacy in bipolar disorder have become available since the introduction of lithium, including anticonvulsants and second-generation (atypical) antipsychotics. In contrast to many of these medications, lithium is available generically and is relatively affordable. These features, added to lithium's effectiveness, have given it longevity among the psychopharmacological treatment options for bipolar disorder.

---

## Structure-Activity Relations

---

Lithium is the lightest alkali metal and a monovalent cation, and it shares some properties with sodium, potassium, and calcium. It is the third element of the periodic table. Substitution of or competition with other cations may contribute to its effects ([Baldessarini 1996](#); [Ward et al. 1994](#)).

---

## Pharmacological Profile

---

Lithium is minimally protein bound, does not undergo biotransformation, and is renally eliminated ([Kilts 2000](#)). Its narrow therapeutic index necessitates careful drug monitoring. Lithium appears to affect multiple neurotransmitter systems (see "Neurotransmitter Effects" subsection under "Mechanisms of Action"), and it alters second-messenger systems such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) ([Ward et al. 1994](#)).



---

# Pharmacokinetics and Disposition

---

Lithium is available in multiple preparations, including lithium carbonate tablets and capsules, lithium citrate, and slow-release formulations ([Jefferson et al. 1983](#)). Lithium is absorbed from the gastrointestinal tract and is renally excreted unchanged within approximately 24 hours ([Baldessarini 1996](#); [Baldessarini and Tarazi 2001](#)). Peak plasma concentrations are reached within 1-2 hours with rapid-release preparations and within 4-5 hours with sustained-release formulations ([Finley et al. 1995](#)). Lithium is not protein bound and is evenly distributed in total body water space ([Jermain et al. 1991](#)). Lithium excretion is controlled by osmotic factors and is a function of renal sufficiency ([Birch et al. 1980](#)). Steady-state concentrations are achieved within 4-5 days ([Keck and McElroy 2002](#)).

---

## Mechanism of Action

---

Despite extensive research, the exact mechanism of lithium's action as a mood stabilizer has yet to be elucidated. Multiple theories, based on animal models and on limited studies in humans, have been proposed. In the following pages we review theories centering on lithium's effects on various neurotransmitter systems, on intracellular second-messenger systems, and on signal transduction, as well as a unifying theory focused on lithium's neuroprotective effects.

# Neurotransmitter Effects

Lithium brings about changes in several of the major neurotransmitter systems in the brain, with the overall effect being stimulation of inhibitory transmission and inhibition of excitatory signals ([Malhi et al. 2013](#)). Chronic administration of lithium in mice increases and stabilizes glutamate uptake. This modulatory action could, in part, explain lithium's antimanic effect because it results in overall reduction of an excitatory neurotransmitter ([Dixon and Hokin 1998](#)). Lithium also normalizes low cerebrospinal fluid (CSF) levels of  $\gamma$ -aminobutyric acid (an inhibitory neurotransmitter) in bipolar subjects (see [Berrettini et al. 1983, 1986](#); [Brambilla et al. 2003](#)).

Lithium enhances norepinephrine and serotonin function in the central nervous system, which could explain its antidepressant effects ([Price et al. 1990](#); [Schildkraut et al. 1969](#); [Stern et al. 1969](#)). Of particular interest is lithium's confirmed antagonistic action at serotonin 1A (5-HT<sub>1A</sub>) and serotonin 1B (5-HT<sub>1B</sub>) autoreceptors ([Haddjeri et al. 2000](#); [Massot et al. 1999](#)); such action would have the effect of increasing serotonin availability in the synaptic cleft ([Shaldubina et al. 2001](#)). Clinically, 5-HT<sub>1A</sub> receptors may be involved in alleviation of depression, and 5-HT<sub>1B</sub> receptors may play a role in the regulation of sleep, sensorimotor inhibition, and locomotor activity ([Monti et al. 1995](#); [Sipes and Geyer 1996](#)).

## Inositol Depletion

There has been much focus on the role of the inositol cycle in the clinical effects of lithium. Lithium is a noncompetitive

inhibitor of inositol monophosphatase, depleting free inositol within 5 days of treatment initiation ([Berridge et al. 1989](#)). These changes last for 3–4 weeks after lithium is discontinued ([Moore et al. 1999](#)). Depletion of free inositol can lead to effects on neurotransmitter and intracellular second-messenger systems linked to the inositol cycle. For example, adrenergic, serotonergic, and cholinergic receptor subtypes are coupled to the cycle via G proteins, and the cycle in turn regulates protein kinase C action, which appears to be influenced by lithium treatment in mania ([Hahn et al. 2005](#)).

Of note, depression is associated with low CSF levels of inositol in humans ([Barkai et al. 1978](#)). Exogenous inositol can alleviate depression ([Levine et al. 1993, 1995](#)) and panic attacks ([Benjamin et al. 1995](#)). [Belmaker et al. \(1996\)](#) suggested a complex “pendulum” relationship between inositol and lithium that may provide a basis for understanding lithium’s antimanic and antidepressant effects.

## Glycogen Synthase Kinase Inhibition

Glycogen synthase kinase 3 (GSK-3) is an enzyme with direct involvement in gene transcription, synaptic plasticity, and cell structure ([Malhi et al. 2013](#)). Both lithium ([Klein and Melton 1996](#); [Li et al. 2007](#)) and valproate inhibit GSK-3, suggesting that signaling pathways that converge in GSK-3 are important in bipolar disorder ([G. Chen et al. 1999](#)). GSK-3 is an inhibitor of the Wnt protein-signaling pathway, which affects neuronal signal transduction. Lithium thus would be predicted to mimic Wnt signaling ([Phiel and Klein 2001](#)). Wnt signaling triggers a cascade of

events that leads to stimulation of protein kinase C activity ([Grahame-Smith 1998](#); [Williams and Harwood 2000](#)). Thus, lithium's actions on both the inositol cycle and the GSK-3 signaling pathway lead to a common effect on protein kinase C. Because this enzyme's activity has been reported to be increased in bipolar disorder, protein kinase C inhibitors have been investigated for their potential treatment utility ([Zarate and Manji 2009](#)).

## Neurotrophic and Neuroprotective Effects

A unifying theory posits that lithium's mechanism of action may be related to its neurotrophic and neuroprotective effects ([Quiroz et al. 2010](#)). Patients treated with lithium have larger cortical and hippocampal volumes ([Hajek et al. 2012](#); [Moore et al. 2000](#)), and these effects are independent of treatment response ([Hajek et al. 2014](#)). One proposed mechanism is lithium's activation of the transcription factor cyclic adenosine monophosphate response element-binding protein (CREB), which in turn increases the expression of brain-derived neurotrophic factor and the antiapoptotic bcl-2 (b-cell lymphoma 2) proteins ([Alda 2015](#); [Quiroz et al. 2010](#)). Another proposed mechanism is inhibition of GSK-3 and subsequent activation of the Akt neuroprotective pathway ([Tajes et al. 2009](#)).

---

## Indications and Efficacy

---

# Bipolar Disorder

## Acute Mania

[Cade \(1949\)](#) first published data on the efficacy of lithium in mania more than 60 years ago. As we approach the end of the second decade of the twenty-first century, lithium remains one of the most efficacious treatments for bipolar disorder.

**Lithium versus placebo.** Lithium has been shown in studies to be more efficacious than placebo in the treatment of acute mania ([Bowden et al. 1994, 2005](#); [Fountoulakis et al. 2012](#); [Goodwin et al. 1969](#); [Keck et al. 2009](#); [Kushner et al. 2006](#); [Maggs 1963](#); [Poolsup et al. 2000](#); [Schou et al. 1954](#); [Smith et al. 2007](#); [Stokes et al. 1971](#); [Yildiz et al. 2011](#)). A review of response rates in randomized trials of medication treatment indicated that lithium was at least somewhat efficacious in the treatment of mania, with a response rate of 70% (87 of 124 patients) ([Keck et al. 2000](#)).

**Lithium versus antipsychotics.** Early studies with lithium established its antimanic efficacy relative to first-generation (typical) antipsychotics ([Garfinkel et al. 1980](#); [Johnson et al. 1968](#); [Poolsup et al. 2000](#); [Prien et al. 1972](#); [Segal et al. 1998](#); [Shopsin et al. 1975](#); [Spring et al. 1970](#); [Takahashi et al. 1975](#)). A study by [Prien et al. \(1972\)](#) comparing lithium against chlorpromazine found that although chlorpromazine was more effective in reducing manic symptoms in severely ill patients, lithium also reduced symptoms while causing fewer side effects. However, a later meta-analysis concluded that lithium was

more effective than chlorpromazine in acute mania ([Poolsup et al. 2000](#)). A review of studies by [Goodwin and Zis \(1979\)](#) found lithium to be efficacious in at least 70% of patients, as defined by remission or marked improvement. In a 3-week double-blind study of lithium, haloperidol, and their combination for acute mania, patients who received haloperidol or haloperidol plus lithium had more significant improvement compared with those who received lithium alone ([Garfinkel et al. 1980](#)). The combination of lithium and haloperidol was as well tolerated as haloperidol alone. [Segal et al. \(1998\)](#) reported that inpatients with acute mania responded equally well to lithium, haloperidol, and the second-generation agent risperidone.

Lithium has also been studied in comparison with second-generation antipsychotic medications ([Berk et al. 1999](#); [Bowden et al. 2005](#); [Fountoulakis et al. 2012](#); [Keck et al. 2009](#); [Kushner et al. 2006](#); [Li et al. 2007](#); [Niufan et al. 2008](#); [Poolsup et al. 2000](#); [Segal et al. 1998](#); [Smith et al. 2007](#); [Yildiz et al. 2011](#)). However, many of these trials were focused on assessing the efficacy of the antipsychotic in a noninferiority approach rather than on demonstrating significant differences between the medications. For example, in a direct comparison with lithium, olanzapine produced greater improvement in manic symptoms over 4 weeks, but it also produced more weight gain ([Niufan et al. 2008](#)). By and large, antipsychotics appear to work faster than lithium but carry higher risks for weight gain and other metabolic effects ([Fountoulakis et al. 2012](#); [Yildiz et al. 2011](#)).

In a recent study, the addition of lithium to therapy with extended-release quetiapine was found to be more efficacious than add-on placebo (i.e., quetiapine monotherapy) in patients with bipolar mania ([Bourin et al.](#)

2014). In a study in which patients with acute mania who had not adequately responded to lithium or divalproex were randomly assigned to receive adjunctive ziprasidone at two dosage ranges (20–40 mg/day or 60–80 mg/day) or placebo for 3 weeks in addition to their mood stabilizer (Sachs et al. 2012b), ziprasidone failed to show clinical or statistical separation from placebo. However, the high proportion of enrolled subjects that did not meet all eligibility criteria for the study may have contributed to the negative findings (Sachs et al. 2012a). In one study, adjunctive gabapentin added to lithium was found to be effective in treating acute mania (Astaneh and Rezaei 2012).

**Lithium versus anticonvulsants.** Double-blind randomized studies suggest that carbamazepine and lithium are equally effective in the treatment of acute mania (Fountoulakis et al. 2012; Lerer et al. 1987; Okuma et al. 1990; Poolsup et al. 2000; Small et al. 1991; Yildiz et al. 2011). In a direct comparison of lithium and divalproex, Bowden et al. (1994) demonstrated a similar advantage for both agents over placebo, with lithium and divalproex each achieving response in about 48% of patients over 3 weeks. A 12-week study of patients randomly assigned to open treatment with lithium or divalproex yielded additional evidence of the two agents' comparable efficacy and tolerability over a longer-than-usual study period (Bowden et al. 2008, 2010). A meta-analysis of available randomized controlled trials likewise showed that lithium and valproate were equally effective in acute mania (Poolsup et al. 2000). In a meta-analysis examining the efficacy of lithium, valproate, and carbamazepine in mania, no significant differences in efficacy were found among the three agents (Emilien et al. 1996). However, only some of the included

studies were placebo controlled. Anticonvulsants were generally better tolerated than lithium. The presence of neurological abnormalities may predict a better response to anticonvulsants than to lithium in mania. One study found that patients with electroencephalogram abnormalities are more likely to respond to valproate than to lithium ([Reeves et al. 2001](#)).

Mixed mania—the co-occurrence of mania with depression—may predict a poorer response to lithium. [Freeman et al. \(1992\)](#), in a direct comparison of lithium and valproate, showed that a favorable response to valproate was associated with high pretreatment depressive symptom scores ([Fountoulakis et al. 2012](#)). To further investigate the relation between co-occurring depressive symptoms and treatment response in acute mania, [Swann et al. \(1997\)](#) designed a parallel-group study of lithium versus divalproex and analyzed outcomes relative to the presence of a mixed affective state. They found that the presence of depressive symptoms during an acute manic episode was associated with a poorer response to lithium and a better response to divalproex. Lithium plus topiramate showed no superiority to lithium plus placebo in acute mania ([Mirsepassi et al. 2013](#)).

## **Psychotic Mania**

Lithium is equally effective in psychotic and nonpsychotic mania, and early improvement in psychotic symptoms was found to predict higher remission and response rates ([de Sousa et al. 2012](#)).

## **Bipolar Depression**



Lithium is considered a first-line treatment for acute bipolar depression ([Compton and Nemeroff 2000](#)). [Goodwin and Jamison \(1990\)](#) analyzed placebo-controlled trials in bipolar depression and found that 79% of bipolar patients had either a complete or a partial response to lithium. Placebo-controlled trials showing the efficacy of lithium in bipolar depression include those by [Baron et al. \(1975\)](#), [Donnelly et al. \(1978\)](#), [Fieve et al. \(1968\)](#), [Goodwin et al. \(1969, 1972\)](#), [Greenspan et al. \(1970\)](#), [Mendels \(1975\)](#), and [Noyes et al. \(1974\)](#). These studies generally were small (involving between 3 and 40 patients [[Goodwin et al. 1972](#)]).

A recent meta-analytic summary of the above-listed short studies showed a significant advantage for lithium over placebo in bipolar disorder versus unipolar depression ([Selle et al. 2014](#)). In a study in which 802 patients were randomly assigned to 8 weeks of treatment with lithium (600–1,800 mg/day), quetiapine (300 mg/day or 600 mg/day), or placebo ([Young et al. 2010](#)), lithium failed to separate significantly from placebo on the main efficacy measure (Montgomery-Åsberg Depression Rating Scale [MADRS] score); however, the study was powered to show an effect for quetiapine, and the mean serum level in lithium-treated subjects was low (0.6 mmol/L).

In the Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) trial, 482 patients with bipolar I or II disorder, the majority (>88%) of whom were experiencing depressive symptoms at study entry ([Nierenberg et al. 2016](#)), were randomly assigned to receive lithium plus adjunctive personalized treatment (APT,  $n=240$ ) or quetiapine plus APT ( $n=242$ ) for 6 months. In this study, which used new clinical trials methodology, participants in the lithium group were not given a second-generation antipsychotic, and those in the quetiapine group

were not given lithium; however, other adjunctive treatments were provided in accordance with best-practice guidelines ([Nierenberg et al. 2013](#)). Both groups showed improvement, with 20% achieving sustained response over the study period, and no differences in outcome were detected between the lithium and quetiapine groups ([Nierenberg et al. 2013](#)).

In the **L**ithium Treatment **M**oderate-dose **U**se **S**tudy (LiTMUS) study ([Nierenberg et al. 2013](#)), 283 bipolar I and II patients were randomly assigned to receive optimized personalized treatment (OPT; evidence-based, guideline-informed care) alone or OPT plus lithium at a moderate dosage. The lithium dosage was fixed at 600 mg/day for the first 2 months of the study but was allowed to change based on clinical need after that. Over the 6 months of the trial, the two groups had similar scores on clinical outcome measures, with a sustained remission rate of 27%. Although the addition of lithium conferred no advantage over OPT alone, fewer patients in the lithium-plus-OPT group than in the OPT-only group received second-generation antipsychotics.

In 2004, an expert consensus report recommended lithium as monotherapy for mild to moderate depression in bipolar I disorder and as a component of an initial medication regimen in severe nonpsychotic and psychotic depression ([Keck et al. 2004](#)).

## **Rapid Cycling**

In 1974, [Dunner and Fieve](#) observed that bipolar patients who had not responded to long-term lithium prophylaxis were more likely to have had four or more mood episodes per year, giving rise to the belief that lithium is not effective in treating rapid cycling. However, subsequent studies have

shown that rapid-cycling bipolar disorder responds poorly to most available treatments and that treatment with lithium does improve the burden of illness. In a study examining lithium's efficacy in rapid-cycling bipolar disorder, [Dunner et al. \(1977\)](#) found that patients who had received lithium for at least 1 year had a higher percentage of "well time" relative to baseline and reported that their mood episodes were shorter and less severe. In an analysis of retrospective and prospective data from 51 patients with rapid-cycling bipolar disorder, [Wehr et al. \(1988\)](#) showed that even among patients with continuous rapid cycling, the manic phases were abbreviated and attenuated. A long-term prospective study of open-label treatment with lithium found a higher rate of recurrence among rapid cyclers versus non-rapid cyclers but similar improvement in symptoms and morbidity (as measured by percentage of time ill, episode frequency, and time to recurrence) ([Baldessarini et al. 2000](#)). Finally, a meta-analysis of clinical studies comparing subjects with rapid-cycling and non-rapid-cycling bipolar disorder showed that although lithium was less effective in preventing recurrence among rapid cyclers, it did have beneficial effects on severity and duration of episodes ([Kupka et al. 2003](#)). In a 20-month double-blind, parallel-group comparison study, [Calabrese et al. \(2005\)](#) evaluated lithium versus divalproex monotherapy for maintenance treatment in rapid-cycling patients who had been stabilized on a combination of lithium and divalproex. The rates of relapse were similar for lithium-treated and divalproex-treated patients.

## **Prophylaxis and Maintenance**

Prophylactic or maintenance therapy is often considered after resolution of an acute mood episode. Lithium is the

best-studied drug for this indication. [Tondo et al. \(1998\)](#) found lithium to be effective in long-term use (>1 year) in decreasing frequency of mood episodes and “time ill” in patients with bipolar I or bipolar II disorder. Benefits of lithium treatment were not significantly different among patients with psychotic or mixed episodes, rapid cycling, or more classic forms. There was no decrease in efficacy with long-term use. Despite finding evidence for lithium’s efficacy, [Kulhara et al. \(1999\)](#) noted that only 24% of the patients followed in a lithium clinic were free of mood episodes while receiving lithium prophylaxis (average duration of monitoring: 11 years). Treatment nonadherence and/or subtherapeutic lithium serum levels (<0.4 mEq/L), high numbers of psychosocial stressors, higher numbers of depressive episodes before lithium treatment, and poor social support predicted poorer response to lithium prophylaxis. In contrast, starting lithium early in the course of illness predicted a better response to treatment ( $P<0.001$ ), after episode polarity, sex, age at onset, duration of illness, and duration of lithium prophylaxis were accounted for ([Franchini et al. 1999](#)).

In a comparison of lithium, divalproex, and placebo in a 1-year treatment study of patients with bipolar I disorder who had recently recovered from an index manic episode, [Bowden et al. \(2000\)](#) found that median times to 50% survival without any mood episode were 40 weeks for divalproex, 24 weeks for lithium, and 28 weeks for placebo, although the differences were not statistically significant. Patients who received divalproex remained in treatment significantly longer than did those who received lithium.

In a study comparing the prophylactic efficacy of lithium versus placebo, [Prien et al. \(1973\)](#) found that lithium was more effective than placebo in preventing relapses

requiring hospitalization. [Bowden et al. \(2003\)](#) compared the efficacy of lamotrigine, lithium, and placebo in preventing relapse to mood episodes among bipolar I subjects with a recent manic or hypomanic episode. After completing a stabilization phase during which treatment with lamotrigine was initiated and other medications were discontinued, subjects were randomly assigned to one of the three drug groups and followed for 18 months. Both lithium and lamotrigine were superior to placebo in prolonging the time to any mood episode, with lithium predominantly effective against manic, hypomanic, or mixed episodes and lamotrigine predominantly effective against depressive episodes. A similar study in bipolar I subjects with a recent depressive episode ([Calabrese et al. 2003](#)) reported the same findings. A post hoc analysis of the two studies revealed that lithium not only delayed the time between random assignment and onset of subsyndromal symptoms but also delayed the time between onset of subsyndromal symptoms and emergence of the full mood episode ([Frye et al. 2006](#)). In a study by [Weisler et al. \(2011\)](#), bipolar subjects who had been stabilized on quetiapine were randomly assigned to continue quetiapine or be switched to lithium or placebo for up to 104 weeks. Both lithium and quetiapine were superior to placebo in prevention of manic or depressive episodes. In a meta-analysis of 19 randomized controlled blinded trials, [Davis et al. \(1999\)](#) found lithium to be more efficacious than placebo in preventing relapse. In a meta-analysis by [Geddes et al. \(2004\)](#) involving 770 participants, lithium was found to be more effective than placebo in preventing all relapses and manic relapses, but its efficacy in preventing depressive relapses was less robust. In another systematic review and meta-analysis of randomized and quasi-randomized

controlled trials, lithium, compared with placebo, was effective in the prevention of relapse in bipolar disorder, especially manic episodes ([Beynon et al. 2009](#)). [Popovic et al. \(2012\)](#) used a new metric—the polarity index (number needed to treat [NNT] for prevention of depression divided by NNT for prevention of mania)—to define the profiles of drugs used in the maintenance treatment of bipolar disorder. A polarity index of 1.39 was calculated for lithium, a value indicating its relatively greater antimanic versus antidepressant prophylactic efficacy.

The Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) study examined the effects of lithium monotherapy, valproate monotherapy, or lithium-plus-valproate combination therapy for relapse prevention in a large international cohort ([BALANCE Investigators and Collaborators et al. 2010](#)). More than 300 patients with bipolar I disorder initially completed a “run-in” phase during which they took both lithium and valproate. Of those who tolerated the combination, a subsequent randomization phase assigned subjects to lithium alone, valproate alone, or continued combination treatment for up to 2 years of follow-up. The primary outcome measure was time to new intervention (either medication change or hospitalization) for an emerging mood episode. The study results showed that the combination of lithium and valproate was superior to valproate alone and also suggested that lithium monotherapy was superior to valproate monotherapy. The apparent discrepancy between the latter finding and the conclusions of [Bowden et al. \(2010\)](#) described above may reflect differences in the population studied and in the outcome measures used; alternatively, the valproate dosage in the BALANCE study may have been suboptimal for preventing acute mania.

In a double-blind, randomized maintenance trial of lithium versus olanzapine, bipolar patients experiencing mixed or manic symptoms first received open-label co-treatment with lithium and olanzapine ([Tohen et al. 2005](#)). Those whose symptoms remitted were then randomly assigned to monotherapy with either lithium or olanzapine for 52 weeks. Recurrence rates were similar for the two groups, with 38.8% of patients on lithium and 30.0% of those on olanzapine experiencing a relapse. Whereas the two drugs were comparable in prevention of depressive episodes, olanzapine was more effective than lithium in prevention of manic and mixed episodes.

**Maintenance dosing.** Once-daily dosing of lithium at bedtime yields higher brain-to-serum ratios of lithium levels compared with twice-daily dosing schedules ([Soares et al. 2001](#)). Investigators have observed substantial variations in brain lithium levels among people with similar serum lithium levels ([González et al. 1993](#)). In a study evaluating maintenance treatment with lithium at dosages yielding low (0.4–0.6 mmol/L) versus standard (0.8–1.0 mmol/L) serum levels, [Gelenberg et al. \(1989\)](#) found that the risk of relapse was 2.6 times higher in patients randomly assigned to maintenance lithium at the low serum level. However, in a reanalysis of the data ([Perlis et al. 2002](#)), the higher relapse rate observed with the low serum level was found to be associated with the abrupt reduction in lithium dosage that occurred following randomization in patients who were switched from the standard range to the low range. Thus, an abrupt reduction in lithium dosage may negatively impact the course of illness.

[Nolen and Weisler \(2013\)](#) conducted a post hoc analysis of a double-blind trial in patients with bipolar disorder who



were stabilized on quetiapine after a manic, depressive, or mixed episode and then randomly assigned to continue quetiapine or be switched to lithium or placebo for up to 104 weeks. Times to recurrence of any mood episode, as well as to recurrence of a manic or a depressive episode, were longer for patients with serum lithium levels of 0.6–1.2 mEq/L than for patients with serum lithium levels less than 0.6 mEq/L. No difference in time to recurrence was found between patients receiving placebo and patients with lithium levels lower than 0.6 mEq/L, providing evidence that maintenance lithium dosages should be high enough to achieve plasma levels of at least 0.6 mEq/L for prevention of mania and depressive episodes in bipolar disorder. One limitation of this study was that subjects were not randomly assigned to the lithium dosing groups. In a similar post hoc analysis by [Severus et al. \(2010\)](#), subjects were first stabilized on a combination of lithium and olanzapine and then randomly assigned to lithium (at dosages aimed at achieving low [0.6 mmol/L], medium [0.6–0.79 mmol/L], or high [ $>0.8$  mmol/L] serum levels) or olanzapine (10 mg/day or 10–20 mg/day) for the maintenance phase. The low-serum-level lithium group had a significantly higher risk of relapse to manic or mixed—but not to depressive—episodes compared with the medium- and the high-lithium-level groups and had an increased risk of depression compared with the high-dosage olanzapine group. These findings provide further evidence that lithium levels should be higher than 0.6 mmol/L for optimal protection against relapse to manic, mixed, or depressive episodes.



# Unipolar Depression (Major Depressive Disorder)

An analysis of five controlled trials of lithium augmentation of antidepressant treatment in patients with unipolar depression found significant improvement in 56%–96% of patients ([Austin et al. 1991](#); [Carvalho et al. 2009](#); [Heit and Nemeroff 1998](#); [Heninger et al. 1983](#); [Kantor et al. 1986](#); [Schöpf et al. 1989](#); [Stein and Bernadt 1993](#); [Zusky et al. 1988](#)). Two separate meta-analyses of randomized, double-blind, placebo-controlled trials in unipolar and bipolar depression evaluated lithium's efficacy in augmenting and accelerating clinical response to antidepressant treatment ([Crossley and Bauer 2007](#)). Although there was firm evidence of lithium's efficacy as an augmentation agent, there was only modest evidence of its efficacy in accelerating response to antidepressants. In a naturalistic study by [Köhler et al. \(2013\)](#), patients with unipolar depression who had not responded to the first antidepressant they received were 1) started on adjunctive lithium, 2) started on a second-generation antipsychotic (SGA), 3) switched to a different antidepressant, or 4) given a combination of two antidepressants. Patients who received lithium or SGA augmentation showed greater improvement compared with patients switched to another antidepressant or an antidepressant combination. This study was limited by lack of randomization and failure to define nonresponse.

In treatment-refractory depression, open-label data support the addition of lithium to antidepressants, including tricyclic antidepressants (TCAs), trazodone, and selective serotonin reuptake inhibitors (SSRIs) ([Bschor et al. 2001](#);

de Montigny et al. 1981, 1983, 1985; Dinan 1993; Fontaine et al. 1991; Price et al. 1986). Double-blind and open-label studies support the use of lithium for augmentation of TCAs, monoamine oxidase inhibitors (MAOIs), trazodone, mirtazapine, and SSRIs (Baumann et al. 1996; Fava et al. 1994; Heninger et al. 1983; Joffe et al. 1993; Kantor et al. 1986; Katona et al. 1995; Nierenberg et al. 2006; Schöpf et al. 1989; Schüle et al. 2009; Zusky et al. 1988). In the large Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) multisite trial, 15.9% of subjects who did not experience remission with citalopram monotherapy and another medication trial achieved remission after the addition of lithium (Nierenberg et al. 2006). Single studies have found that severe depression (Bschor et al. 2013), weight loss and psychomotor retardation (Alvarez et al. 1997), more than three lifetime major depressive episodes, and a family history of major depressive or bipolar disorder in a first-degree relative (Sugawara et al. 2010) may predict a good response to lithium augmentation in treatment-resistant depression. These studies are limited by small heterogeneous samples, variations in treatment duration, use of mostly nonblinded, retrospective study designs, and absence of a placebo comparator.

Timing of onset of lithium action when the drug is used as an adjunct to antidepressant treatment remains unclear. A meta-analysis of placebo-controlled trials of lithium augmentation in treatment-resistant depression found that a minimum lithium dosage of 800 mg/day (or dosing to produce a serum level of  $\geq 0.5$  mEq/L) and a treatment duration of at least 2 weeks favored lithium augmentation as compared with placebo (Bauer et al. 1999).

# Suicide: Is Lithium Protective?

Up to 50% of bipolar patients attempt suicide ([Compton and Nemeroff 2000](#)). In an analysis of studies of lithium treatment ([Schou 1998](#)), bipolar patients treated with lithium had a lower overall mortality rate than bipolar patients in general and did not have a significantly higher suicide rate than the general population. [Tondo et al. \(1997\)](#) reviewed studies of the use of lithium in the treatment of major mood disorders; these included 28 studies that involved more than 17,000 patients. Risks of completed and attempted suicides were 8.6-fold higher in patients who were not given lithium compared with those who were. A recent review by [Lewitzka et al. \(2015\)](#) confirmed the antisuicidal effects of lithium. In meta-analyses of studies of lithium treatment in major mood disorders, [Tondo et al. \(2001\)](#), [Baldessarini et al. \(2006\)](#), [Guzzetta et al. \(2007\)](#), and [Cipriani et al. \(2013\)](#) found significantly lower suicide risk for subjects who were receiving treatment with lithium. Methodological problems exist in the studies that have examined lithium and suicide risk, and large-scale prospective studies are needed to inform treatment decisions ([Gelenberg 2001](#)). In the first randomized, placebo-controlled trial investigating the effect of adjunctive lithium treatment in prevention of suicidal behavior, which was conducted by [Lauterbach et al. \(2008\)](#), survival analysis showed no significant difference in suicidal acts between lithium- and placebo-treated groups. However, post hoc analysis showed that all completed suicides occurred in the placebo group, suggesting that lithium may be effective in reducing the risk of completed suicide.

In a retrospective cohort population-based study of subjects enrolled in two large integrated health plans with a diagnosis of bipolar disorder who were treated with lithium or divalproex, [Goodwin et al. \(2003\)](#) found that the risks of suicide attempt and suicide death were lower during treatment with lithium than during treatment with divalproex. In a national registry-based follow-up study in Finland exploring the association between medication use and hospitalizations due to a suicide attempt, suicide death, and overall mortality with different psychotropic agents in bipolar disorder, [Toffol et al. \(2015\)](#) found that lithium was associated with a lower risk of suicide attempts as well as decreased suicide and all-cause mortality. In an intriguing systematic review of the association between mortality rates from suicide and the levels of lithium in drinking water, [Vita et al. \(2015\)](#) reported that higher lithium levels in drinking water are associated with reduced suicide risk in the general population.

---

## Use in Special Populations

---

### Children and Adolescents

Lithium is FDA approved for the treatment of bipolar disorder in adolescents and has been shown to be significantly more efficacious than placebo for both bipolar disorder and substance abuse, but not for major depressive disorder ([Findling et al. 2015](#); [Geller et al. 1998a, 1998b](#); [Ryan et al. 1999](#)). Lithium had a large effect size in the open-label treatment of acute manic or mixed episodes in children and adolescents ([Kowatch et al. 2000](#)) and of acute

depressive episodes in adolescents with bipolar I disorder ([Patel et al. 2006](#)), and it had a medium effect size in the randomized, placebo-controlled treatment of acute manic or mixed episodes in children and adolescents with bipolar I disorder ([Findling et al. 2015](#)). In a randomized, double-blind maintenance trial of lithium versus divalproex in children and adolescents ages 5–17 years ([Findling et al. 2005](#)), lithium-treated patients and divalproex-treated patients did not differ in time to relapse. However, in the Treatment of Early Age Mania (TEAM) study, risperidone was more effective than lithium or divalproex in children ages 6–15 years, whereas there was no difference in efficacy between lithium and divalproex. The incidence of metabolic side effects was higher with risperidone than with lithium, but the discontinuation rate was higher with lithium than with risperidone ([Geller et al. 2012](#)). An earlier study examining predictors of side effects associated with lithium administration in children found that when weight and serum lithium levels were controlled, younger age was associated with more side effects ([Campbell et al. 1991](#)).

## The Elderly

Lithium has shown effectiveness in elderly patients. In a retrospective trial, significantly more patients age 55 years or older improved with lithium than with valproate, especially in cases of classic mania, whereas the two drugs showed similar response rates when the analysis considered only the cases of mixed mania ([S.T. Chen et al. 1999](#)). The lithium serum-level range associated with improvement in elderly patients was similar to the therapeutic range in younger adults:  $\geq 0.8$  mmol/L.

Medical comorbidity may be a particular consideration in elderly patients. Volume depletion, use of nonsteroidal anti-inflammatory drugs, or use of thiazide diuretics can increase lithium levels ([Stoudemire et al. 1990](#)). The lithium dosage required to achieve therapeutic serum concentrations decreases threefold from middle to old age, with this trend continuing into the ninth and tenth decades of life ([Rej et al. 2014b](#)). In a population-based retrospective cohort study involving 1,388 bipolar patients ages 66 years and older, medical hospitalizations, 1-year acute medical health utilization outcomes, and medical comorbidity rates were not different among lithium users as compared with valproate users or nonlithium/nonvalproate users during 1-year follow-up ([Rej et al. 2015](#)).

Meta-analyses show that lithium is associated with increased risk of reduced urinary concentrating ability, but there is little evidence for a clinically significant reduction in renal function in most patients, and the risk of end-stage renal failure is low ([McKnight et al. 2012](#)). Lithium use is associated with an increased risk of renal failure among the older (ages 50 years and above) age group ([Close et al. 2014](#); [Rej et al. 2014a](#)). However, chronic lithium use at lower dosages did not affect renal function in elderly patients with mild cognitive impairment and dementia over a 4-year study period ([Aprahamian et al. 2014](#)). Because lithium is cleared almost exclusively by the kidneys, patients with end-stage renal disease receiving hemodialysis cannot eliminate lithium other than through dialysis. Lithium should be given only after a dialysis treatment and need not be given daily ([Stoudemire et al. 1990](#)).

Because lithium appears to have neuroprotective effects that may reduce oxidative damage, its potential role in prevention of neurocognitive decline in aging and

prevention of Alzheimer's disease has been suggested ([Bachmann et al. 2005](#); [Chen et al. 2000](#); [Cui et al. 2007](#); [Engel et al. 2006](#); [Mohammadianinejad et al. 2014](#); [Phiel et al. 2003](#); [Shao et al. 2005](#); [Su et al. 2004](#); [Tsaltas et al. 2007](#); [Yoshida et al. 2006](#)). A Danish study that followed more than 4,800 patients with newly diagnosed bipolar disorder over 10 years found that long-term treatment with lithium, but not with other psychopharmacological agents, was associated with a reduced risk of developing dementia ([Kessing et al. 2010](#)). A study that analyzed data from a national health insurance database in Taiwan concluded that lithium use was significantly related to a reduced risk of stroke in patients with bipolar disorder. The association between lithium use and reduced stroke risk was strongest for patients who received the highest lithium dosages, experienced the longest durations of lithium treatment, and had the highest rates of lithium exposure ([Lan et al. 2015](#)).

## Pregnant or Lactating Women and Their Children

The risks and benefits of lithium treatment must be carefully assessed in the context of pregnancy and breast feeding. Undertreated or untreated women with bipolar disorder are at increased risk for perinatal complications and poor pregnancy outcomes ([Jablensky et al. 2005](#); [Lee and Lin 2010](#)). A prospective observational study by [Diav-Citrin et al. \(2014\)](#) that compared lithium-exposed pregnancies with disease-matched and nonteratogenic-exposed control pregnancies found higher rates of miscarriage and preterm delivery in the lithium-exposed group compared with the nonteratogenic exposure group,

but no difference in rates of stillbirth or ectopic pregnancy. Data suggest that lithium exposure during pregnancy is less harmful than experts believed in past decades ([Cohen et al. 1994](#)). In fact, although the overall risk of Ebstein's anomaly—a rare cardiac malformation with an incidence of 1 in 20,000 live births—may be higher with lithium use (relative risk of 10–20 vs. the general population) than without, the prevalence associated with first-trimester lithium exposure is 0.05%–0.1% ([Cohen and Rosenbaum 1998](#)). In the observational study by [Diav-Citrin et al. \(2014\)](#), rates of major congenital anomalies after exclusion of genetic or cytogenetic anomalies were not significantly different in the lithium-exposed group compared with the bipolar patients not exposed to lithium and the nonteratogenic exposure group ([Diav-Citrin et al. 2014](#)). Cardiovascular anomalies occurred more frequently in the lithium-exposed group compared with the nonteratogenic exposure group, but after exclusion of anomalies that spontaneously resolved, there were no differences between the groups, and there was also no difference between groups in the rates of noncardiovascular anomalies ([Diav-Citrin et al. 2014](#)). The risk of cardiovascular anomalies with lithium is substantially lower than the risk of neural tube defects associated with some anticonvulsants used for mood stabilization. Overall, lithium is not a high-risk teratogen.

Lithium freely crosses the placenta. Lithium-exposed neonates are more likely than nonexposed neonates to be born preterm, to have lower birthweights, and to have longer hospital stays ([Newport et al. 2005](#)). Because birth complications are directly correlated with placental lithium concentrations, brief suspension (24–48 hours) of lithium



therapy before delivery has been suggested ([Newport et al. 2005](#)).

Although lithium is today considered a first-line treatment for bipolar disorder during pregnancy ([Larsen et al. 2015](#)), many women wish to discontinue all psychotropic medications or to discontinue lithium ([McCrea et al. 2015](#)) during pregnancy. In a longitudinal study of 89 women with bipolar disorder who continued or discontinued mood stabilizer treatment during pregnancy, [Viguera et al. \(2007b\)](#) reported an overall risk of recurrence of 71%. Risk of recurrence was twofold greater in women who discontinued mood stabilizer treatment compared with those who did not, and time to recurrence was 11 times shorter if the mood stabilizer was discontinued abruptly instead of gradually. Risk of recurrence was 1.6 times higher in women using a mood stabilizer other than lithium ([Viguera et al. 2007b](#)). In an earlier study of relapse after lithium discontinuation in pregnant and nonpregnant women with bipolar disorder, [Viguera et al. \(2000\)](#) found that rates of relapse were initially similar in the two groups but increased sharply during the postpartum period (70% vs. 24% in nonpregnant patients matched for time after discontinuation) ([Viguera et al. 2000](#)). This high risk of recurrence has prompted experts in the field to recommend postpartum prophylactic treatment with a mood stabilizer for women with bipolar disorder ([Cohen et al. 1995](#)).

Lithium is secreted in breast milk and is passed on to the infant. For this reason, and also because of a small number of case reports of adverse effects in nursing infants of mothers taking lithium, the American Academy of Pediatrics (AAP) had previously considered lithium use to be contraindicated in breast-feeding women ([Chaudron and Jefferson 2000](#)). However, that recommendation was

revised in 2001 to the recommendation that lithium be used with caution in breast feeding due to reports of adverse events ([American Academy of Pediatrics Committee on Drugs 2001](#)). The Committee on Drugs of the AAP now reports that lithium is present at clinically significant levels (10% or more of therapeutic maternal plasma concentration) in human milk. The AAP currently recommends that in addition to receiving counseling about the benefits of breast feeding, parents be informed of the potential risks for infants exposed to clinically significant levels and cautioned that the long-term effects of this exposure are unknown ([Sachs and Committee on Drugs 2013](#)). In a study of 10 mother-infant pairs, serum lithium levels in the infants ranged from 0.09 to 0.3 mEq/L (mean 0.16 mEq/L). Transient elevations in infant thyroid-stimulating hormone, blood urea nitrogen, and creatinine levels were observed without evident long-term effects ([Viguera et al. 2007a](#)). The study authors concluded that breast feeding in the context of lithium therapy may be considered reasonable for a healthy infant when the mother's bipolar disorder is clinically stable, lithium monotherapy or a simple medication regimen is being used, and the pediatrician is supportive of the mother's breast feeding while she is being treated with lithium.

---

## Side Effects and Toxicology

---

### Laboratory Monitoring

Before lithium therapy is started, a medical history should be obtained, as well as baseline renal laboratory tests

(blood urea nitrogen, creatinine level), thyroid function tests, and an electrocardiogram for patients older than 40 years ([American Psychiatric Association 2002](#), [McKnight et al. 2012](#)). The American Psychiatric Association practice guideline for the treatment of bipolar disorder suggests that renal function should be assessed every 2-3 months and thyroid function should be tested once or twice during the first 6 months of treatment. After the first 6 months, renal laboratory tests and thyroid function tests should be monitored every 6-12 months or as clinically indicated ([American Psychiatric Association 2002](#); [McKnight et al. 2012](#); [Shine et al. 2015](#)).

## Cognitive Side Effects and Weight Gain

Cognitive side effects and weight gain have been reported to be the most disturbing side effects experienced in patients receiving lithium maintenance treatment, whereas self-reported noncompliance was mostly associated with lithium's effects on cognition and coordination ([Gitlin et al. 1989](#)). [Stoll et al. \(1996\)](#) reported on a case series in which seven patients with lithium-associated cognitive deficits improved when switched to treatment with divalproex sodium. Lithium is associated with clinically significant weight gain (>7%) ([McKnight et al. 2012](#)), which may pose a greater risk for patients who are obese before commencement of lithium treatment compared with those who are at normal weight ([Bowden et al. 2006](#)).

## Neurotoxicity

Neurotoxicity, delirium, and encephalopathy have been reported with lithium use. Specific populations with underlying neurological vulnerability have been noted to be at higher risk. Also, certain circumstances, such as concomitant electroconvulsive therapy or use of other psychotropics—especially first-generation antipsychotics—have been found to increase the risk of neurotoxic adverse effects from lithium treatment.

Neurotoxic reactions are potentially irreversible. Permanent neurological deficits reported after episodes of lithium intoxication ([Apte and Langston 1983](#); [Donaldson and Cuningham 1983](#)) have included deficits in recent memory, ataxia, and movement disorders. Early hemodialysis may help prevent permanent sequelae in these cases. [Donaldson and Cuningham \(1983\)](#) also reported persistent neurological sequelae of lithium toxicity involving multiple sites within the nervous system. In a case series of 90 patients, [Adityanjee et al. \(2005\)](#) reported that the most common sequela was cerebellar dysfunction. The typical neurological signs of irreversible lithium neurotoxicity include cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction, and dementia ([Ivkovic and Stern 2014](#)). [Himmelhoch et al. \(1980\)](#) found a greater incidence of lithium-induced neurotoxicity in the elderly. Other risk factors include longer duration of exposure to higher lithium levels and presence of medical comorbidities, including nephrogenic diabetes insipidus, abnormal thyroid function and impaired renal function, preexisting neurological disease, and drug combinations including antipsychotics ([Ivkovic and Stern 2014](#); [Netto and Phutane 2012](#); [Oakley et al. 2001](#)).

# Tremor

A fine postural tremor affects between 4% and 65% of patients who receive lithium ([Gelenberg and Jefferson 1995](#)). A severe tremor may indicate toxicity. Elimination of caffeine may actually worsen tremor because renal lithium clearance can be reduced with reduction of caffeine intake ([Jefferson 1988](#)). Lithium tremor, which resembles essential tremor, may worsen with age.

# Thyroid Abnormalities

In a chart review of 135 patients who received maintenance treatment with lithium, 38% had abnormal values on thyroid function tests (thyroid-stimulating hormone and/or free thyroxine index), with an association between laboratory abnormalities and length of time on lithium ([Fagiolini et al. 2006](#)). In a systematic review and meta-analysis, [McKnight et al. \(2012\)](#) reported that in comparison with placebo-treated subjects, lithium-treated patients had a sixfold higher risk of hypothyroidism and increased levels of thyroid-stimulating hormone. In a retrospective study of 209 patients who received lithium, [Kirov \(1998\)](#) found that 14.9% of the females and 3.4% of the males developed hypothyroidism. Female patients and patients older than 50 years were more likely to develop hypothyroidism ([Kirov 1998](#); [Shine et al. 2015](#)). Other reports have suggested that subclinical hypothyroidism during lithium therapy is much more common than previous cross-sectional studies had indicated ([Lombardi et al. 1993](#)). A family history of thyroid disease may lead to earlier onset of the hypothyroidism that occurs with lithium

use ([Kusalic and Engelsmann 1999](#)). Female patients with high serum lithium concentrations should have regular thyroid function testing ([Shine et al. 2015](#)).

## Parathyroid Abnormalities

Lithium has been associated with hypercalcemia and hyperparathyroidism ([Saunders et al. 2009](#)). A meta-analysis by [McKnight et al. \(2012\)](#) found that lithium-treated patients showed a 10% increase in levels of parathyroid hormone and calcium ([McKnight et al. 2012](#)) compared with control subjects. Similar increases in parathyroid hormone ([Albert et al. 2013](#)) and calcium ([Albert et al. 2013](#); [Shine et al. 2015](#)) in lithium-treated patients have been reported in other studies as well. Monitoring of calcium levels at baseline and yearly, or more frequently in the presence of clinical symptoms, is suggested ([McKnight et al. 2012](#)).

## Renal Complications

Lithium has multiple renal effects, including those that occur early in treatment and those that occur with chronic use. Lithium can induce tubular dysfunction early in treatment, with reduced urinary concentrating capacity developing over the first 8 weeks of treatment. Nephrogenic diabetes insipidus occurs in 20%–87% of patients on lithium ([Azab et al. 2015](#); [Markowitz et al. 2000](#); [Stone 1999](#)). These effects may be partially mediated by lithium's action on water and sodium channels in the kidney ([Grünfeld and Rossier 2009](#)); thus, there has been renewed interest in using amiloride, a sodium channel-blocking

diuretic, in an attempt to modify lithium's toxicity ([Azab et al. 2015](#); [Bedford et al. 2008](#)).

Another important renal effect of lithium is chronic kidney disease, which tends to occur after 10–20 years of lithium treatment ([Presne et al. 2003](#)) at an estimated prevalence of 1.2% ([Bendz et al. 2010](#)) to 21% ([Lepkifker et al. 2004](#)), depending on the definition of renal insufficiency used. However, the risk of progressing to end-stage renal disease is small (0.5%–1%) ([Bendz et al. 2010](#); [Tredget et al. 2010](#)). The clearest risk factors are duration of lithium use ([Bendz et al. 2010](#); [Bocchetta et al. 2015](#); [Castro et al. 2016](#); [Presne et al. 2003](#)), dosing of lithium more than once a day ([Castro et al. 2016](#)), and higher serum lithium levels ([Castro et al. 2016](#); [Shine et al. 2015](#)); however, additional possible risk factors are older age ([Bendz et al. 2010](#); [Bocchetta et al. 2015](#); [Castro et al. 2016](#); [Close et al. 2014](#); [Presne et al. 2003](#)), female sex ([Castro et al. 2016](#); [Shine et al. 2015](#)), previous episodes of lithium toxicity, and presence of comorbid disorders ([Castro et al. 2016](#); [Lepkifker et al. 2004](#)). The potential for chronic renal disease is the reason that close laboratory monitoring is required for patients on long-term lithium treatment ([Shine et al. 2015](#)). Once-daily dosing and maintaining low lithium levels when possible may be helpful in preventing long-term renal damage ([Castro et al. 2016](#); [Malhi and Tanious 2011](#)). The decision of whether to stop lithium in the setting of renal impairment must be made collaboratively by the patient, the psychiatrist, and the nephrologist. Chronic kidney disease can progress to renal failure even after lithium is stopped; however, with mild or moderate renal dysfunction, there may be improvement if a change is made ([Grünfeld and Rossier 2009](#)).

# Cardiac Changes

Lithium intoxication has been reported to cause cardiac alterations, including sinus bradycardia and sinus node dysfunction ([Steckler 1994](#)). Sinus node dysfunction was found to be more prevalent among patients who had been taking lithium for at least a year than among age-matched control subjects, although clinically significant dysfunction was uncommon ([Rosenqvist et al. 1993](#)). Also, cases of atrioventricular block in patients with therapeutic lithium levels have been reported ([Martin and Piascik 1985](#)). Electrocardiographic T-wave changes, as well as ventricular irritability, may occur ([Mitchell and Mackenzie 1982](#)). In patients with clinical indications for lithium use, the presence of cardiovascular disease does not constitute a contraindication to lithium use. Dosage adjustment and frequent cardiac monitoring are essential for the safe use of lithium in patients with cardiac disease ([Tilkian et al. 1976](#)). Because of the risk of sinus node dysfunction and other cardiac effects, careful monitoring of the pulse and electrocardiographic monitoring are recommended in patients older than 50 years ([Roose et al. 1979](#)).

---

## Drug-Drug Interactions

---

### Lithium With Other Mood Stabilizers

#### Lithium With Anticonvulsants

Lithium is commonly used in combination with other mood stabilizers, and although such combinations can be



synergistic, polypharmacy may increase the risk of adverse reactions ([Freeman and Stoll 1998](#); [Lenox et al. 1996](#)). The combination of lithium and valproate is often used in refractory mania. Interactions may include additive side effects, such as sedation, tremor, or weight gain, but the pharmacokinetics of lithium are not altered by the addition of valproate ([Granneman et al. 1996](#)). Lithium and carbamazepine have been combined for bipolar disorder refractory to lithium alone, but this combination may increase the risk of neurotoxicity ([Chaudhry and Waters 1983](#); [Frances et al. 1996](#); [Kishimoto 1992](#); [Shukla et al. 1984, 1985](#); [Small et al. 1995](#)). Topiramate exhibits no pharmacokinetic interactions with lithium ([Bialer et al. 2004](#)). There are inconsistent reports about interactions between lithium and lamotrigine; whereas [Chen et al. \(1999\)](#) found no significant alterations in the pharmacokinetics of lithium in 20 healthy volunteers, another study showed that co-treatment with lithium may lower the serum concentration of lamotrigine ([Reimers et al. 2005](#)). Gabapentin is also used adjunctively in the treatment of bipolar disorder, and because gabapentin has no known drug interactions, it is likely safe with lithium use ([Frye et al. 1998](#); [Vollmer et al. 1986](#)). Benzodiazepines also do not interact with lithium ([Adler 1986](#); [Modell et al. 1985](#); [Sachs et al. 1990a, 1990b](#)).

## **Lithium With Antipsychotics**

Although many investigators have reported safe and efficacious results from combining lithium and first-generation antipsychotics ([Baastrup et al. 1976](#); [Bigelow et al. 1981](#); [Carman et al. 1981](#); [Garfinkel et al. 1980](#); [Goldney and Spence 1986](#)), neurotoxicity and even tardive dyskinesia can occur ([Cohen and Cohen 1974](#); [Dinan and](#)

Kohen 1989; Mani et al. 1996; Mann et al. 1983; Miller et al. 1986; Perényi et al. 1983, 1984; Spring 1979; Spring and Frankel 1981). Goodwin and Jamison (1990) recommended that when incorporating a first-generation antipsychotic into a regimen of lithium therapy, the antipsychotic should be used at lower dosages, and lithium levels should be maintained below 1.0 mEq/L.

The use of lithium with second-generation antipsychotics also may result in adverse reactions. Use of clozapine with lithium may cause diabetic ketoacidosis, neuroleptic malignant syndrome, and neurological side effects (Blake et al. 1992; Garcia et al. 1994; Lemus et al. 1989; Peterson and Byrd 1996; Pope et al. 1986). Some investigators have reported safe and effective use of risperidone and lithium (Ghaemi et al. 1997; Tohen et al. 1996), although adverse effects, including fever, increased white blood cell counts, increased creatine phosphokinase levels, and delirium, also have been reported (Chen and Cardasis 1996; Swanson et al. 1995). Preliminary data suggest that the combination of lithium and olanzapine is efficacious and well tolerated in acute mania (Madhusoodanan et al. 2000; Sanger et al. 2001). Quetiapine coadministered with lithium did not result in clinically important pharmacokinetic interactions (Potkin et al. 2002). Augmentation of lithium with aripiprazole produced rapid and significant improvement in manic symptoms that was sustained over the long term (Vieta et al. 2008), and there were no clinically meaningful effects on the pharmacokinetics of either drug (Boulton et al. 2012). There were no significant interactions between lurasidone and lithium, and no dosage adjustment for lurasidone was needed when administered with lithium (Chiu et al. 2014).

# Lithium With Antidepressants

Lithium is often used concomitantly with antidepressants in the treatment of bipolar depression and refractory unipolar depression. Serotonin syndrome—a constellation of mental status and behavioral changes (either agitation or sedation), motor symptoms (restlessness, weakness, hyperreflexia, or ataxia), and autonomic dysfunction (nausea and/or vomiting, dizziness, sweating, fever) ([Lejoyeux et al. 1994](#))—has been reported with the use of lithium and serotonergic antidepressants ([Adan-Manes et al. 2006](#); [Fagiolini et al. 2001](#); [Karle and Bjørndal 1995](#); [Mekler and Woggon 1997](#); [Muly et al. 1993](#); [Ohman and Spigset 1993](#); [Shahani 2012](#); [Sobanski et al. 1997](#)).

# Lithium With Nonpsychotropic Medications

When lithium is used concurrently with nonsteroidal anti-inflammatory drugs, signs and symptoms of toxicity and lithium levels must be monitored more carefully because nonsteroidal anti-inflammatory drugs increase the risk of toxicity ([Grandjean and Aubry 2009](#); [Johnson et al. 1993](#)).

Because lithium excretion relies on renal clearance, diuretic medications may affect lithium levels, depending on their site of action. Thiazide diuretics trigger a compensatory increase in reabsorption in the proximal tubule and lead to elevations in lithium levels, whereas loop diuretics do not promote lithium reabsorption and do not greatly affect lithium levels ([Finley et al. 1995](#)). Osmotic diuretics enhance lithium excretion and may serve to

counteract lithium toxicity, and either no change or a slight increase in lithium levels has been reported with potassium-sparing diuretics.

Neurotoxic and other adverse reactions have been associated with the concomitant administration of lithium with calcium channel blockers ([Dubovsky et al. 1987](#); [Finley et al. 1995](#); [Helmuth et al. 1989](#); [Wright and Jarrett 1991](#)). Angiotensin-converting enzyme inhibitors or angiotensin receptor 1 blockers may raise lithium levels ([DasGupta et al. 1992](#); [Finley et al. 1996](#); [Lazarczyk and Giannakopoulos 2014](#)). Serum lithium levels may increase in the context of sodium restriction ([Bennett 1997](#)). Theophylline and caffeine can decrease lithium concentrations ([Cook et al. 1985](#)). Lactulose may result in lithium toxicity, possibly by volume depletion, as reported in a case series ([Bregman et al. 2014](#)).

---

## Conclusion

---

Lithium is an important option in the evidence-based rational treatment of bipolar disorder. Bipolar disorder affects between 1% and 5% of the population ([Akiskal et al. 2000](#)) and causes significant morbidity and mortality, and the diagnosis of bipolar disorder carries a high risk for suicide. A summary published in 1990 estimated that 25%–50% attempt suicide and 19% complete suicide ([Goodwin and Jamison 1990](#)); however, a recent analysis estimated that the pooled suicide rate for bipolar disorder was 164 per 100,000 person-years, with individuals with bipolar disorder accounting for 3.4%–14% of all suicide deaths ([Schaffer et al. 2015](#)).

Lithium has been shown to be effective for acute mania and bipolar depression and as a prophylactic treatment for bipolar disorder. Some data suggest that conditions such as comorbid neurological illness and mixed episodes may be indicators of illness that is more responsive to mood stabilizers other than lithium. Evidence also suggests that lithium can play a role in the treatment of refractory unipolar depression in patients at risk for suicide. Lithium may be less risky than anticonvulsants in pregnancy. Although we continually seek new treatments and hope that they will be more efficacious and better tolerated than older medications, for now lithium remains an important treatment option.

---

## References

---

- Adan-Manes J, Novalbos J, López-Rodríguez R, et al: Lithium and venlafaxine interaction: a case of serotonin syndrome. *J Clin Pharm Ther* 31(4):397-400, 2006 16882112
- Adityanjee MKR, Munshi KR, Thampy A: The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 28(1):38-49, 2005 15714160
- Adler LW: Mixed bipolar disorder responsive to lithium and clonazepam. *J Clin Psychiatry* 47(1):49-50, 1986 3079750
- Akiskal HS, Bourgeois ML, Angst J, et al: Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord* 59 (suppl 1):S5-S30, 2000 11121824
- Albert U, De Cori D, Aguglia A, et al: Lithium-associated hyperparathyroidism and hypercalcaemia: a case-control

- cross-sectional study. *J Affect Disord* 151(2):786–790, 2013 23870428
- Alda M: Lithium in the treatment of bipolar disorder: pharmacology and pharmacogenetics. *Mol Psychiatry* 20(6):661–670, 2015 25687772
- Alvarez E, Pérez-Solá V, Pérez-Blanco J, et al: Predicting outcome of lithium added to antidepressants in resistant depression. *J Affect Disord* 42(2–3):179–186, 1997 9105959
- American Academy of Pediatrics Committee on Drugs: Transfer of drugs and other chemicals into human milk. *Pediatrics* 108(3):776–789, 2001 11533352
- American Psychiatric Association: Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 159 (4 suppl):1–50, 2002 11958165
- Aprahamian I, Santos FS, dos Santos B, et al: Long-term, low-dose lithium treatment does not impair renal function in the elderly: a 2-year randomized, placebo-controlled trial followed by single-blind extension. *J Clin Psychiatry* 75(7):e672–e678, 2014 25093483
- Apte SN, Langston JW: Permanent neurological deficits due to lithium toxicity. *Ann Neurol* 13(4):453–455, 1983 6838176
- Astaneh AN, Rezaei O: Adjunctive treatment with gabapentin in bipolar patients during acute mania. *Int J Psychiatry Med* 43(3):261–271, 2012 22978083
- Austin MPV, Souza FGM, Goodwin GM: Lithium augmentation in antidepressant-resistant patients. A quantitative analysis. *Br J Psychiatry* 159:510–514, 1991 1836411
- Azab AN, Shnaider A, Osher Y, et al: Lithium nephrotoxicity. *Int J Bipolar Disord* 3(1):28, 2015 26043842
- Baastrup PC, Hollnagel P, Sorensen R, Schou M: Adverse reactions in treatment with lithium carbonate and haloperidol. *JAMA* 236(23):2645–2646, 1976 1036539

- Bachmann RF, Schloesser RJ, Gould TD, Manji HK: Mood stabilizers target cellular plasticity and resilience cascades: implications for the development of novel therapeutics. *Mol Neurobiol* 32(2):173-202, 2005 16215281
- BALANCE Investigators and Collaborators, Geddes JR, Goodwin GM, Rendell J, et al: Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* 375(9712):385-395, 2010 20092882
- Baldessarini RJ: Drugs and the treatment of psychiatric disorders: depression and mania, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th Edition. Edited by Hardman JG, Limbird LE. New York, McGraw-Hill, 1996, pp 431-459
- Baldessarini RJ, Tarazi FI: Drugs and the treatment of psychiatric disorders: psychosis and mania, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Edition. Edited by Hardman JG, Limbird LE. New York, McGraw-Hill, 2001, pp 485-520
- Baldessarini RJ, Tondo L, Floris G, Hennen J: Effects of rapid cycling on response to lithium maintenance treatment in 360 bipolar I and II disorder patients. *J Affect Disord* 61(1-2):13-22, 2000 11099736
- Baldessarini RJ, Tondo L, Davis P, et al: Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord* 8(5 Pt 2):625-639, 2006 17042835
- Barkai AI, Dunner DL, Gross HA, et al: Reduced myo-inositol levels in cerebrospinal fluid from patients with affective disorder. *Biol Psychiatry* 13(1):65-72, 1978 623854
- Baron M, Gershon ES, Rudy V, et al: Lithium carbonate response in depression. Prediction by unipolar/bipolar illness, average-evoked response, catechol-O-methyl

- transferase, and family history. *Arch Gen Psychiatry* 32(9):1107-1111, 1975 1101845
- Bauer M, Dopfmer S, Rudy V, et al: Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol* 19(5):427-434, 1999 10505584
- Baumann P, Nil R, Souche A, et al: A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol* 16(4):307-314, 1996 8835706
- Bedford JJ, Weggery S, Ellis G, et al: Lithium-induced nephrogenic diabetes insipidus: renal effects of amiloride. *Clin J Am Soc Nephrol* 3(5):1324-1331, 2008 18596116
- Belmaker RH, Bersudsky Y, Agam G, et al: How does lithium work on manic depression? Clinical and psychological correlates of the inositol theory. *Annu Rev Med* 47:47-56, 1996 8712796
- Bendz H, Schön S, Attman PO, Aurell M: Renal failure occurs in chronic lithium treatment but is uncommon. *Kidney Int* 77(3):219-224, 2010 19940841
- Benjamin J, Levine J, Fux M, et al: Inositol treatment for panic disorder: a double-blind placebo-controlled crossover trial. *Am J Psychiatry* 152:1084-1086, 1995 7793450
- Bennett WM: Drug interactions and consequences of sodium restriction. *Am J Clin Nutr* 65 (2 suppl):678S-681S, 1997 9022564
- Berk M, Ichim L, Brook S: Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int Clin Psychopharmacol* 14(6):339-343, 1999 10565800
- Berrettini WH, Nurnberger JI Jr, Hare TA, et al: Reduced plasma and CSF  $\gamma$ -aminobutyric acid in affective illness:



- effect of lithium carbonate. *Biol Psychiatry* 18(2):185-194, 1983 6403063
- Berrettini WH, Nurnberger JI Jr, Hare TA, et al: CSF GABA in euthymic manic-depressive patients and controls. *Biol Psychiatry* 21(8-9):844-846, 1986 3730464
- Berridge MJ, Downes CP, Hanley MR: Neural and developmental actions of lithium: a unifying hypothesis. *Cell* 59(3):411-419, 1989 2553271
- Beynon S, Soares-Weiser K, Woolacott N, et al: Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. *J Psychopharmacol* 23(5):574-591, 2009 18635701
- Bialer M, Doose DR, Murthy B, et al: Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* 43(12):763-780, 2004 15355124
- Bigelow LB, Weinberger DR, Wyatt RJ: Synergism of combined lithium-neuroleptic therapy: a double-blind, placebo-controlled case study. *Am J Psychiatry* 138(1):81-83, 1981 7192495
- Birch NJ, Greenfield AA, Hullin RP: Pharmacodynamic aspects of long-term prophylactic lithium. *Int Pharmacopsychiatry* 15(2):91-98, 1980 7440099
- Blake LM, Marks RC, Luchins DJ: Reversible neurologic symptoms with clozapine and lithium. *J Clin Psychopharmacol* 12(4):297-299, 1992 1527237
- Bocchetta A, Arda R, Fanni T, et al: Renal function during long-term lithium treatment: a cross-sectional and longitudinal study. *BMC Med* 13(1):12, 2015 25604586
- Boulton DW, Kollia GD, Mallikaarjun S, Kornhauser DM: Lack of a pharmacokinetic drug-drug interaction between lithium and valproate when co-administered with aripiprazole. *J Clin Pharm Ther* 37(5):565-570, 2012 22943745
- Bourin MS, Severus E, Schronen JP, et al: Lithium as add-on to quetiapine XR in adult patients with acute mania: a 6-

week, multicenter, double-blind, randomized, placebo-controlled study. *Int J Bipolar Disord* 2:14, 2014 25505693

Bowden CL, Brugger AM, Swann AC, et al; The Depakote Mania Study Group: Efficacy of divalproex vs lithium and placebo in the treatment of mania (erratum in *JAMA* 271:1830, 1994). *JAMA* 271(12): 918-924, 1994 8120960

Bowden CL, Calabrese JR, McElroy SL, et al; Divalproex Maintenance Study Group: A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry* 57(5):481-489, 2000 10807488

Bowden CL, Calabrese JR, Sachs G, et al; Lamictal 606 Study Group: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 60(4):392-400, 2003 12695317

Bowden CL, Grunze H, Mullen J, et al: A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 66(1):111-121, 2005 15669897

Bowden CL, Calabrese JR, Ketter TA, et al: Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. *Am J Psychiatry* 163(7):1199-1201, 2006 16816224

Bowden C, Göğüş A, Grunze H, et al: A 12-week, open, randomized trial comparing sodium valproate to lithium in patients with bipolar I disorder suffering from a manic episode. *Int Clin Psychopharmacol* 23(5):254-262, 2008 18703934

Bowden CL, Mosolov S, Hranov L, et al: Efficacy of valproate versus lithium in mania or mixed mania: a

- randomized, open 12-week trial. *Int Clin Psychopharmacol* 25(2):60-67, 2010 20101186
- Brambilla P, Perez J, Barale F, et al: GABAergic dysfunction in mood disorders. *Mol Psychiatry* 8(8):721-737, 715, 2003 12888801
- Bregman A, Fritz K, Xiong GL: Lactulose-associated lithium toxicity: a case series. *J Clin Psychopharmacol* 34(6):742-743, 2014 25133791
- Bschor T, Canata B, Müller-Oerlinghausen B, et al: Predictors of response to lithium augmentation in tricyclic antidepressant-resistant depression. *J Affect Disord* 64(2):261-265, 2001 11313093
- Bschor T, Uhr M, Baethge C, et al: Acute antidepressive efficacy of lithium monotherapy, not citalopram, depends on recurrent course of depression. *J Clin Psychopharmacol* 33(1):38-44, 2013 23277245
- Cade JF: Lithium salts in the treatment of psychotic excitement. *Med J Aust* 2(10):349-352, 1949 18142718
- Calabrese JR, Bowden CL, Sachs G, et al; Lamictal 605 Study Group: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 64(9):1013-1024, 2003 14628976
- Calabrese JR, Shelton MD, Rapport DJ, et al: A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 162(11):2152-2161, 2005 16263857
- Campbell M, Silva RR, Kafantaris V, et al: Predictors of side effects associated with lithium administration in children. *Psychopharmacol Bull* 27(3):373-380, 1991 1775612
- Carman JS, Bigelow LB, Wyatt RJ: Lithium combined with neuroleptics in chronic schizophrenic and schizoaffective patients. *J Clin Psychiatry* 42(3):124-128, 1981 6110654
- Carvalho AF, Machado JR, Cavalcante JL: Augmentation strategies for treatment-resistant depression. *Curr Opin*

- Psychiatry 22(1):7-12, 2009 19122528
- Castro VM, Roberson AM, McCoy TH, et al: Stratifying risk for renal insufficiency among lithium-treated patients: an electronic health record study. Neuropsychopharmacology 41(4):1138-1143, 2016 26294109
- Chaudhry RP, Waters BG: Lithium and carbamazepine interaction: possible neurotoxicity. J Clin Psychiatry 44(1):30-31, 1983 6401711
- Chaudron LH, Jefferson JW: Mood stabilizers during breastfeeding: a review. J Clin Psychiatry 61(2):79-90, 2000 10732654
- Chen B, Cardasis W: Delirium induced by lithium and risperidone combination. Am J Psychiatry 153(9):1233-1234, 1996 8780436
- Chen C, Veronese L, Yin Y: The effects of lamotrigine on the pharmacokinetics of lithium. Br J Clin Pharmacol 50(3):193-195, 2000 10971302
- Chen G, Huang LD, Jiang YM, Manji HK: The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. J Neurochem 72(3):1327-1330, 1999 10037507
- Chen G, Rajkowska G, Du F, et al: Enhancement of hippocampal neurogenesis by lithium. J Neurochem 75(4):1729-1734, 2000 10987856
- Chen ST, Altshuler LL, Melnyk KA, et al: Efficacy of lithium vs. valproate in the treatment of mania in the elderly: a retrospective study. J Clin Psychiatry 60(3):181-186, 1999 10192594
- Chisholm D, van Ommeren M, Ayuso-Mateos JL, Saxena S: Cost-effectiveness of clinical interventions for reducing the global burden of bipolar disorder. Br J Psychiatry 187:559-567, 2005 16319409
- Chiu YY, Ereshefsky L, Preskorn SH, et al: Lurasidone drug-drug interaction studies: a comprehensive review. Drug Metabol Drug Interact 29(3):191-202, 2014 24825095

- Cipriani A, Hawton K, Stockton S, Geddes JR: Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 346:f3646, 2013 23814104
- Close H, Reilly J, Mason JM, et al: Renal failure in lithium-treated bipolar disorder: a retrospective cohort study. *PLoS One* 9(3):e90169, 2014 24670976
- Cohen LS, Rosenbaum JF: Psychotropic drug use during pregnancy: weighing the risks. *J Clin Psychiatry* 59 (suppl 2):18-28, 1998 9559756
- Cohen LS, Friedman JM, Jefferson JW, et al: A reevaluation of risk of in utero exposure to lithium. *JAMA* 271(2):146-150, 1994 8031346
- Cohen LS, Sichel DA, Robertson LM, et al: Postpartum prophylaxis for women with bipolar disorder. *Am J Psychiatry* 152(11): 1641-1645, 1995 7485628
- Cohen WJ, Cohen NH: Lithium carbonate, haloperidol, and irreversible brain damage. *JAMA* 230(9):1283-1287, 1974 4479505
- Compton MT, Nemeroff CB: The treatment of bipolar depression. *J Clin Psychiatry* 61 (suppl 9):57-67, 2000 10826663
- Cook BL, Smith RE, Perry PJ, Calloway RA: Theophylline-lithium interaction. *J Clin Psychiatry* 46(7):278-279, 1985 4008452
- Crossley NA, Bauer M: Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry* 68(6):935-940, 2007 17592920
- Cui J, Shao L, Young LT, Wang JF: Role of glutathione in neuroprotective effects of mood stabilizing drugs lithium and valproate. *Neuroscience* 144(4):1447-1453, 2007 17184924
- DasGupta K, Jefferson JW, Kobak KA, Greist JH: The effect of enalapril on serum lithium levels in healthy men. *J Clin Psychiatry* 53(11):398-400, 1992 1459971

- Davis JM, Janicak PG, Hogan DM: Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. *Acta Psychiatr Scand* 100(6):406-417, 1999 10626918
- de Montigny C, Grunberg F, Mayer A, Deschenes JP: Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. *Br J Psychiatry* 138:252-256, 1981 7272619
- de Montigny C, Cournoyer G, Morissette R, et al: Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression. Correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system. *Arch Gen Psychiatry* 40(12):1327-1334, 1983 6418109
- de Montigny C, Elie R, Caillé G: Rapid response to the addition of lithium in iprindole-resistant unipolar depression: a pilot study. *Am J Psychiatry* 142(2):220-223, 1985 3918468
- de Sousa RT, Busnello JV, Forlenza OV, et al: Early improvement of psychotic symptoms with lithium monotherapy as a predictor of later response in mania. *J Psychiatr Res* 46(12):1564-1568, 2012 23000368
- Diav-Citrin O, Shechtman S, Tahover E, et al: Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. *Am J Psychiatry* 171(7):785-794, 2014 24781368
- Dinan TG: Lithium augmentation in sertraline-resistant depression: a preliminary dose-response study. *Acta Psychiatr Scand* 88(4):300-301, 1993 8256650
- Dinan TG, Kohen D: Tardive dyskinesia in bipolar affective disorder: relationship to lithium therapy. *Br J Psychiatry* 155:55-57, 1989 2575003
- Dixon JF, Hokin LE: Lithium acutely inhibits and chronically up-regulates and stabilizes glutamate uptake by presynaptic nerve endings in mouse cerebral cortex.

- Proc Natl Acad Sci U S A 95(14):8363-8368, 1998 9653192
- Donaldson IM, Cuninghame J: Persisting neurologic sequelae of lithium carbonate therapy. Arch Neurol 40(12):747-751, 1983 6625989
- Donnelly EF, Goodwin FK, Waldman IN, Murphy DL: Prediction of antidepressant responses to lithium. Am J Psychiatry 135(5):552-556, 1978 645948
- Dubovsky SL, Franks RD, Allen S: Verapamil: a new antimanic drug with potential interactions with lithium. J Clin Psychiatry 48(9):371-372, 1987 3114243
- Dunner DL, Fieve RR: Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 30(2):229-233, 1974 4589148
- Dunner DL, Patrick V, Fieve RR: Rapid cycling manic depressive patients. Compr Psychiatry 18(6):561-566, 1977 923228
- Emilien G, Maloteaux JM, Seghers A, Charles G: Lithium compared to valproic acid and carbamazepine in the treatment of mania: a statistical meta-analysis. Eur Neuropsychopharmacol 6(3):245-252, 1996 8880085
- Engel T, Goñi-Oliver P, Lucas JJ, et al: Chronic lithium administration to FTDP-17 tau and GSK-3beta overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but pre-formed neurofibrillary tangles do not revert. J Neurochem 99(6):1445-1455, 2006 17059563
- Fagiolini A, Buysse DJ, Frank E, et al: Tolerability of combined treatment with lithium and paroxetine in patients with bipolar disorder and depression. J Clin Psychopharmacol 21(5):474-478, 2001 11593071
- Fagiolini A, Kupfer DJ, Scott J, et al: Hypothyroidism in patients with bipolar I disorder treated primarily with lithium. Epidemiol Psychiatr Soc 15(2):123-127, 2006 16865933

- Fava M, Rosenbaum JF, McGrath PJ, et al: Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *Am J Psychiatry* 151(9):1372-1374, 1994 8067495
- Fieve RR, Platman SR, Plutchik RR: The use of lithium in affective disorders. I. Acute endogenous depression. *Am J Psychiatry* 125(4):487-491, 1968 4886102
- Findling RL, McNamara NK, Youngstrom EA, et al: Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44(5):409-417, 2005 15843762
- Findling RL, Robb A, McNamara NK, et al: Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study. *Pediatrics* 136(5):885-894, 2015 26459650
- Finley PR, Warner MD, Peabody CA: Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 29(3):172-191, 1995 8521679
- Finley PR, O'Brien JG, Coleman RW: Lithium and angiotensin-converting enzyme inhibitors: evaluation of a potential interaction. *J Clin Psychopharmacol* 16(1):68-71, 1996 8834421
- Fontaine R, Ontiveros A, Elie R, Vézina M: Lithium carbonate augmentation of desipramine and fluoxetine in refractory depression. *Biol Psychiatry* 29(9):946-948, 1991 1904782
- Fountoulakis KN, Kasper S, Andreassen O, et al: Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry. *Eur Arch Psychiatry Clin Neurosci* 262 (1 suppl 1):1-48, 2012 22622948
- Frances A, Docherty JP, Kahn DA: Treatment of bipolar disorder. *J Clin Psychiatry* 57 (suppl):5-58, 1996
- Franchini L, Zanardi R, Smeraldi E, Gasperini M: Early onset of lithium prophylaxis as a predictor of good long-



- term outcome. *Eur Arch Psychiatry Clin Neurosci* 249(5):227-230, 1999 10591987
- Freeman MP, Stoll AL: Mood stabilizer combinations: a review of safety and efficacy. *Am J Psychiatry* 155(1):12-21, 1998 9433333
- Freeman TW, Clothier JL, Pazzaglia P, et al: A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry* 149(1):108-111, 1992 1728157
- Frye MA, Kimbrell TA, Dunn RT, et al: Gabapentin does not alter single-dose lithium pharmacokinetics. *J Clin Psychopharmacol* 18(6):461-464, 1998 9864078
- Frye MA, Yatham LN, Calabrese JR, et al: Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. *J Clin Psychiatry* 67(11):1721-1728, 2006 17196051
- Garcia G, Crismon ML, Dorson PG: Seizures in two patients after the addition of lithium to a clozapine regimen. *J Clin Psychopharmacol* 14(6):426-428, 1994 7884026
- Garfinkel PE, Stancer HC, Persad E: A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. *J Affect Disord* 2(4):279-288, 1980 6450787
- Geddes JR, Burgess S, Hawton K, et al: Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 161(2):217-222, 2004 14754766
- Gelenberg AJ: Can lithium help to prevent suicide? (editorial). *Acta Psychiatr Scand* 104(3):161-162, 2001 11531652
- Gelenberg AJ, Jefferson JW: Lithium tremor. *J Clin Psychiatry* 56(7):283-287, 1995 7615481
- Gelenberg AJ, Kane JM, Keller MB, et al: Comparison of standard and low serum levels of lithium for

- maintenance treatment of bipolar disorder. *N Engl J Med* 321(22):1489-1493, 1989 2811970
- Geller B, Cooper TB, Sun K, et al: Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry* 37(2):171-178, 1998a 9473913
- Geller B, Cooper TB, Zimmerman B, et al: Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. *J Affect Disord* 51(2):165-175, 1998b 10743849
- Geller B, Luby JL, Joshi P, et al: A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. *Arch Gen Psychiatry* 69(5):515-528, 2012 22213771
- Ghaemi SN, Sachs GS, Baldassano CF, Truman CJ: Acute treatment of bipolar disorder with adjunctive risperidone in outpatients. *Can J Psychiatry* 42(2):196-199, 1997 9067070
- Gitlin MJ, Cochran SD, Jamison KR: Maintenance lithium treatment: side effects and compliance. *J Clin Psychiatry* 50(4):127-131, 1989 2925600
- Goldney RD, Spence ND: Safety of the combination of lithium and neuroleptic drugs. *Am J Psychiatry* 143(7):882-884, 1986 2872825
- González RG, Guimaraes AR, Sachs GS, et al: Measurement of human brain lithium in vivo by MR spectroscopy. *AJNR Am J Neuroradiol* 14(5):1027-1037, 1993 8237676
- Goodwin FK, Jamison KR: *Manic Depressive Illness*. New York, Oxford University Press, 1990
- Goodwin FK, Zis AP: Lithium in the treatment of mania: comparisons with neuroleptics. *Arch Gen Psychiatry* 36(8 Spec No):840-844, 1979 36866

- Goodwin FK, Murphy DL, Bunney WE Jr: Lithium-carbonate treatment in depression and mania. A longitudinal double-blind study. *Arch Gen Psychiatry* 21(4): 486-496, 1969 4896983
- Goodwin FK, Murphy DL, Dunner DL, Bunney WE Jr: Lithium response in unipolar versus bipolar depression. *Am J Psychiatry* 129(1):44-47, 1972 4556087
- Goodwin FK, Fireman B, Simon GE, et al: Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA* 290(11):1467-1473, 2003 13129986
- Grahame-Smith DG: Disorder of synaptic homeostasis as a cause of depression and a target for treatment, in *Antidepressant Therapy at the Dawn of the Third Millennium*. Edited by Briley M, Montgomery S. London, Martin Dunitz, 1998, pp 111-140
- Grandjean EM, Aubry JM: Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety. *CNS Drugs* 23(5):397-418, 2009 19453201
- Granneman GR, Schneck DW, Cavanaugh JH, Witt GF: Pharmacokinetic interactions and side effects resulting from concomitant administration of lithium and divalproex sodium. *J Clin Psychiatry* 57(5):204-206, 1996 8626351
- Greenspan K, Schildkraut JJ, Gordon EK, et al: Catecholamine metabolism in affective disorders. 3. MHPG and other catecholamine metabolites in patients treated with lithium carbonate. *J Psychiatr Res* 7(3):171-183, 1970 5440858
- Grünfeld JP, Rossier BC: Lithium nephrotoxicity revisited. *Nat Rev Nephrol* 5(5):270-276, 2009 19384328
- Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ: Lithium treatment reduces suicide risk in recurrent major depressive disorder. *J Clin Psychiatry* 68(3):380-383, 2007 17388706

- Haddjeri N, Szabo ST, de Montigny C, Blier P: Increased tonic activation of rat forebrain 5-HT(1A) receptors by lithium addition to antidepressant treatments. *Neuropsychopharmacology* 22(4):346-356, 2000 10700654
- Hahn CG, Umapathy, Wang HY, et al: Lithium and valproic acid treatments reduce PKC activation and receptor-G protein coupling in platelets of bipolar manic patients. *J Psychiatr Res* 39(4):355-363, 2005 16044535
- Hajek T, Kopecek M, Höschl C, Alda M: Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis. *J Psychiatry Neurosci* 37(5):333-343, 2012 22498078
- Hajek T, Bauer M, Simhandl C, et al: Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. *Psychol Med* 44(3):507-517, 2014 23721695
- Heit S, Nemeroff CB: Lithium augmentation of antidepressants in treatment-refractory depression. *J Clin Psychiatry* 59 (suppl 6):28-33, discussion 34, 1998 9674934
- Helmuth D, Ljaljevic Z, Ramirez L, Meltzer HY: Choreoathetosis induced by verapamil and lithium treatment. *J Clin Psychopharmacol* 9(6):454-455, 1989 2512332
- Heninger GR, Charney DS, Sternberg DE: Lithium carbonate augmentation of antidepressant treatment. An effective prescription for treatment-refractory depression. *Arch Gen Psychiatry* 40(12):1335-1342, 1983 6418110
- Himmelhoch JM, Neil JF, May SJ, et al: Age, dementia, dyskinesias, and lithium response. *Am J Psychiatry* 137(8):941-945, 1980 7416295
- Ivkovic A, Stern TA: Lithium-induced neurotoxicity: clinical presentations, pathophysiology, and treatment. *Psychosomatics* 55(3):296-302, 2014 24388123

- Jablensky AV, Morgan V, Zubrick SR, et al: Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. *Am J Psychiatry* 162(1):79-91, 2005 15625205
- Jefferson JW: Lithium tremor and caffeine intake: two cases of drinking less and shaking more. *J Clin Psychiatry* 49(2):72-73, 1988 3338980
- Jefferson JW, Greist JH: *Primer of Lithium Therapy*. Baltimore, MD, Williams & Wilkins, 1977
- Jefferson JW, Greist JH, Ackerman DL: *Lithium Encyclopedia for Clinical Practice*. Washington, DC, American Psychiatric Press, 1983
- Jermain DM, Crismon ML, Martin ES 3rd: Population pharmacokinetics of lithium. *Clin Pharm* 10(5):376-381, 1991 2049899
- Joffe RT, Singer W, Levitt AJ, MacDonald C: A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry* 50(5):387-393, 1993 8489327
- Johnson G, Gershon S, Hekimian LJ: Controlled evaluation of lithium and chlorpromazine in the treatment of manic states: an interim report. *Compr Psychiatry* 9(6):563-573, 1968 4883428
- Johnson AG, Seideman P, Day RO: Adverse drug interactions with nonsteroidal anti-inflammatory drugs (NSAIDs). Recognition, management and avoidance. *Drug Saf* 8(2):99-127, 1993 8452660
- Kantor D, McNevin S, Leichner P, et al: The benefit of lithium carbonate adjunct in refractory depression—fact or fiction? *Can J Psychiatry* 31(5):416-418, 1986 3089576
- Karle J, Bjørndal F: [Serotonergic syndrome—in combination therapy with lithium and fluoxetine]. *Ugeskr Laeger* 157(9):1204-1205, 1995 7701669

- Katona CLE, Abou-Saleh MT, Harrison DA, et al: Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *Br J Psychiatry* 166(1):80-86, 1995 7894881
- Keck PE Jr, McElroy SL: Clinical pharmacodynamics and pharmacokinetics of antimanic and mood-stabilizing medications. *J Clin Psychiatry* 63 (suppl 4):3-11, 2002 11913673
- Keck PE Jr, Mendlwicz J, Calabrese JR, et al: A review of randomized, controlled clinical trials in acute mania. *J Affect Disord* 59 (suppl 1):S31-S37, 2000 11121825
- Keck PE Jr, Perlis RH, Otto MW, et al: The Expert Consensus Guideline Series: Treatment of bipolar disorder 2004. *Postgrad Med Special Report* (December):1-120, 2004
- Keck PE, Orsulak PJ, Cutler AJ, et al; CN138-135 Study Group: Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *J Affect Disord* 112(1-3):36-49, 2009 18835043
- Kessing LV, Forman JL, Andersen PK: Does lithium protect against dementia? *Bipolar Disord* 12(1):87-94, 2010 20148870
- Kilts CD: In vivo imaging of the pharmacodynamics and pharmacokinetics of lithium. *J Clin Psychiatry* 61 (suppl 9):41-46, 2000 10826660
- Kirov G: Thyroid disorders in lithium-treated patients. *J Affect Disord* 50(1):33-40, 1998 9716277
- Kishimoto A: The treatment of affective disorder with carbamazepine: prophylactic synergism of lithium and carbamazepine combination. *Prog Neuropsychopharmacol Biol Psychiatry* 16(4):483-493, 1992 1641493
- Klein PS, Melton DA: A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A* 93(16):8455-8459, 1996 8710892

- Kline NS: A narrative account of lithium usage in psychiatry, in *Lithium: Its Role in Psychiatric Research and Treatment*. Edited by Gershon S, Shopsin B. New York, Plenum, 1973, pp 5-24
- Köhler S, Unger T, Hoffmann S, et al: Comparing augmentation with non-antidepressants over sticking to antidepressants after treatment failure in depression: a naturalistic study. *Pharmacopsychiatry* 46(2):69-76, 2013 23093475
- Kowatch RA, Suppes T, Carmody TJ, et al: Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 39(6): 713-720, 2000 10846305
- Kulhara P, Basu D, Mattoo SK, et al: Lithium prophylaxis of recurrent bipolar affective disorder: long-term outcome and its psychosocial correlates. *J Affect Disord* 54(1-2):87-96, 1999 10403151
- Kupka RW, Luckenbaugh DA, Post RM, et al: Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. *J Clin Psychiatry* 64(12):1483-1494, 2003 14728111
- Kusalic M, Engelsmann F: Effect of lithium maintenance therapy on thyroid and parathyroid function. *J Psychiatry Neurosci* 24(3):227-233, 1999 10354657
- Kushner SF, Khan A, Lane R, Olson WH: Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord* 8(1):15-27, 2006 16411977
- Lan CC, Liu CC, Lin CH, et al: A reduced risk of stroke with lithium exposure in bipolar disorder: a population-based retrospective cohort study. *Bipolar Disord* 17(7):705-714, 2015 26394555
- Larsen ER, Damkier P, Pedersen LH, et al: Use of psychotropic drugs during pregnancy and breast-

- feeding. *Acta Psychiatr Scand Suppl* 132(445):1-28, 2015 26344706
- Lauterbach E, Felber W, Müller-Oerlinghausen B, et al: Adjunctive lithium treatment in the prevention of suicidal behaviour in depressive disorders: a randomised, placebo-controlled, 1-year trial. *Acta Psychiatr Scand* 118(6):469-479, 2008 18808400
- Lazarczyk MJ, Giannakopoulos P: Temporal association as a prerequisite factor of valsartan-induced lithium toxicity. *Bipolar Disord* 16(6):662-666, 2014 24372930
- Lee HC, Lin HC: Maternal bipolar disorder increased low birthweight and preterm births: a nationwide population-based study. *J Affect Disord* 121(1-2):100-105, 2010 19501914
- Lejoyeux M, Ades J, Rouillon F: Serotonin syndrome: incidence, symptoms and treatment. *CNS Drugs* 2:132-143, 1994
- Lemus CZ, Lieberman JA, Johns CA: Myoclonus during treatment with clozapine and lithium: the role of serotonin. *Hillside J Clin Psychiatry* 11(2):127-130, 1989 2488054
- Lenox RH, McNamara RK, Watterson JM, Watson DG: Myristoylated alanine-rich C kinase substrate (MARCKS): a molecular target for the therapeutic action of mood stabilizers in the brain? *J Clin Psychiatry* 57 (suppl 13):23-31, discussion 32-33, 1996 8970502
- Lepkifker E, Sverdlik A, Iancu I, et al: Renal insufficiency in long-term lithium treatment. *J Clin Psychiatry* 65(6):850-856, 2004 15291664
- Lerer B, Moore N, Meyendorff E, et al: Carbamazepine versus lithium in mania: a double-blind study. *J Clin Psychiatry* 48(3):89-93, 1987 3546274
- Levine J, Gonsalves M, Babur I, et al: Inositol 6 g daily may be effective in depression but not in schizophrenia. *Hum Psychopharmacol* 8(1):49-53, 1993



- Levine J, Barak Y, Gonzalves M, et al: Double-blind, controlled trial of inositol treatment of depression. *Am J Psychiatry* 152(5):792-794, 1995 7726322
- Lewitzka U, Severus E, Bauer R, et al: The suicide prevention effect of lithium: more than 20 years of evidence—a narrative review. *Int J Bipolar Disord* 3(1):32, 2015 26183461
- Li X, Friedman AB, Zhu W, et al: Lithium regulates glycogen synthase kinase-3 $\beta$  in human peripheral blood mononuclear cells: implication in the treatment of bipolar disorder. *Biol Psychiatry* 61(2):216-222, 2007 16806104
- Lombardi G, Panza N, Biondi B, et al: Effects of lithium treatment on hypothalamic-pituitary-thyroid axis: a longitudinal study. *J Endocrinol Invest* 16(4):259-263, 1993 8514981
- Madhusoodanan S, Brenner R, Suresh P, et al: Efficacy and tolerability of olanzapine in elderly patients with psychotic disorders: a prospective study. *Ann Clin Psychiatry* 12(1):11-18, 2000 10798821
- Maggs R: Treatment of manic illness with lithium carbonate. *Br J Psychiatry* 109:56-65, 1963
- Malhi GS, Tanious M: Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations. *CNS Drugs* 25(4):289-298, 2011 21425882
- Malhi GS, Tanious M, Das P, et al: Potential mechanisms of action of lithium in bipolar disorder. Current understanding. *CNS Drugs* 27(2):135-153, 2013 23371914
- Mani J, Tandel SV, Shah PU, Karnad DR: Prolonged neurological sequelae after combination treatment with lithium and antipsychotic drugs. *J Neurol Neurosurg Psychiatry* 60(3):350-351, 1996 8609524
- Mann SC, Greenstein RA, Eilers R: Early onset of severe dyskinesia following lithium-haloperidol treatment. *Am J*

- Psychiatry 140(10):1385–1386, 1983 6624983
- Markowitz GS, Radhakrishnan J, Kambham N, et al: Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol 11(8):1439–1448, 2000 10906157
- Martin CA, Piascik MT: First degree A-V block in patients on lithium carbonate. Can J Psychiatry 30(2):114–116, 1985 3922608
- Massot O, Rousselle JC, Fillion MP, et al: 5-HT<sub>1B</sub> receptors: a novel target for lithium. Possible involvement in mood disorders. Neuropsychopharmacology 21(4): 530–541, 1999 10481837
- McCrea RL, Nazareth I, Evans SJ, et al: Lithium prescribing during pregnancy: a UK primary care database study. PLoS ONE 10(3):e0121024, 2015 25793580
- McKnight RF, Adida M, Budge K, et al: Lithium toxicity profile: a systematic review and meta-analysis. Lancet 379(9817):721–728, 2012 22265699
- Mekler G, Woggon B: A case of serotonin syndrome caused by venlafaxine and lithium. Pharmacopsychiatry 30(6):272–273, 1997 9442552
- Mendels J: Lithium in the treatment of depressive states, in Lithium Research and Therapy. Edited by Johnson FN. New York, Academic Press, 1975, pp 43–62
- Miller F, Menninger J, Whitcup SM: Lithium-neuroleptic neurotoxicity in the elderly bipolar patient. J Clin Psychopharmacol 6(3):176–178, 1986 2872237
- Mirsepasi Z, Mazinani R, Fadaei F, et al: Topiramate add-on lithium carbonate for treatment of acute mania. Iran J Psychiatry Behav Sci 7(2):11–15, 2013 24644505
- Mitchell JE, Mackenzie TB: Cardiac effects of lithium therapy in man: a review. J Clin Psychiatry 43(2):47–51, 1982 7056703
- Modell JG, Lenox RH, Weiner S: Inpatient clinical trial of lorazepam for the management of manic agitation. J Clin Psychopharmacol 5(2):109–113, 1985 3988969

- Mohammadianinejad SE, Majdinasab N, Sajedi SA, et al: The effect of lithium in post-stroke motor recovery: a double-blind, placebo-controlled, randomized clinical trial. *Clin Neuropharmacol* 37(3):73-78, 2014 24824661
- Monti JM, Monti D, Jantos H, Ponzoni A: Effects of selective activation of the 5-HT<sub>1B</sub> receptor with CP-94,253 on sleep and wakefulness in the rat. *Neuropharmacology* 34(12):1647-1651, 1995 8788962
- Moore GJ, Bebchuk JM, Parrish JK, et al: Temporal dissociation between lithium-induced changes in frontal lobe myo-inositol and clinical response in manic-depressive illness. *Am J Psychiatry* 156(12):1902-1908, 1999 10588403
- Moore GJ, Bebchuk JM, Wilds IB, et al: Lithium-induced increase in human brain grey matter. *Lancet* 356(9237):1241-1242, 2000 11072948
- Muly EC, McDonald W, Steffens D, Book S: Serotonin syndrome produced by a combination of fluoxetine and lithium. *Am J Psychiatry* 150(10):1565, 1993 8379573
- Netto I, Phutane VH: Reversible lithium neurotoxicity: review of the literature. *Prim Care Companion CNS Disord* 14(1), 2012 22690368
- Newport DJ, Viguera AC, Beach AJ, et al: Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. *Am J Psychiatry* 162(11):2162-2170, 2005 16263858
- Nierenberg AA, Fava M, Trivedi MH, et al: A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR\*D report. *Am J Psychiatry* 163(9):1519-1530, quiz 1665, 2006 16946176
- Nierenberg AA, Friedman ES, Bowden CL, et al: Lithium treatment moderate-dose use study (LiTMUS) for bipolar disorder: a randomized comparative effectiveness trial of optimized personalized treatment with and without

lithium. Am J Psychiatry 170(1):102-110, 2013  
23288387

Nierenberg AA, McElroy SL, Friedman ES, et al: Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. J Clin Psychiatry 77(1):90-99, 2016 26845264

Niufan G, Tohen M, Qiuqing A, et al: Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. J Affect Disord 105(1-3):101-108, 2008 17531327

Nolen WA, Weisler RH: The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). Bipolar Disord 15(1):100-109, 2013 23228201

Noyes R Jr, Dempsey GM, Blum A, Cavanaugh GL: Lithium treatment of depression. Compr Psychiatry 15(3):187-193, 1974 4826041

Oakley PW, Whyte IM, Carter GL: Lithium toxicity: an iatrogenic problem in susceptible individuals. Aust N Z J Psychiatry 35(6):833-840, 2001 11990895

Ohman R, Spigset O: Serotonin syndrome induced by fluvoxamine-lithium interaction. Pharmacopsychiatry 26(6):263-264, 1993 8127934

Okuma T, Yamashita I, Takahashi R, et al. Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study. Pharmacopsychiatry 23(3):143-150, 1990 1973844

Patel NC, DelBello MP, Bryan HS, et al: Open-label lithium for the treatment of adolescents with bipolar depression. J Am Acad Child Adolesc Psychiatry 45:289-297, 2006 16540813

Perényi A, Rihmer Z, Bánki CM: Parkinsonian symptoms with lithium, lithium-neuroleptic, and lithium-

- antidepressant treatment. *J Affect Disord* 5(2):171-177, 1983 6133888
- Perényi A, Szücs R, Frecska E: Tardive dyskinesia in patients receiving lithium maintenance therapy. *Biol Psychiatry* 19(11): 1573-1578, 1984 6151403
- Perlis RH, Sachs GS, Lafer B, et al: Effect of abrupt change from standard to low serum levels of lithium: a reanalysis of double-blind lithium maintenance data. *Am J Psychiatry* 159(7):1155-1159, 2002 12091193
- Peterson GA, Byrd SL: Diabetic ketoacidosis from clozapine and lithium cotreatment. *Am J Psychiatry* 153(5):737-738, 1996 8615434
- Phiel CJ, Klein PS: Molecular targets of lithium action. *Annu Rev Pharmacol Toxicol* 41:789-813, 2001 11264477
- Phiel CJ, Wilson CA, Lee VM, Klein PS: GSK-3 $\alpha$  regulates production of Alzheimer's disease amyloid-beta peptides. *Nature* 423(6938):435-439, 2003 12761548
- Poolsup N, Li Wan Po A, de Oliveira IR: Systematic overview of lithium treatment in acute mania. *J Clin Pharm Ther* 25(2): 139-156, 2000 10849192
- Pope HG Jr, Cole JO, Choras PT, Fulwiler CE: Apparent neuroleptic malignant syndrome with clozapine and lithium. *J Nerv Ment Dis* 174(8):493-495, 1986 3090198
- Popovic D, Reinares M, Goikolea JM, et al: Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. *Eur Neuropsychopharmacol* 22(5):339-346, 2012 22000157
- Potkin SG, Thyrum PT, Bera R, et al: Open-label study of the effect of combination quetiapine/lithium therapy on lithium pharmacokinetics and tolerability. *Clin Ther* 24(11):1809-1823, 2002 12501876
- Presne C, Fakhouri F, Noël LH, et al: Lithium-induced nephropathy: Rate of progression and prognostic factors. *Kidney Int* 64(2):585-592, 2003 12846754

- Price LH, Charney DS, Heninger GR: Variability of response to lithium augmentation in refractory depression. *Am J Psychiatry* 143(11):1387-1392, 1986 3096155
- Price LH, Charney DS, Delgado PL, Heninger GR: Lithium and serotonin function: implications for the serotonin hypothesis of depression. *Psychopharmacology (Berl)* 100(1):3-12, 1990 2404294
- Prien RF, Caffey EM Jr, Klett CJ: Comparison of lithium carbonate and chlorpromazine in the treatment of mania. Report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. *Arch Gen Psychiatry* 26(2):146-153, 1972 4551257
- Prien RF, Caffey EM Jr, Klett CJ: Prophylactic efficacy of lithium carbonate in manic-depressive illness. Report of the Veterans Administration and National Institute of Mental Health collaborative study group. *Arch Gen Psychiatry* 28(3):337-341, 1973 4569674
- Quiroz JA, Machado-Vieira R, Zarate CA Jr, Manji HK: Novel insights into lithium's mechanism of action: neurotrophic and neuroprotective effects. *Neuropsychobiology* 62(1):50-60, 2010 20453535
- Reeves RR, Struve FA, Patrick G: Does EEG predict response to valproate versus lithium in patients with mania? *Ann Clin Psychiatry* 13(2):69-73, 2001 11534927
- Reimers A, Skogvoll E, Sund JK, Spigset O: Drug interactions between lamotrigine and psychoactive drugs: evidence from a therapeutic drug monitoring service. *J Clin Psychopharmacol* 25(4):342-348, 2005 16012277
- Rej S, Beaulieu S, Segal M, et al: Lithium dosing and serum concentrations across the age spectrum: from early adulthood to the tenth decade of life. *Drugs Aging* 31(12):911-916, 2014a 25331906
- Rej S, Shulman K, Herrmann N, et al: Prevalence and correlates of renal disease in older lithium users: a

- population-based study. *Am J Geriatr Psychiatry* 22(11): 1075–1082, 2014b 24566239
- Rej S, Yu C, Shulman K, et al: Medical comorbidity, acute medical care use in late-life bipolar disorder: a comparison of lithium, valproate, and other pharmacotherapies. *Gen Hosp Psychiatry* 37(6):528–532, 2015 26254672
- Roose SP, Nurnberger JI, Dunner DL, et al: Cardiac sinus node dysfunction during lithium treatment. *Am J Psychiatry* 136(6):804–806, 1979 443464
- Rosenqvist M, Bergfeldt L, Aili H, Mathé AA: Sinus node dysfunction during long-term lithium treatment. *Br Heart J* 70(4): 371–375, 1993 8217448
- Ryan ND, Bhatara VS, Perel JM: Mood stabilizers in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 38(5):529–536, 1999 10230184
- Sachs GS, Rosenbaum JF, Jones L: Adjunctive clonazepam for maintenance treatment of bipolar affective disorder. *J Clin Psychopharmacol* 10(1):42–47, 1990a 2106533
- Sachs GS, Weilburg JB, Rosenbaum JF: Clonazepam vs. neuroleptics as adjuncts to lithium maintenance. *Psychopharmacol Bull* 26(1):137–143, 1990b 1973545
- Sachs GS, Vanderburg DG, Edman S, et al: Adjunctive oral ziprasidone in patients with acute mania treated with lithium or divalproex, part 2: influence of protocol-specific eligibility criteria on signal detection. *J Clin Psychiatry* 73(11):1420–1425, 2012a 23218158
- Sachs GS, Vanderburg DG, Karayal ON, et al: Adjunctive oral ziprasidone in patients with acute mania treated with lithium or divalproex, part 1: results of a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 73(11):1412–1419, 2012b 23218157
- Sachs HC; Committee On Drugs: The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics* 132(3):e796–e809, 2013 23979084

- Sanger TM, Grundy SL, Gibson PJ, et al: Long-term olanzapine therapy in the treatment of bipolar I disorder: an open-label continuation phase study. *J Clin Psychiatry* 62(4):273-281, 2001 11379842
- Saunders BD, Saunders EF, Gauger PG: Lithium therapy and hyperparathyroidism: an evidence-based assessment. *World J Surg* 33(11):2314-2323, 2009 19252941
- Schaffer A, Isometsä ET, Tondo L, et al: Epidemiology, neurobiology and pharmacological interventions related to suicide deaths and suicide attempts in bipolar disorder: Part I of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. *Aust N Z J Psychiatry* 49(9):785-802, 2015 26185269
- Schildkraut JJ, Logue MA, Dodge GA: The effects of lithium salts on the turnover and metabolism of norepinephrine in rat brain. *Psychopharmacology (Berl)* 14(2): 135-141, 1969 5350622
- Schöpf J, Baumann P, Lemarchand T, Rey M: Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition. Results of a placebo-controlled double-blind study. *Pharmacopsychiatry* 22(5):183-187, 1989 2682692
- Schou M: The effect of prophylactic lithium treatment on mortality and suicidal behavior: a review for clinicians. *J Affect Disord* 50(2-3):253-259, 1998 9858084
- Schou M, Juel-Nielsen N, Stromgren E, Voldby H: The treatment of manic psychoses by the administration of lithium salts. *J Neurol Neurosurg Psychiatry* 17(4):250-260, 1954 13212414
- Schüle C, Baghai TC, Eser D, et al: Lithium but not carbamazepine augments antidepressant efficacy of mirtazapine in unipolar depression: an open-label study. *World J Biol Psychiatry* 10(4 Pt 2):390-399, 2009 18609420



- Segal J, Berk M, Brook S: Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clin Neuropharmacol* 21(3):176-180, 1998 9617509
- Selle V, Schalkwijk S, Vázquez GH, Baldessarini RJ: Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. *Pharmacopsychiatry* 47(2):43-52, 2014 24549862
- Severus WE, Lipkovich IA, Licht RW, et al: In search of optimal lithium levels and olanzapine doses in the long-term treatment of bipolar I disorder. A post-hoc analysis of the maintenance study by Tohen et al. 2005. *Eur Psychiatry* 25(8):443-449, 2010 20430594
- Shahani L: Venlafaxine augmentation with lithium leading to serotonin syndrome. *J Neuropsychiatry Clin Neurosci* 24(3):E47, 2012 23037683
- Shaldubina A, Agam G, Belmaker RH: The mechanism of lithium action: state of the art, ten years later. *Prog Neuropsychopharmacol Biol Psychiatry* 25(4):855-866, 2001 11383981
- Shao L, Young LT, Wang JF: Chronic treatment with mood stabilizers lithium and valproate prevents excitotoxicity by inhibiting oxidative stress in rat cerebral cortical cells. *Biol Psychiatry* 58(11):879-884, 2005 16005436
- Shine B, McKnight RF, Leaver L, Geddes JR: Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet* 386(9992):461-468, 2015 26003379
- Shopsin B, Gershon S, Thompson H, Collins P: Psychoactive drugs in mania. A controlled comparison of lithium carbonate, chlorpromazine, and haloperidol. *Arch Gen Psychiatry* 32(1):34-42, 1975 1089401
- Shukla S, Godwin CD, Long LEB, Miller MG: Lithium-carbamazepine neurotoxicity and risk factors. *Am J Psychiatry* 141(12): 1604-1606, 1984 6439058

- Shukla S, Cook BL, Miller MG: Lithium-carbamazepine versus lithium-neuroleptic prophylaxis in bipolar illness. *J Affect Disord* 9(3):219-222, 1985 2867109
- Sipes TE, Geyer MA: Functional behavioral homology between rat 5-HT1B and guinea pig 5-HT1D receptors in the modulation of prepulse inhibition of startle. *Psychopharmacology (Berl)* 125(3):231-237, 1996 8815958
- Small JG, Klapper MH, Milstein V, et al: Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry* 48(10):915-921, 1991 1929761
- Small JG, Klapper MH, Marhenke JD, et al: Lithium combined with carbamazepine or haloperidol in the treatment of mania. *Psychopharmacol Bull* 31(2):265-272, 1995 7491378
- Smith LA, Cornelius V, Warnock A, et al: Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. *Bipolar Disord* 9(6):551-560, 2007 17845269
- Soares JC, Boada F, Spencer S, et al: Brain lithium concentrations in bipolar disorder patients: preliminary (7)Li magnetic resonance studies at 3 T. *Biol Psychiatry* 49(5):437-443, 2001 11274655
- Sobanski T, Bagli M, Laux G, Rao ML: Serotonin syndrome after lithium add-on medication to paroxetine. *Pharmacopsychiatry* 30(3):106-107, 1997 9211572
- Spring GK: Neurotoxicity with combined use of lithium and thioridazine. *J Clin Psychiatry* 40(3):135-138, 1979 106047
- Spring G, Frankel M: New data on lithium and haloperidol incompatibility. *Am J Psychiatry* 138(6):818-821, 1981 6113770
- Spring G, Schweid D, Gray C, et al: A double-blind comparison of lithium and chlorpromazine in the treatment of manic states. *Am J Psychiatry* 126(9):1306-1310, 1970 4905019

- Steckler TL: Lithium- and carbamazepine-associated sinus node dysfunction: nine-year experience in a psychiatric hospital. *J Clin Psychopharmacol* 14(5):336-339, 1994 7806689
- Stein G, Bernadt M: Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. *Br J Psychiatry* 162: 634-640, 1993 8149115
- Stern DN, Fieve RR, Neff NH, Costa E: The effect of lithium chloride administration on brain and heart norepinephrine turnover rates. *Psychopharmacology (Berl)* 14(4):315-322, 1969 5350631
- Stokes PE, Shamoian CA, Stoll PM, Patton MJ: Efficacy of lithium as acute treatment of manic-depressive illness. *Lancet* 1(7713):1319-1325, 1971 4103395
- Stoll AL, Locke CA, Vuckovic A, Mayer PV: Lithium-associated cognitive and functional deficits reduced by a switch to divalproex sodium: a case series. *J Clin Psychiatry* 57(8):356-359, 1996 8752018
- Stone KA: Lithium-induced nephrogenic diabetes insipidus. *J Am Board Fam Pract* 12(1):43-47, 1999 10050642
- Stoudemire A, Moran MG, Fogel BS: Psychotropic drug use in the medically ill: Part I. *Psychosomatics* 31(4):377-391, 1990 2247565
- Su Y, Ryder J, Li B, et al: Lithium, a common drug for bipolar disorder treatment, regulates amyloid-beta precursor protein processing. *Biochemistry* 43(22):6899-6908, 2004 15170327
- Sugawara H, Sakamoto K, Harada T, Ishigooka J: Predictors of efficacy in lithium augmentation for treatment-resistant depression. *J Affect Disord* 125(1-3):165-168, 2010 20089312
- Swann AC, Bowden CL, Morris D, et al: Depression during mania. Treatment response to lithium or divalproex. *Arch Gen Psychiatry* 54(1):37-42, 1997 9006398

- Swanson CL Jr, Price WA, McEvoy JP: Effects of concomitant risperidone and lithium treatment (letter). *Am J Psychiatry* 152(7): 1096, 1995 7540798
- Tajes M, Yeste-Velasco M, Zhu X, et al: Activation of Akt by lithium: pro-survival pathways in aging. *Mech Ageing Dev* 130(4):253-261, 2009 19162061
- Takahashi R, Sakuma A, Itoh K, et al: Comparison of efficacy of lithium carbonate and chlorpromazine in mania. Report of collaborative study group on treatment of mania in Japan. *Arch Gen Psychiatry* 32(10):1310-1318, 1975 1101844
- Tilkian AG, Schroeder JS, Kao JJ, Hultgren HN: The cardiovascular effects of lithium in man. A review of the literature. *Am J Med* 61(5):665-670, 1976 790953
- Toffol E, Hätönen T, Tanskanen A, et al: Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: a nationwide registry-based prospective cohort study. *J Affect Disord* 183:159-165, 2015 26005778
- Tohen M, Zarate CA Jr, Centorrino F, et al: Risperidone in the treatment of mania. *J Clin Psychiatry* 57(6):249-253, 1996 8666562
- Tohen M, Greil W, Calabrese JR, et al: Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry* 162(7):1281-1290, 2005 15994710
- Tondo L, Jamison KR, Baldessarini RJ: Effect of lithium maintenance on suicidal behavior in major mood disorders. *Ann N Y Acad Sci* 836:339-351, 1997 9616808
- Tondo L, Baldessarini RJ, Hennen J, Floris G: Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. *Am J Psychiatry* 155(5): 638-645, 1998 9585715

- Tondo L, Hennen J, Baldessarini RJ: Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. *Acta Psychiatr Scand* 104(3): 163-172, 2001 11531653
- Tredget J, Kirov A, Kirov G: Effects of chronic lithium treatment on renal function. *J Affect Disord* 126(3):436-440, 2010 20483164
- Tsaltas E, Kontis D, Boulougouris V, et al: Enhancing effects of chronic lithium on memory in the rat. *Behav Brain Res* 177(1):51-60, 2007 17141335
- Vieta E, T'joen C, McQuade RD, et al: Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *Am J Psychiatry* 165(10):1316-1325, 2008 18381903
- Viguera AC, Nonacs R, Cohen LS, et al: Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. *Am J Psychiatry* 157(2):179-184, 2000 10671384
- Viguera AC, Newport DJ, Ritchie J, et al: Lithium in breast milk and nursing infants: clinical implications. *Am J Psychiatry* 164(2):342-345, 2007a 17267800
- Viguera AC, Whitfield T, Baldessarini RJ, et al: Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry* 164(12):1817-1824, quiz 1923, 2007b 18056236
- Vita A, De Peri L, Sacchetti E: Lithium in drinking water and suicide prevention: a review of the evidence. *Int Clin Psychopharmacol* 30(1):1-5, 2015 25025988
- Vollmer KO, von Hodenberg A, Kölle EU: Pharmacokinetics and metabolism of gabapentin in rat, dog and man. *Arzneimittelforschung* 36(5):830-839, 1986 3730018
- Ward ME, Musa MN, Bailey L: Clinical pharmacokinetics of lithium. *J Clin Pharmacol* 34(4):280-285, 1994 8006194

- Wehr TA, Sack DA, Rosenthal NE, Cowdry RW: Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. *Am J Psychiatry* 145(2):179-184, 1988 3341463
- Weisler RH, Nolen WA, Neijber A, et al; Trial 144 Study Investigators: Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). *J Clin Psychiatry* 72(11):1452-1464, 2011 22054050
- Williams RS, Harwood AJ: Lithium therapy and signal transduction. *Trends Pharmacol Sci* 21(2):61-64, 2000 10664610
- Wright BA, Jarrett DB: Lithium and calcium channel blockers: possible neurotoxicity. *Biol Psychiatry* 30(6):635-636, 1991 1932412
- Yildiz A, Vieta E, Leucht S, Baldessarini RJ: Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology* 36(2):375-389, 2011 20980991
- Yoshida S, Maeda M, Kaku S, et al: Lithium inhibits stress-induced changes in tau phosphorylation in the mouse hippocampus. *J Neural Transm (Vienna)* 113(11):1803-1814, 2006 16855914
- Young AH, McElroy SL, Bauer M, et al; EMBOLDEN I (Trial 001) Investigators: A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 71(2):150-162, 2010 20122369
- Zarate CA, Manji HK: Protein kinase C inhibitors: rationale for use and potential in the treatment of bipolar disorder. *CNS Drugs* 23(7):569-582, 2009 19552485
- Zusky PM, Biederman J, Rosenbaum JF, et al: Adjunct low dose lithium carbonate in treatment-resistant depression: a placebo-controlled study. *J Clin Psychopharmacol* 8(2):120-124, 1988 3131389

# CHAPTER 37

## Valproate

Charles L. Bowden, M.D.

---

### History and Discovery

---

Valproate was the first mood stabilizer to be studied as an alternative to lithium ([Lambert et al. 1966](#)). An enteric-coated formulation, divalproex sodium, was approved in the United States for the treatment of mania in 1995. An extended-release (ER) formulation of divalproex was approved for migraine in 2001 and for mania in 2006. Valproate, either as divalproex or as other formulations, is now approved worldwide for the treatment of mania.

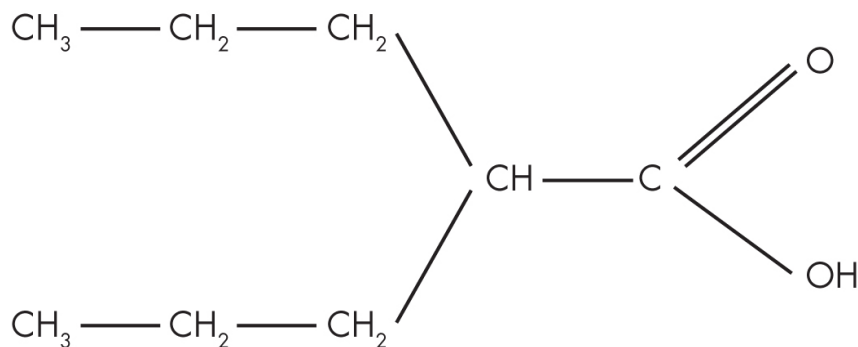
---

### Pharmacological Profile

---

Valproic acid (dipropylacetic acid; [Figure 37-1](#)) is an eight-carbon, branched-chain carboxylic acid that is structurally distinct from other antiepileptic and psychotropic compounds ([Bocci and Beretta 1976](#); [Levy 1984](#)). Its three-

dimensional structure overlays that of naturally occurring fatty acids (e.g., oleic and linolenic acids). Valproate binds in a saturable manner to the neuronal membrane sites to which these longer-chain fatty acids attach. Some of valproate's molecular mechanisms are likely a consequence of this physiochemical property.



---

**FIGURE 37-1.** Chemical structure of valproic acid.

---

## Pharmacokinetics and Disposition

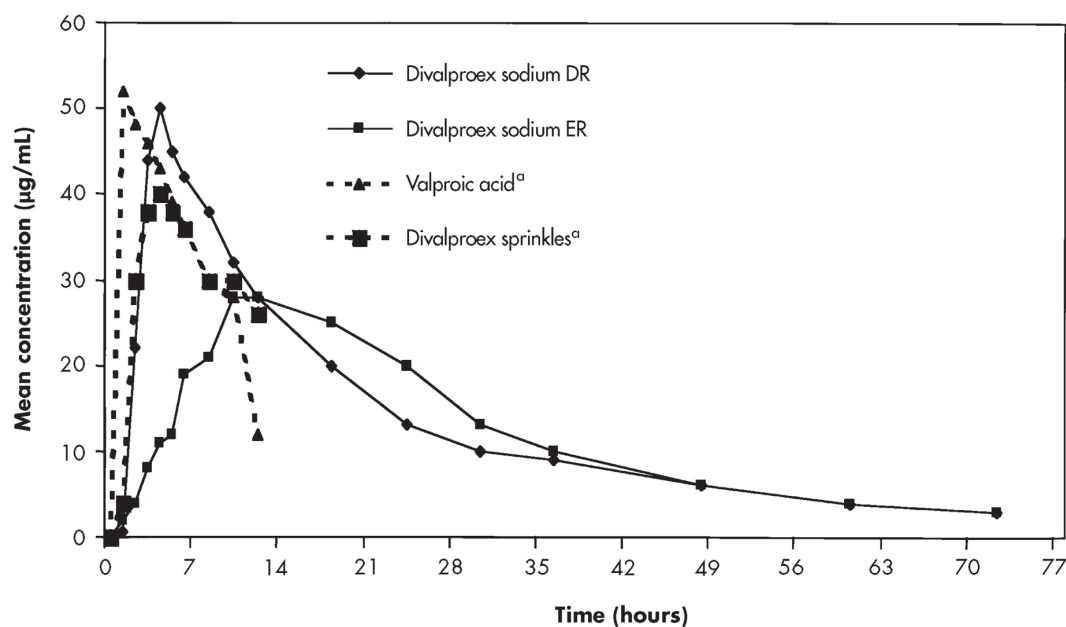
---

Valproate is commercially available in the United States in five oral preparations: 1) divalproex sodium, an enteric-coated, stable-coordination compound containing equal proportions of valproic acid and sodium valproate in a 1:1 molar ratio; 2) valproic acid; 3) sodium valproate; 4) divalproex sodium sprinkle capsule (containing coated particles of divalproex sodium), which can be ingested intact or pulled apart and contents sprinkled on food; and 5) an extended-release form of divalproex that provides once-daily dosing and a substantially flatter peak-to-trough ratio. Sodium valproate is available for intravenous use and,



as such, has been demonstrated to provide reduction in manic symptoms within 1 day or less (Grunze et al. 1999). Valproate can also be compounded in suppository form for rectal administration. The valproate ion is the common compound in plasma.

The bioavailability of valproate approaches 100% with all preparations (Wilder 1992). With the exception of divalproex sodium, all preparations taken orally are rapidly absorbed. Sodium valproate and valproic acid attain peak serum concentrations within 2 hours. Divalproex sodium reaches peak serum concentrations within 3–8 hours. The ER form of divalproex sodium has an earlier onset of absorption than the regular-release tablets and approximately a 20% smaller difference in trough and peak serum levels than regular-release divalproex (Figure 37-2).



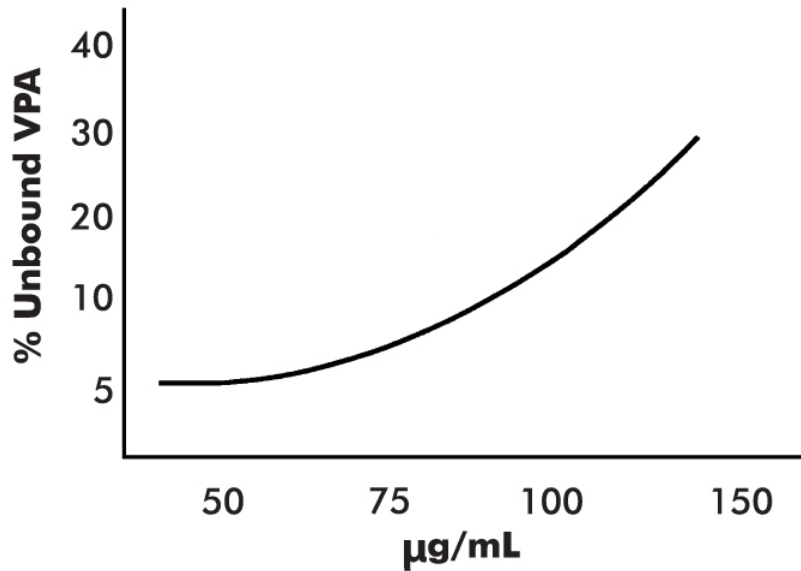
**FIGURE 37-2.** Mean plasma valproate concentrations with different formulations.

DR=delayed-release; ER=extended-release.

<sup>a</sup>Data derived from different studies after 500-mg doses.

*Source.* Abbott Laboratories, data on file.

Valproate is highly protein bound, predominantly to serum albumin and proportional to the albumin concentration. Although patients with low levels of albumin have a higher fraction of unbound drug, the steady-state level of total drug is not altered. Only the unbound drug crosses the blood-brain barrier and is bioactive. Thus, when valproate is displaced from protein-binding sites through drug interactions, the total drug concentration may not change; however, the pharmacologically active unbound drug does increase and may produce signs and symptoms of toxicity. Moreover, when the plasma concentration of valproate rises in response to dosage increases, the amount of unbound (active) valproate increases disproportionately and is metabolized, with an apparent increase in clearance of total drug, yielding lower-than-expected total plasma concentrations ([Levy 1984](#); [Wilder 1992](#)) ([Figure 37-3](#)). In addition, protein binding of valproate is increased by low-fat diets and decreased by high-fat diets. Because of lower serum protein levels, women and elderly patients will generally have a higher proportion of the active free moiety.



**FIGURE 37-3.** Total valproate (VPA) concentrations in the presence of.

As the total concentration of VPA increases, protein-binding sites become saturated, and the percentage of unbound to bound VPA increases.

*Source.* Reprinted from Wilder BJ: "Pharmacokinetics of Valproate and Carbamazepine." *Journal of Clinical Psychopharmacology* 12 (1, suppl):64S-68S, 1992. Copyright © 1992, Williams & Wilkins. Used with permission.

The concentration range required for good clinical effect in mania is approximately 45–125 µg/mL ([Bowden et al. 1996](#)). Patients who are able to tolerate higher serum levels—up to around 125 µg/mL—may experience greater improvement ([Allen et al. 2006](#)). An open report suggested that individuals with rapid cycling in the context of bipolar II disorder or cyclothymic disorder may respond to serum valproate concentrations of less than 50 µg/mL ([Jacobsen 1993](#)). In maintenance treatment, patients whose serum valproate levels were maintained between 75 and 99 µg/mL

had superior outcomes compared with patients whose serum levels were either lower or higher than this range ([Keck et al. 2005](#)). Valproate is metabolized in the liver, primarily through glucuronidation.

When used for the treatment of bipolar disorder, valproate is usually begun at a dosage of 15–20 mg/kg/day. The drug can be “orally loaded” at 20–30 mg/kg/day in patients with acute mania to induce a more rapid response. The dosage of valproate is increased according to the patient’s response and tolerance of side effects, usually by 250–500 mg/day every 1–3 days, to serum concentrations of 45–125 µg/mL. Of note, sedation, increased appetite, and reductions in white blood cell counts and platelet counts all become more frequent at serum concentrations greater than 100 µg/mL ([Bowden et al. 2000](#)).

---

## Mechanism of Action

---

Valproate stimulates extracellular signal-regulated kinase (ERK) and indirectly inhibits glycogen synthase kinase 3 (GSK-3) ([Cournoyer and Desrosiers 2009](#)). Valproate also stimulates the activity of bcl-2, a neuroprotective substance ([Gray et al. 2003](#)). Valproate inhibits histone deacetylase, and many of the drug’s subcellular effects (e.g., increasing brain-derived neurotrophic factor) are likely a consequence of this action ([Harwood and Agam 2003](#); [Perova et al. 2010](#)).

---

## Indications and Efficacy

---

# Acute Mania in Bipolar Disorder

In a placebo-controlled study, patients with more severe manic symptoms experienced greater benefits from valproate versus placebo than did patients with milder manic symptomatology ([Bowden et al. 2006](#)). In this study, the antimanic response to valproate occurred as early as 5 days following initiation of treatment.

Valproate has been studied in adjunctive regimens with various antipsychotics, with findings consistently pointing to greater efficacy for combination treatment than for monotherapy ([Bowden 2011](#); [Marcus et al. 2011](#); [Müller-Oerlinghausen et al. 2000](#); [Tohen et al. 2002](#); [Yatham et al. 2003](#)). A 3-week double-blind, placebo-controlled study ([Sachs et al. 2002](#)) evaluated the efficacy of risperidone or haloperidol in combination with a mood stabilizer in two groups of bipolar patients: 1) patients who had received treatment with either valproate or lithium at an adequate dosage for at least 2 weeks and were still manic (in which case they were randomly assigned to add-on treatment with risperidone, haloperidol, or placebo) and 2) patients who were manic but had not yet received mood stabilizer treatment (in which case either lithium or valproate was started concurrently with randomization to the add-on treatment). Patients who started mood stabilizer treatment on entering the study showed no advantage from the add-on antipsychotic, whereas patients who were already receiving valproate or lithium but were still symptomatic at study entry *did* demonstrate an advantage from the combination treatment ([Sachs et al. 2002](#)). These findings suggest that in most circumstances, combination therapy is most effective in—and should be limited to—patients whose

symptoms have not responded to a relatively short period of adequate monotherapy treatment.

Few studies of any antimanic agent have addressed its effectiveness in hypomanic episodes, which are more common than manic episodes, even in diagnostically bipolar I patients. In an 8-week randomized, double-blind, placebo-controlled study in outpatients with bipolar and related disorders manifesting hypomanic symptomatology (operationalized as a Young Mania Rating Scale (YMRS) score between 10 and 20), divalproex ER was significantly more effective than placebo in reducing hypomanic/mild manic symptoms ( $P=0.024$ ) and nonsignificantly more effective than placebo in improving depression ([McElroy et al. 2010](#)).

## Acute Depression in Bipolar Disorder

An 8-week randomized, placebo-controlled, blinded study reported that divalproex-treated subjects experienced significantly greater improvement than placebo-treated patients in both depressive and anxious symptomatology, based on Hamilton Rating Scale for Depression (Ham-D) and Hamilton Anxiety Scale (Ham-A) scores ([Davis et al. 2005](#)).

In a 6-week randomized, blinded study in bipolar depression, divalproex was superior to placebo, with primary improvement noted on core mood symptoms rather than on anxiety or insomnia ([Ghaemi et al. 2007](#)). [Smith et al. \(2010\)](#) conducted a meta-analysis of these and two other small randomized, blinded studies in acute bipolar depression and found significant reductions in depression scale scores for valproate compared with placebo

(standardized mean difference:  $-0.35$ ; range:  $-0.69$  to  $-0.02$ ). Tolerability was good, but improvement of anxiety was modest and not significant. Valproate also has shown significant prophylactic benefit in reducing risk of relapse to depression, both as monotherapy and as an adjunct to selective serotonin reuptake inhibitor (SSRI) treatment. In a 1-year randomized, double-blind study of bipolar patients who were initially manic, divalproex was more effective than lithium or placebo in delaying time to clinical depression ([Gyulai et al. 2003](#)). In those subjects who developed depression, divalproex augmented with either paroxetine or sertraline was superior to either antidepressant alone in treatment of the depression ([Gyulai et al. 2003](#)). [Ketter et al. \(2011\)](#) calculated a number needed to treat (NNT) of 11 for divalproex in prevention of bipolar depression; by comparison, an NNT of 49 was calculated for lithium, 15 for lamotrigine, 12 for olanzapine, and 64 for aripiprazole ([Ketter et al. 2011](#)).

## Maintenance Treatment of Bipolar Disorder

One large double-blind, placebo-controlled maintenance study of valproate monotherapy has been published ([Bowden et al. 2000](#)). Patients who recovered with open treatment with either divalproex or lithium were randomly assigned to maintenance treatment with divalproex, lithium, or placebo. The divalproex group did not differ significantly from the placebo group on time to any mood episode ( $P=0.06$ ), in part because the rate of relapse to mania with placebo was lower than anticipated. However, a post hoc analysis of the study data found that divalproex

was superior to placebo on secondary outcome measures, with lower rates of discontinuation for either any recurrent mood episode or a depressive episode ([Bowden 2004](#)). Divalproex was superior to lithium on some comparisons, including longer duration of successful prophylaxis in the study and less deterioration in depressive symptom scores. Among the subset of patients who received divalproex in the open acute phase, those randomly assigned to receive divalproex in the double-blind maintenance phase had significantly longer times to recurrence of any mood episode ( $P=0.05$ ) or a depressive episode ( $P=0.03$ ), and the proportion of patients who completed the 1-year study without developing either a manic or a depressive episode was significantly higher for divalproex-treated patients than for placebo-treated patients (41% vs. 13%;  $P=0.01$ ) ([Bowden et al. 2000](#)). This study ([Bowden et al. 2000](#)) is the only investigation published to date that has allowed a statistical test of the relation between acute-episode response to treatment and maintenance treatment outcomes. A post hoc review of the study that used relative risk analysis found that patients taking divalproex were significantly less likely than those taking placebo to have prematurely left the study because of a mood episode (relative risk [RR]=0.63; 95% confidence interval [CI]=0.44-0.90) ([Bowden 2004](#)). A post hoc analysis of time to any mood episode or early discontinuation for any reason, a measure of effectiveness that has been incorporated in more recent maintenance studies in bipolar disorder, indicated a significant advantage for divalproex over lithium ( $P>0.004$ ) ([Bowden 2003a](#)).

A comparison of valproate and lithium in a randomized, blinded trial of rapid-cycling patients reported that only one-quarter of the patients enrolled met criteria for an



acute bimodal response to either drug, with fewer than 25% of the patients who entered the randomized maintenance phase retaining benefit without relapse for the entire 20-month period. These findings indicate that monotherapy regimens with either valproate or lithium are unlikely to be effective in more than a small minority of rapid-cycling patients ([Calabrese et al. 2005](#)).

Additional evidence of the low likelihood of maintaining remission comes from a study of bipolar patients with a recently remitted manic episode who were followed up for 6 months of continuation valproate or lithium plus adjunctive therapy consisting of random assignment to either olanzapine or risperidone. The adjunctive therapy reduced the proportion relapsed among patients randomized to olanzapine, but not among patients randomized to risperidone ([Yatham et al. 2016](#)). In a systematic review and meta-analysis of randomized controlled maintenance treatment studies in bipolar disorder, lithium plus valproate seemed to be more effective in preventing manic episodes than in preventing depressive episodes. Lamotrigine appeared to be more protective against depressive episodes. The analyses suggested that the combination was likely to be superior to either drug alone ([Miura et al. 2014](#)).

Older adults with bipolar disorder have high rates of hospitalization for medical conditions. In a large cohort study of bipolar patients ages 66 years or older who had recently been discharged from a psychiatric hospitalization, 1-year rates of acute medical, nonpsychiatric health use did not differ according to which medication—lithium, valproate, or another agent (e.g., antipsychotics)—patients were receiving ([Rej et al. 2015](#)). Along with male sex and a history of medical hospitalization, severity of mental illness

(e.g., being hospitalized for bipolar disorder) may be a more important driver of future acute medical health service use compared with choice of pharmacotherapy. A proactive collaborative approach with primary care and home care may potentially prevent intensive acute medical health service use in older adults with bipolar disorder and other severe mental illnesses.

Over the past decade, more studies employing enriched designs in adjunctive treatment have been conducted for all drugs. Such studies are more likely to yield superiority for the adjunctive regimen, because the only patients eligible are those who have failed to respond to monotherapy regimens. Most of these studies have added atypical antipsychotics—or, in one case, lamotrigine—to regimens of valproate or lithium. Despite the design inequality, the designs have the merit of following a common pattern of clinical practice. In all of these studies, valproate has been adequately tolerated along with the added drug. In most adjunctive design studies, no separate analysis of the results for valproate and lithium has been reported. In a study of adjunctive ziprasidone or placebo added to the regimens of patients who continued to have manic symptoms while taking valproate or lithium, the adjunctive therapy was superior to continued lithium monotherapy, whereas the outcome of valproate monotherapy was equal to that of valproate plus ziprasidone ([Bowden 2011](#)).

A 12-week randomized, blinded comparison of valproate and olanzapine showed equivalent efficacy in mania for the two treatments ([Zajecka et al. 2002](#)). A 47-week study of the two drugs reported low rates of completion for both treatments (15% vs. 16%), with earlier symptomatic remission with olanzapine but equivalent efficacy for the two drugs over the remaining portion of the study ([Tohen et](#)

[al. 2003](#)). For both drugs, patients who were in remission at the end of week 3 of treatment were significantly more likely to complete the 47-week trial compared with those who were not in remission at that point (divalproex: 26.2% vs. 11.1%; olanzapine: 20.3% vs. 10.6%;  $P=0.001$ ). This finding indicates that acute treatment response to a drug (either valproate or olanzapine) during a manic episode is predictive of effective treatment with that drug in maintenance therapy. In both studies, weight gain was greater with olanzapine than with divalproex, and divalproex was associated with a significant reduction in cholesterol levels, compared with an increase in cholesterol levels with olanzapine ([Tohen et al. 2003](#); [Zajecka et al. 2002](#)).

## Mania Secondary to Head Trauma or Neurodevelopmental/Neurodegenerative Disorders

Evidence suggesting that secondary or complicated mania responds well to valproate is mixed. In an open study of 56 valproate-treated patients with mania, response was associated with the presence of nonparoxysmal abnormalities on the electroencephalogram, but not with neurological soft signs or abnormalities on computed axial tomography scans of brain ([McElroy et al. 1988](#)). A study from the 1980s ([Pope et al. 1988](#)) had suggested that manic patients who had experienced a closed-head injury before the onset of bipolar disorder were more likely to respond successfully to valproate treatment for mood symptoms. Furthermore, case reports have described successful

valproate treatment of mood symptoms in individuals with DSM-III ([American Psychiatric Association 1980](#)) organic brain syndromes ([Kahn et al. 1988](#)) and of bipolar symptoms in patients with DSM-III mental retardation ([Kastner et al. 1990](#); [Sovner 1989](#)).

## Bipolar Disorder in Children and Adolescents

Few adequately powered and designed studies have been conducted in pediatric bipolar disorder. Findings from the first placebo-controlled trial of divalproex in bipolar children and adolescents (ages 10–17 years) indicated that divalproex was not significantly superior to placebo, and side effects were similar for divalproex and placebo ([Wagner et al. 2009](#)).

In the only blinded, randomized study to compare two medications in young adolescent patients with bipolar disorder, risperidone compared with valproate showed somewhat earlier onset of improvement and resulted in a higher proportion of patients responding by the end of the 6-week trial ([Pavuluri et al. 2010](#)). This study lacked a placebo control group.

Attention-deficit/hyperactivity disorder (ADHD) symptoms are commonly intertwined with specific symptoms of bipolar disorder in youth. In a pragmatic study of 40 patients between the ages of 6 and 17 years with bipolar I (77%) or bipolar II (23%) disorder, YMRS scores of 14 or greater, and ADHD symptomatology, subjects were first given divalproex. Thirty-two subjects achieved improvement of 50% or greater on YMRS scores, whereas only 3 showed improvement in ADHD symptoms. Mixed amphetamines or

placebo were then added to the regimens of the 30 subjects who entered the placebo crossover phase. Amphetamines plus divalproex were superior to divalproex alone in improving ADHD symptoms. Both regimens were well tolerated, and no patient experienced worsening of manic symptoms ([Scheffer et al. 2005](#)).

In a double-blind, randomized, placebo-controlled study in children ages 8–10 years who met criteria for oppositional defiant disorder or conduct disorder and had experienced temper and mood lability but did not meet full criteria for bipolar disorder, patients were randomly assigned to 6 weeks of divalproex or placebo, followed by 6 weeks of placebo or divalproex (in a crossover design). By the end of the first phase, 8 of the 10 patients who received divalproex had responded, compared with none of those who received placebo. Of the 15 patients who completed both phases, 12 had superior responses to divalproex ([Donovan et al. 2000](#)).

## Agitation and Clinical Decline in Elderly Patients With Dementia

Patients with dementia are frequently institutionalized for agitation and behavioral disturbances. In a randomized, blinded study in which 56 nursing home patients with agitation and dementia received either placebo or individualized doses of divalproex, the drug-placebo difference on Brief Psychiatric Rating Scale Agitation scores significantly favored divalproex. Side effects occurred in 68% of the divalproex group versus 33% of the placebo group and were generally rated as mild ([Porsteinsson et al. 2001](#)). Six weeks of open continuation treatment resulted in

further improvement of agitation. Divalproex serum levels were greater than 40 µg/mL in both the acute blinded phase and the open continuation phase ([Porsteinsson et al. 2003](#)). Patients with dementia should generally receive valproate dosages lower than 1,000 mg/day to ensure adequate tolerability ([Profenno et al. 2005](#)). A small randomized, placebo-controlled study of valproate in the treatment of aggression in dementia failed to find any difference between valproate and placebo, although the fixed dosage used (valproate 480 mg/day) may have been inadequate ([Sival et al. 2002](#)).

Valproate also was studied for its potential utility in preventing or delaying illness progression in 313 nursing home residents with moderate Alzheimer's disease who had not yet experienced agitation or psychosis. Time to emergence of clinically significant agitation or psychosis did not differ between valproate and placebo groups, and valproate was associated with serious adverse effects in the patients ([Tariot et al. 2011](#)). Taken in the aggregate, these studies suggest that although valproate at relatively low dosages can improve dementia-related agitation in some patients, valproate has no utility in slowing or preventing disease progression in Alzheimer's dementia.

## Irritability and Aggression

Valproate has been reported to be effective in reducing irritability and aggression among diverse patient populations, including individuals with autism spectrum disorders or personality disorders. In a 12-week double-blind study of children and adolescents with autism spectrum disorders, irritability measures were significantly

improved with divalproex compared with placebo. Overall, 62% of the divalproex-treated subjects versus 9% of the placebo subjects (odds ratio=16.7) were responders ([Hollander et al. 2010](#)).

In a randomized, placebo-controlled, double-blind study, 249 patients with Cluster B personality disorders, intermittent explosive disorder, or posttraumatic stress disorder were treated for 12 weeks with either divalproex or placebo. Although divalproex did not separate from placebo in the combined analysis of all patient groups, aggression and irritability scores among the 96 Cluster B patients showed significant improvement over the course of the study ([Hollander et al. 2003](#)).

## Co-Therapy in Schizophrenia

Adjunctive use of valproate in the treatment of schizophrenia has increased, with one report indicating that more than one-third of psychiatric inpatients with a diagnosis of schizophrenia received valproate during hospitalization ([Citrome et al. 2000](#)). In a 4-week randomized, double-blind study, 242 schizophrenic patients were assigned to receive either monotherapy with an antipsychotic (risperidone or olanzapine) or adjunctive treatment with divalproex plus the antipsychotic drug. Compared with patients receiving monotherapy, those who received combination therapy showed significantly greater improvement on Positive and Negative Syndrome Scale (PANSS)-Total and PANSS positive symptom subscale scores from day 3 through day 21, but not at day 28. Platelet counts decreased with combination therapy. Cholesterol levels increased with olanzapine or risperidone

monotherapy compared with the significantly lower levels seen with the combination treatment. Weight gain did not differ for patients receiving olanzapine versus patients receiving divalproex plus olanzapine; however, weight gain was greater for divalproex plus risperidone (7.5 lbs) than for risperidone (4.2 lbs) ([Casey et al. 2003](#)).

## Bipolar Disorder With Comorbid Alcohol Use Disorder

Bipolar disorder is often associated with substance use disorders, particularly alcoholism. In the largest prospective, blinded, placebo-controlled study, 59 bipolar I patients with DSM-IV ([American Psychiatric Association 1994](#)) alcohol dependence were treated with lithium carbonate and psychosocial interventions for 24 weeks, with half randomly assigned to receive adjunctive valproate. The addition of valproate was associated with significantly fewer heavy drinking days, fewer drinks per heavy drinking day, and fewer drinks per drinking day. Higher serum valproate concentrations were correlated with improved alcohol use outcomes. Both manic and depressive symptoms improved equivalently ([Salloum et al. 2005](#)).

In a 12-week double-blind, placebo-controlled trial, divalproex treatment was associated with a significantly reduced rate of relapse to heavy drinking, but no significant differences were found in other alcohol-related outcomes. Significantly greater decreases in irritability were found in the divalproex-treated group, but no significant between-group differences were seen on measures of impulsivity ([Brady et al. 2002](#)).



---

# Predictors of Positive Response to Valproate Versus Lithium

---

## Mixed Mania

Patients with mixed manic presentations experienced greater symptom improvement with divalproex than with lithium treatment in two randomized studies ([Freeman et al. 1992](#); [Swann et al. 1997](#)), one of which (Swann et al.) was placebo controlled (reviewed in [Bowden 1995](#)). Patients with mixed manic symptoms and patients with pure manic symptoms showed equivalent improvement with divalproex, a finding that indicates the drug's broad efficacy across mania subtypes ([Swann et al. 1997](#)). By contrast, during maintenance treatment, patients with mixed mania had equivalent responses to divalproex and lithium, with evidence of higher rates of adverse effects as a function of illness features of mixed mania, compared with rates of adverse effects in patients with euphoric mania ([Bowden et al. 2005](#); [Singh et al. 2013](#)). These results suggest that effective long-term management of mixed manic states requires medication regimens that are more complex than monotherapy.

## High Lifetime Number of Mood Episodes

Divalproex was significantly more effective than lithium among manic patients with a history of more than 10 mood

episodes ([Swann et al. 1999](#)) or more than two depressive episodes ([Swann et al. 2000](#)).

---

## Side Effects and Toxicology

---

Valproate has been extensively used over several decades; thus, its adverse-effect profile is well characterized ([DeVane 2003](#); [Prevey et al. 1996](#)). Compared with patients treated for migraine or mania, patients treated for epilepsy are more likely to experience adverse events consequent to the generally higher dosages of valproate required and the more complex drug regimens used in epilepsy. In a large 1-year placebo-controlled study in patients with bipolar disorder, tremor and weight gain were the only symptoms more commonly reported with divalproex than with placebo ([DeVane 2003](#)).

## Gastrointestinal Effects

Common gastrointestinal effects of valproate include nausea, vomiting, diarrhea, dyspepsia, and anorexia. These are dose dependent, are usually encountered at the start of treatment, and are often transient ([DeVane 2003](#)). Immediate-release formulations of valproic acid are more likely than ER and enteric-coated formulations to cause adverse events ([Horne and Cunanan 2003](#); [Zarate et al. 1999](#)).

## Tremor

Tremor consequent to valproate resembles benign essential tremor and may respond to a reduction in dosage. Use of the ER or enteric-coated formulation may lessen the frequency of tremor ([Wilder 1992](#); [Zarate et al. 1999](#)).

## Sedation

Mild sedation is common at initiation of valproate treatment. This adverse effect is dose dependent and may be minimized by dosage reduction, slower titration, use of ER formulations, or taking all medication at bedtime.

## Pancreatitis

Idiosyncratic acute pancreatitis is an infrequent adverse event associated with valproate. In clinical trials, rates of amylase elevation with valproate were similar to those with placebo ([Pellock et al. 2002](#)), suggesting that precautionary amylase levels offer little benefit in predicting pancreatitis. Therefore, clinicians should routinely assess patients' clinical symptoms to identify possible signs of pancreatitis.

## Hematological Effects

Leukopenia and thrombocytopenia are directly related to higher valproate serum levels, usually 100 µg/mL or greater ([Acharya and Bussel 1996](#); [Bowden et al. 2000](#)). Thrombocytopenia is usually mild and rarely associated with bleeding complications. Management consists of dosage reduction. Platelet counts below 75,000/mm<sup>3</sup> should be monitored and regularly reassessed, because counts

lower than this level are more frequently associated with bruising or bleeding ([Zarate et al. 1999](#)).

## Hepatotoxicity

None of the longer-term studies of the past decade and a half has found evidence of hepatic dysfunction or significant worsening of hepatic indices in valproate-treated patients compared with placebo-treated or comparator-treated patients ([Bowden et al. 2000](#); [Tohen et al. 2002](#); [Zajacka et al. 2002](#)).

The risk of liver toxicity from valproate is largely limited to patients younger than 2 years, in whom hepatic function is still immature ([Tohen et al. 2003](#)). In a long-term study of divalproex (versus lithium) in adult outpatients with bipolar I disorder, full-dosage regimens for 1 year were associated with improvements in laboratory indices of hepatic function, and no hepatotoxicity was reported in the 187 patients taking divalproex ([Bowden et al. 2000](#)). A 47-week placebo-controlled study of olanzapine augmentation of divalproex or lithium in outpatients with bipolar disorder likewise found no evidence of adverse hepatic effects among patients who received divalproex ([Tohen et al. 2003](#)).

One risk factor for the development of hepatotoxicity is concomitant administration of other anticonvulsants (e.g., carbamazepine, phenytoin) that cause induction of enzymes involved in the metabolism of valproate, leading to increased concentrations of an active and hepatotoxic metabolite, 2-propyl-4-pentenoic acid.

## Weight Gain

Weight gain of 3–24 lbs is seen in 3%–20% of patients taking valproic acid for periods ranging from 3 to 12 months ([Bowden 2003b](#)). Weight gain has been consistently less with valproate than with olanzapine in comparison studies (1.22 kg vs. 2.79 kg) ([Tohen et al. 2003](#); [Zajacka et al. 2002](#)). Valproate serum levels greater than 125 µg/mL are more likely than lower levels to cause weight gain ([Bowden 2000](#)). If increased appetite and weight gain occur with valproate, the dosage should be lowered so long as clinical effectiveness is maintained; alternatively, valproate should be discontinued and replaced with a regimen without risk of weight gain.

## Cognitive Effects

Valproate infrequently produces adverse effects on cognitive functioning, and it improves cognition in some patients ([Prevey et al. 1996](#)). In a 20-week randomized, observer-blinded, parallel-group trial, the addition of valproate to carbamazepine resulted in improvement in short-term verbal memory ([Aldenkamp et al. 2000](#)). No adverse cognitive effects associated with use of valproate were seen in a group of elderly patients (mean age=77 years) ([Craig and Tallis 1994](#)).

## Lipid Profile Effects

Several studies indicate that valproate significantly reduces total and low-density lipoprotein (LDL) cholesterol levels and increases high-density lipoprotein (HDL) cholesterol levels in long-term treatment ([Geller et al. 2012](#)), and that it protects against the adverse effects of some antipsychotic

drugs on lipid function ([Bowden et al. 2000](#); [Casey et al. 2003](#); [Tohen et al. 2003](#)). A 3-week study in mania indicated reductions in cholesterol, HDL, and LDL compared with placebo and reported the effect to be limited to those subjects who had total cholesterol levels of 200 mg/dL or greater at study entry ([Bowden et al. 2006](#)).

## Polycystic Ovarian Syndrome

The prevalence of menstrual disturbances in women with bipolar disorder is higher than that in the general population. A cross-sectional study of women found evidence of a higher rate of polycystic ovarian syndrome (PCOS) in subjects who reported valproate as a component of their prior treatment regimen ([Joffe et al. 2006](#)). A study of 10 lithium-treated, 10 valproate-treated, and 2 carbamazepine-treated women with bipolar disorder found a high frequency of menstrual dysfunction in all groups. Hormonal assessment of estrone, luteinizing hormone, follicle-stimulating hormone, testosterone, and dehydroepiandrosterone (DHEA) yielded no abnormal values in any patient ([Rasgon et al. 2000](#)). Obesity may be a mechanistic pathway whereby valproate (and potentially other drugs) predisposes women to PCOS. It is advisable to treat weight gain as a risk factor for possible development of PCOS and intervene as needed to avoid clinically significant weight gain.

## Hair Loss

Hair loss may occur early in treatment and is usually transient. Frequency of hair loss may be greater in women

than in men ([Lajee and Parsonage 1980](#)). Dosage reduction and separation of valproate dosing from meals can be helpful in controlling this effect; supplemental zinc and selenium ingestion via multivitamin tablets also may be useful.

## Use During Pregnancy and Lactation

### Teratogenic and Developmental Effects

Valproate is associated with an increased incidence of birth defects, including neural tube defects, craniofacial anomalies, limb abnormalities, and cardiovascular anomalies, if infants are exposed to valproic acid in the first 10 weeks of gestation ([Kinrys et al. 2003](#); [Samrén et al. 1997](#)). Neural tube defects, the most serious of the congenital anomalies, occur in 1%–4% of such infants. Most of the available data involved patients with epilepsy, who generally receive valproate dosages higher than those used for bipolar disorder and migraine and who are often concurrently taking other teratogenic anticonvulsants ([Bowden 2003b](#)). The risk of malformations is increased with higher dosages and higher serum levels of valproate, as well as with concomitant use of other anticonvulsants (because of higher concentrations of 2-propyl-4-pentenoic acid, a teratogenic agent); is possibly decreased with supplemental folic acid; and is definitely reduced with lower dosages of valproate ([Bowden 2003b](#)). The inhibitory effect of valproate on histone deacetylase, linked to Wnt signaling, which is involved in cell division, is a plausible mechanism by which teratogenic effects could develop.

Because alternative treatment strategies lacking teratogenic risk are available that can effectively manage

bipolar symptoms, valproate should generally be discontinued in patients who are trying to conceive, and if pregnancy occurs, valproate should not be reinstated until after the first trimester.

Cognitive effects of prenatal exposure to valproate have been found. When assessed at age 3 years, children who had experienced fetal exposure to valproate had IQ scores 6–9 points lower than those of children who had fetal exposure to lamotrigine, carbamazepine, or phenytoin ([Meador et al. 2009](#)).

## Breast Feeding

Valproate is minimally present in breast milk. [Piontek et al. \(2000\)](#) reported that among six mother–infant pairs, serum valproate levels in the infants ranged from 0.9% to 2.3% of the mother's serum levels, with absolute serum levels of 0.7–1.56 µg/mL. The valproate concentration in an infant was 1.5% of the maternal concentration ([Wisner and Perel 1998](#)).

## Overdose

Recovery from overdose-induced coma has occurred with serum valproate concentrations greater than 2,000 µg/mL. In addition, serum valproate concentrations have been reduced by hemodialysis and hemoperfusion, and valproate-induced coma has been reversed with naloxone ([Rimmer and Richens 1985](#)).

---

## Drug-Drug Interactions

---



Because valproate is highly protein bound and extensively metabolized by the liver, a number of potential interactions may occur with other protein-bound or extensively metabolized drugs ([Fogel 1988](#); [Rimmer and Richens 1985](#)). Thus, free fraction concentrations of valproate in serum can be increased, and valproate toxicity can be precipitated, by coadministration of other highly protein-bound drugs (e.g., aspirin) that can displace valproate from its protein-binding sites.

In the context of coadministration, valproate's competitive inhibition of lamotrigine excretion via glucuronidation requires that lamotrigine be started at a lower dosage—usually 25 mg every other day—with increases implemented cautiously. Lamotrigine's steady-state plasma concentrations are also generally lower when the drug is used with valproate, although not in all patients.

---

## Conclusion

---

Valproate's broad spectrum of efficacy in bipolar and related disorders and generally good tolerability make it a foundation of treatment for many patients with bipolar disorders. For optimal results, most patients should be treated with the formulation that permits once-daily dosing and has the lowest peak-to-trough serum level, which in the United States currently is divalproex ER. Although onset of action of valproate occurs quickly with use of loading-dose strategies, gradual dosage titration is the preferred method of treatment initiation for all but the most severe manic states. Medication tolerability is of paramount importance

in fostering patient adherence to long-term treatment regimens.

During maintenance treatment, it is often necessary to reduce the dosage if adverse effects persist. Valproate is principally effective in and prophylactic for manic symptoms, although its prophylactic benefits in depression are now relatively well established. A history of multiple affective episodes or a current presentation characterized by irritability may be a particularly strong indicator of a favorable response to valproate. Although some patients may achieve acute and sustained remission with valproate monotherapy, many patients are more effectively treated with combinations, including other mood stabilizers and adjunctive medications. All current medications with established or putative roles in bipolar disorder can be combined with valproate.

---

## References

---

- Acharya S, Bussel JB: Hematologic toxicity of sodium valproate. *J Pediatr Neurol* 14:303-307, 1996
- Aldenkamp AP, Baker G, Mulder OG, et al: A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia* 41(9):1167-1178, 2000 10999556
- Allen MH, Hirschfeld RM, Wozniak PJ, et al: Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *Am J Psychiatry* 163(2):272-275, 2006 16449481

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Bocci U, Beretta G: Esperienze sugli alcoolisti e tossicomania con dipropilacetate di sodio. Lavoro Neuropsichiatrico 58:51-61, 1976
- Bowden CL: Predictors of response to divalproex and lithium. J Clin Psychiatry 56 (suppl 3):25-30, 1995 7883739
- Bowden CL: Valproate in mania, in Bipolar Medications: Mechanisms of Action. Edited by Manji HK, Bowden CL, Belmaker RH. Washington, DC, American Psychiatric Press, 2000, pp 357-365
- Bowden CL: Acute and maintenance treatment with mood stabilizers. Int J Neuropsychopharmacol 6(3):269-275, 2003a 12974993
- Bowden CL: Valproate. Bipolar Disord 5(3): 189-202, 2003b 12780873
- Bowden CL: Relationship of acute mania symptomatology to maintenance treatment response. Curr Psychiatry Rep 6(6):473-477, 2004 15538997
- Bowden CL: The role of ziprasidone in adjunctive use with lithium or valproate in maintenance treatment of bipolar disorder. Neuropsychiatr Dis Treat 7:87-92, 2011 21552310
- Bowden CL, Janicak PG, Orsulak P, et al: Relation of serum valproate concentration to response in mania. Am J Psychiatry 153(6):765-770, 1996 8633687
- Bowden CL, Calabrese JR, McElroy SL, et al; Divalproex Maintenance Study Group: A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 57(5):481-489, 2000 10807488

- Bowden CL, Collins MA, McElroy SL, et al: Relationship of mania symptomatology to maintenance treatment response with divalproex, lithium, or placebo. *Neuropsychopharmacology* 30(10):1932-1939, 2005 15956987
- Bowden CL, Swann AC, Calabrese JR, et al; Depakote ER Mania Study Group: A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry* 67(10):1501-1510, 2006 17107240
- Brady KT, Myrick H, Henderson S, et al: The use of divalproex in alcohol relapse prevention: a pilot study. *Drug Alcohol Depend* 67(3):323-330, 2002 12127203
- Calabrese JR, Shelton MD, Rapport DJ, et al: A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 162(11):2152-2161, 2005 16263857
- Casey DE, Daniel DG, Wassef AA, et al: Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology* 28(1):182-192, 2003 12496955
- Citrome L, Levine J, Allingham B: Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994 to 1998. *Psychiatr Serv* 51(5):634-638, 2000 10783182
- Cournoyer P, Desrosiers RR: Valproic acid enhances protein L-isoaspartyl methyltransferase expression by stimulating extracellular signal-regulated kinase signaling pathway. *Neuropharmacology* 56(5):839-848, 2009 19371592
- Craig I, Tallis R: Impact of valproate and phenytoin on cognitive function in elderly patients: results of a single-blind randomized comparative study. *Epilepsia* 35(2):381-390, 1994 8156961

- Davis LL, Bartolucci A, Petty F: Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord* 85(3):259-266, 2005 15780695
- DeVane CL: Pharmacokinetics, drug interactions, and tolerability of valproate. *Psychopharmacol Bull* 37 (suppl 2):25-42, 2003 14624231
- Donovan SJ, Stewart JW, Nunes EV, et al: Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. *Am J Psychiatry* 157(5):818-820, 2000 10784478
- Fogel BS: Combining anticonvulsants with conventional psychopharmacologic agents, in *Use of Anticonvulsants in Psychiatry: Recent Advances*. Edited by McElroy SL, Pope HG Jr. Clifton, NJ, Oxford Health Care, 1988, pp 77-94
- Freeman TW, Clothier JL, Pazzaglia P, et al: A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry* 149(1):108-111, 1992 1728157
- Geller B, Luby JL, Joshi P, et al: A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. *Arch Gen Psychiatry* 69(5):515-528, 2012 22213771
- Ghaemi SN, Gilmer WS, Goldberg JF, et al: Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. *J Clin Psychiatry* 68(12):1840-1844, 2007 18162014
- Gray NA, Zhou R, Du J, et al: The use of mood stabilizers as plasticity enhancers in the treatment of neuropsychiatric disorders. *J Clin Psychiatry* 64 (suppl 5):3-17, 2003 12720479
- Grunze H, Erfurth A, Amann B, et al: Intravenous valproate loading in acutely manic and depressed bipolar I patients. *J Clin Psychopharmacol* 19(4):303-309, 1999 10440456

- Gyulai L, Bowden CL, McElroy SL, et al: Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology* 28(7):1374-1382, 2003 12784116
- Harwood AJ, Agam G: Search for a common mechanism of mood stabilizers. *Biochem Pharmacol* 66(2):179-189, 2003 12826261
- Hollander E, Tracy KA, Swann AC, et al: Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacology* 28(6):1186-1197, 2003 12700713
- Hollander E, Chaplin W, Soorya L, et al: Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology* 35(4):990-998, 2010 20010551
- Horne RL, Cunanan C: Safety and efficacy of switching psychiatric patients from a delayed-release to an extended-release formulation of divalproex sodium. *J Clin Psychopharmacol* 23(2):176-181, 2003 12640219
- Jacobsen FM: Low-dose valproate: a new treatment for cyclothymia, mild rapid cycling disorders, and premenstrual syndrome. *J Clin Psychiatry* 54(6):229-234, 1993 8331092
- Joffe H, Cohen LS, Suppes T, et al: Valproate is associated with new-onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. *Biol Psychiatry* 59(11):1078-1086, 2006 16448626
- Kahn D, Stevenson E, Douglas CJ: Effect of sodium valproate in three patients with organic brain syndromes. *Am J Psychiatry* 145(8):1010-1011, 1988 3394852
- Kastner T, Friedman DL, Plummer AT, et al: Valproic acid for the treatment of children with mental retardation and mood symptomatology. *Pediatrics* 86(3):467-472, 1990 2117744

- Keck PE Jr, Bowden CL, Meinhold JM, et al: Relationship between serum valproate and lithium levels and efficacy and tolerability in bipolar maintenance therapy. *Int J Psychiatry Clin Pract* 9(4):271-277, 2005 24930925
- Ketter TA, Citrome L, Wang PW, et al: Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions? *Acta Psychiatr Scand* 123(3):175-189, 2011 21133854
- Kinrys G, Pollack MH, Simon NM, et al: Valproic acid for the treatment of social anxiety disorder. *Int Clin Psychopharmacol* 18(3):169-172, 2003 12702897
- Lajee HCK, Parsonage MJ: Unwanted effects of sodium valproate in the treatment of adult patients with epilepsy, in *The Place of Sodium Valproate in the Treatment of Epilepsy*. Edited by Parsonage NJ, Caldwell ADS. London, Royal Society of Medicine, 1980, pp 141-158
- Lambert PA, Carraz G, Borselli S, et al: [Neuropsychotropic action of a new anti-epileptic agent: depamide]. *Ann Med Psychol (Paris)* 124(5):707-710, 1966 5941463
- Levy MN: Cardiac sympathetic-parasympathetic interactions. *Fed Proc* 43(11):2598-2602, 1984 6745448
- Marcus R, Khan A, Rollin L, et al: Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar Disord* 13(2):133-144, 2011 21443567
- McElroy SL, Pope HG Jr, Keck PE Jr: Treatment of psychiatric disorders with valproate: a series of 73 cases. *Psychiatr Psychobiol* 3:81-85, 1988
- McElroy SL, Martens BE, Creech RS, et al: Randomized, double-blind, placebo-controlled study of divalproex extended release loading monotherapy in ambulatory bipolar spectrum disorder patients with moderate-to-

- severe hypomania or mild mania. *J Clin Psychiatry* 71(5):557-565, 2010 20361901
- Meador KJ, Baker GA, Browning N, et al; NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 360(16):1597-1605, 2009 19369666
- Miura T, Noma H, Furukawa TA, et al: Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry* 1(5):351-359, 2014 26360999
- Müller-Oerlinghausen B, Retzow A, Henn FA, et al; European Valproate Mania Study Group: Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Psychopharmacol* 20(2):195-203, 2000 10770458
- Pavuluri MN, Henry DB, Findling RL, et al: Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder. *Bipolar Disord* 12(6):593-605, 2010 20868458
- Pellock JM, Wilder BJ, Deaton R, et al: Acute pancreatitis coincident with valproate use: a critical review. *Epilepsia* 43(11): 1421-1424, 2002 12423394
- Perova T, Kwan M, Li PP, Warsh JJ: Differential modulation of intracellular Ca<sup>2+</sup> responses in B lymphoblasts by mood stabilizers. *Int J Neuropsychopharmacol* 13(6):693-702, 2010 19400980
- Piontek CM, Baab S, Peindl KS, et al: Serum valproate levels in 6 breastfeeding mother-infant pairs. *J Clin Psychiatry* 61(3):170-172, 2000 10817100
- Pope HG Jr, McElroy SL, Satlin A, et al: Head injury, bipolar disorder, and response to valproate. *Compr Psychiatry* 29(1):34-38, 1988 3125002
- Porsteinsson AP, Tariot PN, Erb R, et al: Placebo-controlled study of divalproex sodium for agitation in dementia. *Am*



- J Geriatr Psychiatry 9(1):58-66, 2001 11156753
- Porsteinsson AP, Tariot PN, Jakimovich LJ, et al: Valproate therapy for agitation in dementia: open-label extension of a double-blind trial. Am J Geriatr Psychiatry 11(4):434-440, 2003 12837672
- Prevey ML, Delaney RC, Cramer JA, et al: Effect of valproate on cognitive functioning: comparison with carbamazepine. The Department of Veteran Affairs Epilepsy Cooperative Study 264 Group. Arch Neurol 53(10):1008-1016, 1996 8859063
- Profenno LA, Jakimovich L, Holt CJ, et al: A randomized, double-blind, placebo-controlled pilot trial of safety and tolerability of two doses of divalproex sodium in outpatients with probable Alzheimer's disease. Curr Alzheimer Res 2(5):553-558, 2005 16375658
- Rasgon NL, Altshuler LL, Gudeman D, et al: Medication status and polycystic ovary syndrome in women with bipolar disorder: a preliminary report. J Clin Psychiatry 61(3):173-178, 2000 10817101
- Rej S, Yu C, Shulman K, et al: Medical comorbidity, acute medical care use in late-life bipolar disorder: a comparison of lithium, valproate, and other pharmacotherapies. Gen Hosp Psychiatry 37(6):528-532, 2015 26254672
- Rimmer EM, Richens A: An update on sodium valproate. Pharmacotherapy 5(3):171-184, 1985 3927267
- Sachs GS, Grossman F, Ghaemi SN, et al: Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 159(7):1146-1154, 2002 12091192
- Salloum IM, Cornelius JR, Daley DC, et al: Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. Arch Gen Psychiatry 62(1):37-45, 2005 15630071

- Samrén EB, van Duijn CM, Koch S, et al: Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 38(9):981-990, 1997 9579936
- Scheffer RE, Kowatch RA, Carmody T, et al: Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry* 162(1):58-64, 2005 15625202
- Singh V, Bowden CL, Gonzalez JM, et al: Discriminating primary clinical states in bipolar disorder with a comprehensive symptom scale. *Acta Psychiatr Scand* 127(2):145-152, 2013 22774941
- Sival RC, Haffmans PM, Jansen PA, et al: Sodium valproate in the treatment of aggressive behavior in patients with dementia—a randomized placebo controlled clinical trial. *Int J Geriatr Psychiatry* 17(6): 579-585, 2002 12112183
- Smith LA, Cornelius VR, Azorin JM, et al: Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. *J Affect Disord* 122(1-2):1-9, 2010 19926140
- Sovner R: The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. *J Clin Psychiatry* 50 (suppl):40-43, 1989 2494159
- Swann AC, Bowden CL, Morris D, et al: Depression during mania: treatment response to lithium or divalproex. *Arch Gen Psychiatry* 54(1):37-42, 1997 9006398
- Swann AC, Bowden CL, Calabrese JR, et al: Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. *Am J Psychiatry* 156(8):1264-1266, 1999 10450271
- Swann AC, Bowden CL, Calabrese JR, et al: Mania: differential effects of previous depressive and manic

episodes on response to treatment. *Acta Psychiatr Scand* 101(6):444-451, 2000 10868467

Tariot PN, Schneider LS, Cummings J, et al; Alzheimer's Disease Cooperative Study Group: Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry* 68(8):853-861, 2011 21810649

Tohen M, Chengappa KN, Suppes T, et al: Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry* 59(1):62-69, 2002 11779284

Tohen M, Ketter TA, Zarate CA, et al: Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry* 160(7):1263-1271, 2003 12832240

Wagner KD, Redden L, Kowatch RA, et al: A double-blind, randomized, placebo-controlled trial of divalproex extended-release in the treatment of bipolar disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 48(5):519-532, 2009 19325497

Wilder BJ: Pharmacokinetics of valproate and carbamazepine. *J Clin Psychopharmacol* 12 (1 suppl):64S-68S, 1992 1541720

Wisner KL, Perel JM: Serum levels of valproate and carbamazepine in breastfeeding mother-infant pairs. *J Clin Psychopharmacol* 18(2):167-169, 1998 9555601

Yatham LN, Grossman F, Augustyns I, et al: Mood stabilisers plus risperidone or placebo in the treatment of acute mania: international, double-blind, randomised controlled trial. *Br J Psychiatry* 182:141-147, 2003 12562742 (Erratum appears in *Br J Psychiatry* 182:369, 2003)

Yatham LN, Beaulieu S, Schaffer A, et al: Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: a

CANMAT randomized double-blind trial. *Mol Psychiatry* 21(8):1050-10561, 2016 26460229

Zajecka JM, Weisler R, Sachs G, et al: A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *J Clin Psychiatry* 63(12):1148-1155, 2002 12523875

Zarate CAJr, Tohen M, Narendran R, et al: The adverse effect profile and efficacy of divalproex sodium compared with valproic acid: a pharmacoepidemiology study. *J Clin Psychiatry* 60(4):232-236, 1999 10221283

## CHAPTER 38

# Carbamazepine, Oxcarbazepine, and Licarbazepine

Po W. Wang, M.D.

Terence A. Ketter, M.D.

Robert M. Post, M.D.

**Pharmacotherapy** of bipolar disorders is complex and rapidly evolving. Antipsychotics, antidepressants, anxiolytics, and new-generation anticonvulsants are commonly combined with traditional first-line mood stabilizers (lithium, valproate, carbamazepine) in clinical settings ([American Psychiatric Association 2002](#); [Ketter 2005](#); [Suppes et al. 2005](#)). Clinicians are challenged with integrating complex data regarding efficacy and adverse-effect profiles with pharmacological properties in efforts to provide safe, effective, state-of-the-art pharmacotherapy for patients with bipolar disorder.

In this chapter we review the pharmacology of carbamazepine (CBZ) and its analog oxcarbazepine (OXC). In the past, CBZ was considered an alternative to lithium and valproate rather than a first-line intervention in the treatment of bipolar disorder ([American Psychiatric Association 2002](#)), largely owing to methodological limitations of early studies of efficacy in bipolar disorder, complexity of use due to adverse effects and drug-drug interactions, and lack of a U.S. Food and Drug Administration (FDA) indication for the treatment of bipolar disorder. CBZ received an indication for the treatment of acute manic and mixed episodes in bipolar disorder following evidence from two randomized double-blind, placebo-controlled, parallel-group studies in patients with bipolar disorder ([Weisler et al. 2004, 2005](#)). Importantly, in selected patients, CBZ and OXC may offer favorable efficacy and tolerability—in particular, less weight gain and metabolic problems—and thus can be important treatment alternatives ([Akiskal et al. 2005](#)). Likewise, the active monohydrate metabolite of OXC, licarbazepine, and its prodrug, eslicarbazepine acetate (ESL), may have improved tolerability, although evidence of efficacy in bipolar disorder is lacking.

---

## History and Discovery

---

As one of the first alternatives to lithium and first-generation antipsychotics to become available, CBZ has played an important role in the development of therapeutic interventions for bipolar disorder ([Post et al. 2007](#)). CBZ was developed in 1957 by J.R. Geigy AG in Europe, and its efficacy in epilepsy and paroxysmal pain was established by

the 1960s and in bipolar disorder by the early 1970s ([Takezaki and Hanaoka 1971](#)). In the 1970s, acute mania was managed primarily with lithium and first-generation antipsychotics. Lithium was dramatically effective in patients with classical euphoric mania but was less effective in patients with mixed or dysphoric mania, rapid cycling, a higher number of previous episodes, mood-incongruent delusions, or concurrent substance use disorders ([Ketter and Wang 2002](#)). Furthermore, the fact that starting treatment with lithium required a slow initial dosage titration meant that there was often a substantial delay before the medication's beneficial effects were experienced.

Limitations of lithium and first-generation antipsychotics led investigators to explore other treatment options for bipolar disorder. On the basis of early reports of favorable psychotropic profiles in patients with epilepsy and preliminary observations in mood disorders, systematic investigations of CBZ ([Ballenger and Post 1978](#)) and valproate commenced, and these anticonvulsants emerged as effective in acute mania. CBZ and valproate were used off-label for bipolar disorder in the 1980s and early 1990s, respectively. The CBZ analog OXC was anecdotally reported as useful in bipolar disorder in the 1980s ([Müller and Stoll 1984](#)), but it was not marketed in the United States for the treatment of epilepsy until 2000.

Because of economic concerns such as patent protection limitations and the high cost of obtaining FDA approval, a CBZ indication for bipolar disorder was not initially sought in the United States. A proprietary CBZ beaded extended-release capsule formulation (Equetro) received an FDA indication for the treatment of acute manic and mixed episodes in patients with bipolar disorder in late 2004.

OXC was approved for the treatment of epilepsy in the United States in 2000, following the development of several new anticonvulsants in the 1990s. The new anticonvulsants have heterogeneous psychotropic profiles ([Ketter et al. 2003](#)), with only the older drug phenytoin ([Mishory et al. 2000](#)) and OXC ([Emrich 1990](#)) appearing effective thus far in (albeit small) controlled trials in acute mania and lamotrigine in the acute treatment and maintenance treatment of bipolar depression. As with CBZ, economic concerns such as patent protection limitations and the high cost of obtaining FDA approval are substantial barriers to seeking an OXC acute mania indication in the United States. On the basis of its greater ease of use, some clinicians consider OXC to be an alternative to CBZ ([American Psychiatric Association 2002](#)). However, use of OXC remains limited by the lack of adequate data supporting its efficacy in bipolar disorder.

Licarbazepine, the active monohydroxy metabolite of OXC, was initially assessed by Novartis for treatment of acute mania rather than epilepsy. As of 2015, the three randomized controlled trials of licarbazepine in acute mania (on [clinicaltrials.gov](http://clinicaltrials.gov)) had not yet been published. In 2009, the European Medicines Agency approved ESL, a prodrug for the *S*-enantiomer of licarbazepine (Zebinix; BIAL-Portela and Ca, S.A.), for the treatment of epilepsy. In 2013, the FDA approved ESL (Aptiom, submitted by Sunovion, under license from BIAL-Portela and Ca, S.A.) for epilepsy. Although ESL may have greater tolerability than CBZ and does not carry black box warnings, its efficacy in acute mania has not been established ([Grunze et al. 2015](#)).

---

## Structure-Activity Relationships

---

CBZ is an iminostilbine derivative with a dibenzazepine nucleus. CBZ's carbamyl (carboxamide) group at position 5 appears to be associated with substantial anticonvulsant effects. Like imipramine, CBZ has a tricyclic structure; however, whereas

imipramine has a 5-aryl substituent, CBZ has a 5-carboxamide substituent, and this structural difference is thought to mediate CBZ's markedly different effects compared with imipramine, as described later (see "Mechanisms of Action" section). OXC differs structurally from CBZ only in that it has a ketone substitution at the 10,11-position, and (as noted below) the bulk of the evidence thus far suggests that this structural similarity is paralleled by mechanistic similarity. ESL, like OXC, has a stabilizing subgroup at the 10,11-position (an acetoxymethyl side chain) and is metabolized to the *S*-isomer of the common metabolite of OXC, licarbazepine ([Almeida and Soares-da-Silva 2007](#)).

---

## Pharmacological Profiles

---

CBZ and OXC have preclinical anticonvulsant profiles similar to that of phenytoin and less broad than that of valproate or lamotrigine. CBZ and OXC, like phenytoin, valproate, and lamotrigine, are effective in the maximal electroshock model of generalized tonic and/or clonic seizures and in blocking seizures resulting from amygdala kindling (a model of partial seizures). CBZ and OXC, like phenytoin but unlike valproate and lamotrigine, are not effective in the pentylenetetrazole model of absence seizures and, like phenytoin and lamotrigine but unlike valproate, fail to block kindling development (a model of epileptogenesis).

As expected from their preclinical profiles, CBZ and OXC, like phenytoin, valproate, and lamotrigine, are effective in partial seizures with and without secondary generalization and, like phenytoin but unlike valproate and lamotrigine, are ineffective in absence seizures. CBZ and OXC also have analgesic effects in paroxysmal pain syndromes and thus are effective in trigeminal neuralgia.

ESL, which shares a common active metabolite with OXC, has a similar preclinical anticonvulsant profile. Thus, ESL, like OXC, is effective in the maximal electroshock model of generalized tonic and/or clonic seizures and effective in blocking seizures resulting from amygdala kindling ([Almeida and Soares-da-Silva 2007](#)).

---

## Pharmacokinetics and Disposition

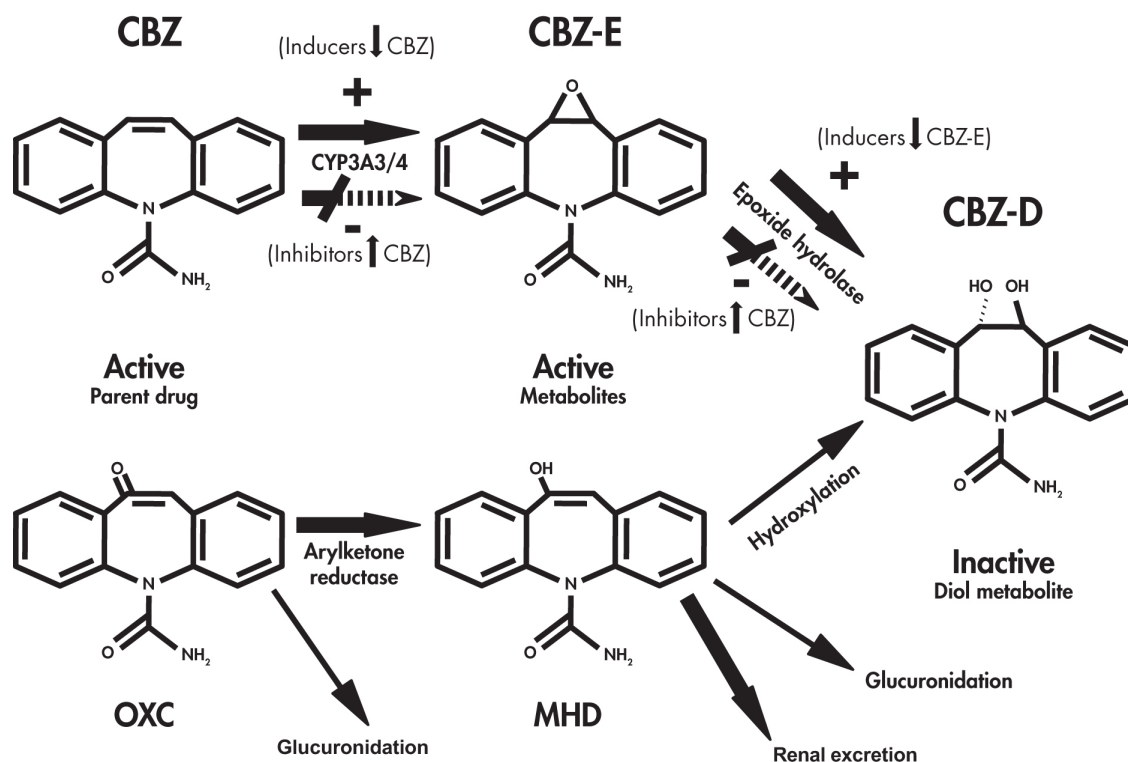
---

### Carbamazepine

CBZ is available in the United States as a proprietary product (Tegretol; Novartis Pharmaceuticals Corporation) supplied as a 100 mg/5 mL suspension; 100-mg chewable tablets; 200-mg tablets; and 100-, 200-, and 400-mg extended-release (Tegretol-XR) tablets ([Physicians' Desk Reference 2015](#)). An additional proprietary beaded extended-release capsule formulation—Carbatrol (Shire US Inc.), marketed for epilepsy, and Equetro (Validus Pharmaceuticals), marketed for bipolar disorder—is supplied in 100-, 200-, and 300-mg strengths ([Physicians' Desk Reference 2015](#)). Intramuscular and depot formulations are not available. CBZ is also available in generic formulations.

CBZ is extensively metabolized, with only about 3% being excreted unchanged in the urine. The main metabolic pathway of CBZ (to its active 10,11-epoxide, CBZ-E) appears to be primarily via cytochrome P450 (CYP) 3A4/5 ([Figure 38-1](#), top), with a minor contribution by CYP2C8 ([Kerr et al. 1994](#)). This epoxide pathway accounts for about 40% of CBZ disposition, and an even greater percentage in patients with induced epoxide

pathway metabolism (Faigle and Feldmann 1995). The frequency distribution of CBZ kinetic parameters is unimodal, consistent with CYP3A3/4 being the crucial isoform. With enzyme induction (of the epoxide pathway, presumably via CYP3A3/4 induction), formation of CBZ-E triples, and thus the CBZ-E/CBZ ratio increases (Eichelbaum et al. 1985). Other pathways include aromatic hydroxylation (25%), which is apparently via CYP1A2 and is not induced concurrently with epoxide formation, and glucuronide conjugation of the carbamoyl side chain (15%) by uridine diphosphoglucuronosyltransferase (UGT), presumably primarily by UGT2B7 (Staines et al. 2004). These other pathways yield inactive metabolites.



**FIGURE 38-1.** Carbamazepine and oxcarbazepine metabolism.

Note. +=enzyme induction; -=enzyme inhibition; CBZ=carbamazepine; CBZ-E=carbamazepine-10,11-epoxide; CBZ-D=carbamazepine-10,11-dihydro-dihydroxide; OXC=oxcarbazepine; MHD=monohydroxy derivative; CYP3A3/4=cytochrome P450 3A3/4 isoenzyme.

CBZ has erratic absorption and a bioavailability of about 80%. Tablets should not be exposed to humidity, because moisture can cause solidification and decrease the drug's bioavailability (Nightingale 1990). CBZ is about 75% bound to plasma proteins and has a moderate volume of distribution of about 1 L/kg. Before autoinduction of the epoxide pathway, the half-life of CBZ is about 24 hours, and clearance is about 25 mL/min. However, after autoinduction (2–4 weeks into therapy), the half-life falls to about 8 hours, and clearance rises to about 75 mL/min. This may require dosage adjustment to maintain adequate blood concentrations and therapeutic effects. The active CBZ-E metabolite has a half-life of about 6 hours and is converted to an inactive diol (CBZ-D) by epoxide hydrolase. The extended-release CBZ formulations given twice daily yield steady-state CBZ concentrations similar to those seen with the immediate-release formulation given four times daily (Garnett et al. 1998; Thakker et al. 1992).



When CBZ is used in the treatment of acute mania, two divergent clinical needs influence the rate of dosage titration. The need for rapid control of the manic syndrome should be balanced against the need to minimize adverse effects (which can be worsened with overly aggressive escalation of CBZ dosage). Thus, although a loading-dose strategy may be tolerated and effective in the treatment of mania with valproate (Keck et al. 1993), the potential for neurotoxic adverse effects (i.e., CNS symptoms such as dizziness, somnolence, cognitive slowness, tremors, ataxia, and slurred speech) limits the use of such an approach with CBZ.

Nonetheless, in the inpatient therapy of mania, CBZ is commonly started at 400–800 mg/day in divided doses and increased as tolerated (by 200 mg/day every 1–4 days) to provide clinical efficacy. In controlled studies, the beaded extended-release capsule formulation was started at 200 mg twice per day and increased daily by 200 mg to a final dosage as high as 1,600 mg/day (Weisler et al. 2004, 2005). Managing dosage titration against adverse effects is more important than targeting a specific blood concentration range. The usual dosage range is 800–1,600 mg/day given in up to three or four divided doses with the immediate-release formulation. Sustained-release formulations permit two divided doses per day and may even allow most or all of the daily dosage to be taken at bedtime in mood disorder patients. Although this strategy is convenient, it may not be feasible in some individuals because of neurotoxicity at the peak serum concentration, which occurs about 4–8 hours after ingesting a dose. CBZ has a fairly rapid onset of antimanic efficacy. Thus, if clinical improvement has not occurred after 7–10 days, the clinician should consider augmentation or alternative strategies.

In a 6-month open-label extension of controlled studies in acute mania, beaded extended-release capsule CBZ was started at 200 mg twice per day and increased by 200 mg every 3 days (versus every day in the acute studies) to a final dosage as high as 1,600 mg/day (Ketter et al. 2004). This approach decreased the incidence of central nervous system (CNS; dizziness, somnolence, ataxia), digestive system (nausea, vomiting), and dermatological (pruritus) adverse effects by about 50%.

In less acute situations, CBZ is often started at 100–200 mg/day and increased as necessary and tolerated by 200 mg/day every 4–7 days. Even more gradual initiation strategies may be necessary to alleviate adverse effects. Thus, starting with 50 mg (half of a chewable 100-mg tablet) at bedtime and increasing by 50 mg every few days can result in a better-tolerated initiation. Often, initial dosages of CBZ may be better tolerated after 1 month of therapy, once autoinduction of CBZ metabolism has decreased the serum CBZ concentrations (Cereghino 1975) and accommodation and tolerance to adverse effects such as sedation have occurred. In two CBZ-versus-lithium maintenance studies, trough serum CBZ concentrations were maintained at 4–12 µg/mL, with a mean of 6.4 µg/mL (Greil et al. 1997) and 7.7 µg/mL (Denicoff et al. 1997).

Because CBZ dosage and serum and cerebrospinal fluid (CSF) concentrations do not correlate with its psychotropic efficacy (Post 1989; Post et al. 1983, 1984a), clinical management involves gradual up-titration of CBZ dosages until adequate therapeutic efficacy is achieved, adverse effects supervene, or serum concentrations exceed 12 µg/mL. The 4–12 µg/mL serum CBZ concentration range used in epilepsy may be considered as a broad target, with CBZ serum concentrations used as checks for pharmacokinetic problems. The active CBZ-E metabolite can yield therapeutic and adverse effects similar to those of CBZ, but it is not detected in conventional CBZ assays. Thus, the unwary clinician may misinterpret the significance of therapeutic or adverse effects associated with low or moderate serum CBZ concentrations.

In responders, a dose-response relationship may be evident, so slowly increasing CBZ dosages to maximize response in the absence of significant adverse effects would be an appropriate clinical strategy. However, if there is no hint of therapeutic response at moderate dosages, it is unlikely that pushing to very high dosages would be beneficial.

## Oxcarbazepine

OXC is available in the United States as a proprietary product (Trileptal; Novartis Pharmaceuticals Corporation) supplied as a 300 mg/5 mL suspension and as 150-, 300-, and 600-mg tablets ([Physicians' Desk Reference 2015](#)). A novel once-daily extended-release formulation of OXC (Oxtellar XR; Supernus Pharmaceuticals Inc.) has also been approved for the adjunctive treatment of partial seizures in adults and in children ages 6–17 years. Limited data suggest that this formulation has enhanced tolerability ([Chung et al. 2016](#)). Intramuscular and depot formulations of OXC are not available.

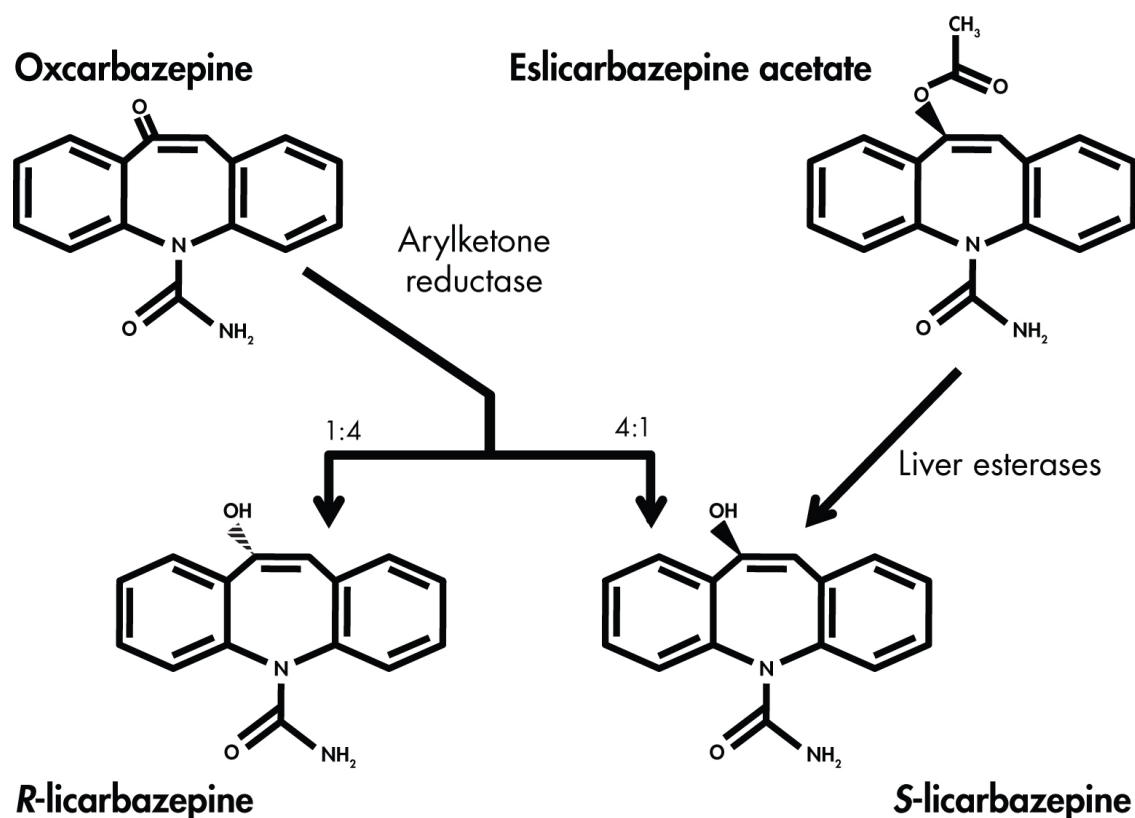
OXC is 96% absorbed, and the modest effect of food on OXC kinetics does not appear to be of therapeutic consequence ([Degen et al. 1994](#)). OXC is 60% bound to plasma proteins. Like CBZ, OXC has a complex metabolism ([Figure 38-1](#), bottom). Thus, OXC is rapidly reduced to an active monohydroxy derivative (MHD) by cytosol arylketone reductase. The MHD form (also called licarbazepine) is 40% bound to plasma proteins, has a moderate volume of distribution of about 0.8 L/kg, and has a half-life of about 9 hours. OXC is eliminated primarily in the form of MHD (70%) and MHD glucuronide conjugates (20%), with a small proportion (10%) eliminated in the form of OXC glucuronide conjugates and CBZ-D. OXC does not cause autoinduction, and it causes substantially less heteroinduction than does CBZ. Thus, as described later in this chapter (see section “Drug-Drug Interactions”), medication interactions are less problematic with OXC than with CBZ ([Baruzzi et al. 1994](#)).

OXC is started at 150 mg/day and increased every other day by 150 mg to a target of 1,200–1,600 mg/day in two to three divided doses. Further dosage increases up to 2,400 mg/day may be clinically indicated. In small trials of OXC in acute mania, mean OXC dosages were 1,400–2,400 mg/day ([Emrich 1990](#); [Emrich et al. 1983](#)). As with CBZ, when used to treat patients with bipolar disorder, OXC is titrated to the desired clinical effect as tolerated, with the serum concentration range used in epilepsy considered as a broad target, and with OXC serum concentrations used as a check for pharmacokinetic problems. Equipotent doses of OXC range from 1.2 to 1.5 times the CBZ dose.

## Eslicarbazepine Acetate

ESL is available in the United States as a proprietary product (Aptiom; Sunovion Pharmaceuticals Corporation) supplied in 200-, 400-, 600-, and 800-mg tablets ([Physicians' Desk Reference 2015](#)). Extended-release, intramuscular, and depot formulations are not available.

Licarbazepine is the active MHD product of OXC, and eslicarbazepine is the *S*-isomer of licarbazepine ([Figure 38-2](#)). ESL is a prodrug of eslicarbazepine. Licarbazepine is 40% bound to plasma proteins, has a moderate volume of distribution (about 0.8 L/kg), and has a half-life of about 20–24 hours ([Zaccara et al. 2015](#)). Elimination is mainly through the kidneys, unchanged or glucuronidated ([Zaccara et al. 2015](#)). ESL pharmacokinetics do not appear to be affected in patients with moderate hepatic impairment ([Almeida et al. 2008](#)).



**FIGURE 38-2.** Oxcarbazepine and eslicarbazepine acetate (ESL) metabolism.

Oxcarbazepine is metabolized to the active monohydroxy derivative as a racemic mixture with a higher (4:1) ratio of the *S*-enantiomer compared with the *R*-enantiomer. ESL is rapidly metabolized to the common but specifically *S*-enantiomer of the monohydroxy derivative (Bialer 2006).

In a recent study evaluating the safety of two dosage-titration regimens of ESL in the treatment of bipolar I patients with acute mania, ESL was started at 600 mg/day or 800 mg/day and increased every 3 days by 600 mg or 800 mg to a target dosage of 1,800 mg/day or 2,400 mg/day, respectively. Despite the aggressive titration schedule, adverse effects were of mostly mild to moderate intensity (Grunze et al. 2015).

Transitioning a patient from OXC to ESL would be expected to be relatively straightforward, with an OXC:ESL dose ratio of 1:1, and could occur within 1 day. By contrast, transitioning a patient from CBZ to ESL would be considerably more complicated, with a CBZ:ESL dose ratio of 1:1.3, and would require at least 1-2 weeks, as clinically determined (Peltola et al. 2015).

## Mechanisms of Action

CBZ and OXC have both structural and mechanistic similarities. However, these agents have such a diversity of biochemical effects that linking these mechanisms to their varying clinical actions presents a considerable challenge.

## Carbamazepine

Although CBZ has a tricyclic structure like that of imipramine, the two agents have markedly different neurochemical, hepatic, and clinical effects. CBZ lacks imipramine's major effects on monoamine reuptake and high affinity for histaminergic, cholinergic, adrenergic  $\beta$ , and dopamine receptors. However, CBZ has a wide range of other cellular and intracellular effects.

One useful way of considering CBZ's diverse mechanisms is from the perspective of onset of action ([Post 1988](#)). CBZ cellular actions with acute onset that might parallel the time course of clinical anticonvulsant effects include decreasing sodium influx and glutamate release, increasing potassium conductance, and interacting with peripheral benzodiazepine and  $\alpha_2$ -adrenergic receptors. Acute or subchronic actions—such as increasing striatal cholinergic neurotransmission; decreasing adenylate cyclase activity stimulated by dopamine, norepinephrine, and serotonin; and decreasing turnover of dopamine, norepinephrine, and  $\gamma$ -aminobutyric acid (GABA)—may be pertinent to CBZ's clinical antimanic effects. Finally, the actions requiring chronic administration—include increasing serum and urinary free cortisol, free tryptophan, substance P sensitivity, and adenosine A<sub>1</sub> receptors and decreasing cerebrospinal somatostatin—may be those that are most closely related to CBZ's clinical antidepressant effects.

## Oxcarbazepine

Compared with the knowledge base on CBZ's mechanisms of action, less is known about OXC (and thus ESL, given their common active molecules). Most evidence thus far suggests that OXC's structural similarity to CBZ is paralleled by mechanistic similarity ([Ambrósio et al. 2002](#)). For example, OXC, like CBZ, appears to decrease sodium ([Benes et al. 1999](#); [Wamil et al. 1994](#)) and calcium ([Stefani et al. 1995](#)) influx, glutamate release ([Ambrósio et al. 2001](#)), and serum thyroxine concentrations ([Isojärvi et al. 2001b](#)); to increase potassium conductance ([McLean et al. 1994](#)) and dopaminergic ([Joca et al. 2000](#)) neurotransmission; and to block adenosine A<sub>1</sub> receptors ([Deckert et al. 1993](#)). However, there may be some mechanistic dissimilarities, particularly given the marked difference between OXC and CBZ in degree of hepatic enzyme induction. For example, OXC appears to be a less potent modulator of voltage-gated calcium channels than is CBZ ([Schmutz et al. 1994](#); [Stefani et al. 1997](#)). The general OXC-CBZ mechanistic overlap is consistent with the hypothesis that OXC and CBZ have similar effects in bipolar disorder, which in turn is consistent with preliminary clinical observations; however, these similarities remain to be established in large controlled clinical studies.

## Eslicarbazepine Acetate

ESL and OXC likely have a similar mode of action because they share the same main active metabolite, licarbazepine (although the oxcarbazepine metabolite is racemic licarbazepine, whereas the ESL metabolite is exclusively the *S*-isomer of licarbazepine) ([Almeida and Soares-da-Silva 2007](#); [Schütz et al. 1986](#)). Thus, ESL behaves as a blocker of the voltage-gated sodium channel (VGSC; [Almeida and Soares-da-Silva 2007](#)). However, whereas ESL reduces VGSC availability through enhancement of slow inactivation, CBZ acts by altering fast inactivation of VGSC ([Hebeisen et al. 2015](#)). Eslicarbazepine and CBZ also differ with regard to submaximal GABA currents, Kv7.2 outward currents, and high- and low-affinity Cav3.2 inward currents ([Keating 2014](#)). OXC and ESL may have some mechanistic differences as well, with CBZ and OXC enhancing excitatory synaptic

transmission via antagonism of the adenosine A<sub>1</sub> receptor at therapeutic doses, whereas ESL does so only at supratherapeutic high dosages (Booker et al. 2015).

## Indications and Efficacy

### Seizure Disorders and Trigeminal Neuralgia

In the United States, CBZ is approved as monotherapy for the treatment of trigeminal neuralgia and complex partial, generalized tonic-clonic, and mixed seizure disorders (Physicians' Desk Reference 2015). OXC is approved for the treatment of partial seizures as monotherapy in adults and as adjunctive therapy in adults and children older than 4 years (Physicians' Desk Reference 2015). ESL is approved by the FDA as monotherapy or adjunctive treatment for partial-onset seizures (Physicians' Desk Reference 2015).

CBZ and OXC appear to have overlapping anticonvulsant effects, with similar efficacy in newly diagnosed epilepsy patients (Dam et al. 1989). However, there may be dissimilarities. For example, switching to OXC may be effective in patients with inadequate response or intolerable adverse effects with CBZ (Beydoun et al. 2000; Van Parys and Meinardi 1994), and adding OXC may improve efficacy in patients with inadequate response to CBZ (Barcs et al. 2000; Glauser et al. 2000).

### Acute Mania

The FDA approved a proprietary CBZ beaded extended-release capsule formulation (Equetro) for the treatment of acute manic and mixed episodes in patients with bipolar disorder in late 2004, but CBZ and OXC are still considered alternative agents in the management of bipolar disorder (American Psychiatric Association 2002). Twenty-six controlled studies have investigated the efficacy of CBZ, OXC, and ESL in acute mania (summarized in Table 38-1). In these studies, there is more compelling evidence for the efficacy of CBZ (18 studies encompassing 594 patients receiving CBZ) than for the efficacy of OXC (5 studies including 119 patients receiving OXC) or ESL (2 studies encompassing 146 patients receiving ESL).

**TABLE 38-1. Carbamazepine (CBZ), oxcarbazepine (OXC), and eslicarbazepine acetate (ESL) in acute mania: 26 double-blind studies**

Study	Design	CBZ/OXC/ESL (N)	Comparator (N)	Duration (days)	CBZ/OXC response	Completed response <sup>a</sup>
Weisler et al. 2004	CBZ vs. PBO	101	103	21	42%	22%
Weisler et al. 2005	CBZ vs. PBO	122	117	21	61%	29%
Zhang et al. 2007	CBZ vs. PBO	41	21	84	88%	57%

*Note.* CPZ=chlorpromazine; DVPX=divalproex; FGA=first-generation antipsychotic; HAL=haloperidol; Li=lithium; PBO=placebo.

<sup>a</sup>Weighted means of patients with response data.

Study	Design	CBZ/OXC/ESL (N)	Comparator (N)	Duration (days)	CBZ/OXC response	Com res
Wagner et al. 2006	OXC vs. PBO	55	55	42	42%	26
Ballenger and Post 1978; Post et al. 1987	PBO-CBZ-PBO	19	—	11–56	63%	Frec rel
Emrich et al. 1985	PBO-OXC-PBO	7	—	Varied	67%	-
Klein et al. 1984	CBZ vs. PBO adjunct (HAL)	14	13	35	71%	54
Müller and Stoll 1984; Gonçalves and Stoll 1985	CBZ vs. PBO adjunct (HAL)	6	6	21	CBZ>PBO	-
Gangadhar et al. 1987	CBZ vs. PBO adjunct (Li)	5	5	28	CBZ>PBO	-
Möller et al. 1989	CBZ vs. PBO adjunct (HAL)	11	9	21	CBZ=PBO	-
Okuma et al. 1989	CBZ vs. PBO adjunct (FGA)	82	80	28	48%	30
Okuma et al. 1979	CBZ vs. FGA (CPZ)	32	28	21–35	66%	54
Grossi et al. 1984	CBZ vs. FGA (CPZ)	18	19	21	67%	70
Emrich 1990	OXC vs. FGA (HAL)	19	19	14	OXC=HAL	-
Stoll et al. 1986	CBZ vs. FGA (HAL) adjunct (CPZ)	14	18	21	86%	67
Brown et al. 1989	CBZ vs. FGA (HAL) adjunct (CPZ)	8	9	28	75%	33

*Note.* CPZ=chlorpromazine; DVPX=divalproex; FGA=first-generation antips  
HAL=haloperidol; Li=lithium; PBO=placebo.

<sup>a</sup>Weighted means of patients with response data.

Study	Design	CBZ/OXC/ESL (N)	Comparator (N)	Duration (days)	CBZ/OXC response	Com res
Müller and Stoll 1984	OXC vs. FGA (HAL) adjunct (HAL)	10	10	14	OXC=HAL	-
Lerer et al. 1987	CBZ vs. Li	14	14	28	29%	79
Small et al. 1991	CBZ vs. Li	24	24	56	33%	33
Emrich 1990	OXC vs. Li	28	24	14	OXC=Li	-
Kakkar et al. 2009	OXC vs. DVPX	30	30	84	OXC=DVPX	-
Lenzi et al. 1986	CBZ vs. Li adjunct (CPZ)	11	11	19	73%	73
Lusznat et al. 1988	CBZ vs. Li adjunct (CPZ, HAL)	22	22	42	CBZ=Li	-
Okuma et al. 1990	CBZ vs. Li adjunct (FGA)	50	51	28	62%	59
Grunze et al. 2015	ESL vs. PBO	120	40	21	63%	50
Grunze et al. 2015	ESL vs. PBO	26	11	21	77%	91
<b>Total</b>		<b>889</b>	<b>739</b>			
<b>Response rates<sup>a</sup></b>	CBZ/OXC/ESL monotherapy				<b>58%</b> (333/579)	
	FGA monotherapy					<b>64</b> (30)
	Li monotherapy					<b>50</b> (19)
	PBO monotherapy					<b>33</b> (113)
<b>Response rates<sup>a</sup></b>	CBZ/OXC adjunctive				<b>59%</b> (106/179)	
	FGA adjunctive					<b>50</b> (15)
	Li adjunctive					<b>61</b> (38)
	PBO adjunctive					<b>33</b> (31)

*Note.* CPZ=chlorpromazine; DVPX=divalproex; FGA=first-generation antips  
HAL=haloperidol; Li=lithium; PBO=placebo.

<sup>a</sup>Weighted means of patients with response data.



## Carbamazepine and Oxcarbazepine

Two trials that found a proprietary CBZ beaded extended-release capsule formulation (Equetro) superior to placebo are of particular interest because they used a randomized double-blind, placebo-controlled design (Weisler et al. 2004, 2005) and led to the FDA indication for the treatment of acute manic and mixed episodes in patients with bipolar disorder. These reports are consistent with multiple earlier studies using placebo-drug-placebo, active comparator (lithium or first-generation antipsychotics), and adjunctive (compared with placebo, lithium, or first-generation antipsychotics added to lithium or antipsychotics) designs. Thus, across studies using diverse paradigms (see Table 38-1), overall antimanic response rates with CBZ were generally comparable to those seen with lithium or first-generation antipsychotics, or in other studies with valproate (Ketter 2010). Taken together, this collection of clinical trials provides substantial evidence for the acute antimanic efficacy of CBZ and preliminary evidence for the acute antimanic efficacy of OXC. For CBZ, this current body of existing data appears greater than that initially utilized by the FDA to approve lithium for the treatment of acute mania.

For CBZ, improvement appears to occur across the entire manic syndrome and does not seem to be due to nonspecific sedative properties because patients often show dramatic clinical improvement in the absence of marked sedation. Because CBZ and OXC are frequently used in combination with other medications in the acute treatment of mania, knowledge of CBZ's extensive and OXC's more limited drug-drug interactions (as described in the later section with that title) is often required to achieve optimal outcomes.

## Eslicarbazepine Acetate

In two 3-week studies of ESL in acute mania, ESL did not separate from placebo on the primary outcome measure of Young Mania Rating Scale change; however, Global Clinical Impression changes were suggestive of efficacy in one of the two studies (Grunze et al. 2015). High rates of placebo response and poor study recruitment (leading to premature study termination) may have contributed to failure in the second study (Grunze et al. 2015).

## Acute Depression

Limited controlled data exist regarding the acute antidepressant effects of CBZ, and there are no published controlled studies of the antidepressant effects of OXC or ESL (Table 38-2). Although CBZ appears to have weaker antidepressant than antimanic properties, some evidence suggests that it may provide antidepressant benefit in about one-third of patients with treatment-resistant depression (Neumann et al. 1984; Post et al. 1986; Small 1990), whereas in a Chinese study, CBZ produced a response rate closer to two-thirds in patients with non-treatment-resistant depression (Zhang et al. 2007). Unfortunately, most of these studies are limited by their use of small samples of heterogeneous (both bipolar and unipolar) patients with highly treatment-resistant depression.

**TABLE 38-2. Carbamazepine (CBZ) in acute depression: four controlled studies**

Study	Design	CBZ (N)	Comparator (N)	Duration (days)	CBZ response	Comparator response
-------	--------	------------	-------------------	--------------------	-----------------	------------------------

*Note.* BP=bipolar; Li=lithium; NS=not stated; PBO=placebo; TMI=trimipramine; UP=unipolar.



Study	Design	CBZ (N)	Comparator (N)	Duration (days)	CBZ response	Comparator response
Post et al. 1986	PBO-CBZ-PBO (24 BP, 11 UP)	35	35	Median 45	34%	—
Zhang et al. 2007	CBZ vs. PBO	47	23	84	64%	35%
Small 1990	CBZ/CBZ+Li vs. Li (4 BP, 24 UP)	NS	NS	28	32%	13%
Neumann et al. 1984	CBZ vs. TMI (5 BP, 5 UP)	5	5	28	CBZ=TMI	—

*Note.* BP=bipolar; Li=lithium; NS=not stated; PBO=placebo; TMI=trimipramine; UP=unipolar.

## Maintenance and Relapse-Prevention Treatment

### Carbamazepine and Oxcarbazepine

A series of 18 double-blind randomized, open randomized, or otherwise partially controlled studies have examined the efficacy of CBZ and OXC in maintenance treatment of bipolar disorder (summarized in Table 38-3). The 15 CBZ trials are consistent with a very substantial open literature suggesting that CBZ may be effective in preventing mood episodes when administered during long-term treatment, either alone or in combination with lithium in previous lithium nonresponders (see Table 38-3). Indeed, five reviews of different subsets of studies included in Table 38-3 broadly indicated that CBZ and lithium monotherapy had comparable prophylactic effects in patients with bipolar disorder (Ceron-Litvoc et al. 2009; Dardennes et al. 1995; Davis et al. 1999; Hirschfeld and Kasper 2004; Smith et al. 2007). CBZ may have equal *prophylactic* antidepressant and antimanic efficacy, in contrast to its less potent *acute* antidepressant compared with antimanic effects. In contrast, data regarding the efficacy of OXC in preventing new mood episodes in patients with bipolar disorder are more limited (Cabrera et al. 1986; Vieta et al. 2008; Wildgrube 1990). A 2008 Cochrane review assessed the available data as inadequate to recommend OXC in the maintenance treatment of bipolar disorder (Vasudev et al. 2008).

**TABLE 38-3. Carbamazepine (CBZ) and oxcarbazepine (OXC) in maintenance treatment of bipolar disorder: 18 controlled or quasi-controlled studies**

Study	Design	CBZ/OXC (N)	Comparator (N)	Duration (years)	CBZ/OXC response	Comparator response
Okuma et al. 1981	CBZ vs. PBO (B, R)	12	10	1	60%	22%

*Note.* B=blinded; C=crossover; Li=lithium; M=mirror image; NR=not randomized; NS=not stated; PBO=placebo; R=randomized.

<sup>a</sup>Weighted means of patients with response data.

Study	Design	CBZ/OXC (N)	Comparator (N)	Duration (years)	CBZ/OXC response	Comparator response
Ballenger and Post 1978; Post et al. 1983	CBZ vs. PBO (B, M)	7	7	1.7	86%	NS
Placidi et al. 1986	CBZ vs. Li (B, R)	20	16	≤3	67%	67%
Watkins et al. 1987	CBZ vs. Li (B, R)	19	18	1.5	84%	83%
Lusznat et al. 1988	CBZ vs. Li (B, R)	16	15	≤1	56%	29%
Coxhead et al. 1992	CBZ vs. Li (B, R)	13	15	1	54%	47%
Bellaire et al. 1988	CBZ vs. Li (R)	46	52	1	CBZ=Li	NS
Greil et al. 1997	CBZ vs. Li (R)	70	74	2.5	45%	65%
Berky and Kovacs 1998	CBZ vs. Li (R)	84	84	1	CBZ=Li	NS
Hartong et al. 2003	CBZ vs. Li (R)	50	44	2	58%	73%
Di Costanzo and Schifano 1991	CBZ+Li vs. Li (R)	8	8	≤5	CBZ+Li>Li	NS
Mosolov 1991	CBZ vs. Li (R?)	30	30	≥1	73%	70%
Cabrera et al. 1986	OXC vs. Li (R)	4	6	≤22	75%	100%
Elphick et al. 1988	CBZ vs. Li (B, C)	8	11	0.75	38%	73%
Denicoff et al. 1997	CBZ vs. Li (B, C)	46	50	1	33%	55%
Kishimoto and Okuma 1985	CBZ vs. Li (C)	18	18	≥2	CBZ>Li	NS
Wildgrube 1990	OXC vs. Li (NR)	8	7	≤33	33%	67%
Vieta et al. 2008	OXC vs. PBO adjunct (B, R)	26	29	1	50%	34%

*Note.* B=blinded; C=crossover; Li=lithium; M=mirror image; NR=not randomized; NS=not stated; PBO=placebo; R=randomized.

<sup>a</sup>Weighted means of patients with response data.

Study	Design	CBZ/OXC (N)	Comparator (N)	Duration (years)	CBZ/OXC response	Comparator response
<b>Total</b>		<b>485</b>	<b>486</b>			
<b>Response rates<sup>a</sup></b>	CBZ/OXC				<b>54%</b> (178/329)	
	Li					<b>64%</b> (185/286)
	PBO					<b>32%</b> (12/38)

*Note.* B=blinded; C=crossover; Li=lithium; M=mirror image; NR=not randomized; NS=not stated; PBO=placebo; R=randomized.

<sup>a</sup>Weighted means of patients with response data.

In one study, the overall analysis suggested that maintenance treatment was more effective with lithium than with CBZ (Greil et al. 1997). However, subgroup differences may exist, such that lithium may be more effective in patients with “classical” bipolar disorder (i.e., bipolar I disorder with no mood-incongruent delusions or comorbidity), whereas CBZ may be more effective in patients with “nonclassical” bipolar disorder (e.g., bipolar II disorder, DSM-IV [American Psychiatric Association 1994] bipolar disorder not otherwise specified, bipolar disorder with mood-incongruent delusions or comorbidity) (Greil et al. 1998).

In another study, lithium maintenance treatment appeared to be more effective than CBZ in patients with no more than 6 months’ prior exposure to either agent (Hartong et al. 2003). However, this advantage was offset by more early discontinuations in the lithium group, so that similar proportions (about one-third) of patients completed 2 years with no episode. Patients taking lithium versus CBZ tended to have somewhat greater risk of episodes in the first 3 months and markedly less risk of episodes after the first 3 months, with a recurrence risk of only 10% per year with lithium after the first 3 months. Patients taking CBZ had a more consistent rate of relapse or recurrence of about 40% per year.

Some CBZ relapse-prevention trials have been criticized for their methodological limitations (Murphy et al. 1989), although such difficulties are common in maintenance studies. (For example, divalproex and lithium failed to separate from placebo on the primary efficacy measure in a 1-year maintenance study [Bowden et al. 2000], a result at least partially due to methodological problems.) Taken together, this collection of randomized placebo-controlled, placebo-drug-placebo, and lithium comparator studies and trials in rapid-cycling and lithium-resistant populations provides substantial evidence for the preventive efficacy of CBZ (Priem and Gelenberg 1989). CBZ may be effective in some individuals with valproate-resistant illness (Post et al. 1984b), and the CBZ-plus-valproate combination may be effective in patients with little or no response to either agent alone (Keck et al. 1992; Ketter et al. 1992).

In a retrospective study, although 22 of 34 (65%) patients with treatment-resistant bipolar disorder responded to primarily adjunctive open CBZ acutely, when patients were

assessed 3–4 years later, only 7 of 34 (21%) and 2 of 34 (6%) were considered probable and clear responders, respectively ([Frankenburg et al. 1988](#)). [Post et al. \(1990; Post and Weiss 2011\)](#) have suggested that loss of CBZ prophylactic efficacy over time may be related to a unique form of contingent tolerance. In these instances, techniques such as switching to another treatment regimen with a different mechanism of action or returning later to CBZ (after a period of not taking CBZ) are worth considering, based on case reports and anecdotal observations.

### Eslicarbazepine Acetate

A 6-month continuation study investigated the efficacy of three different dosages of ESL (300 mg/day, 900 mg/day, and 1,800 mg/day) in preventing symptom recurrence in the bipolar patients who had participated in the earlier placebo-controlled studies of ESL in acute mania. Of the 85 patients who had responded during acute treatment and were randomly assigned to one of the three dosage groups, at least 50% did not show any clinical worsening, although there was no significant difference between dosage groups ([Grunze et al. 2015](#)).

## Response Predictors

Predictors of CBZ and OXC response have not been adequately elucidated. CBZ can be effective in patients with a history of lithium unresponsiveness or intolerance ([Okuma et al. 1979; Post et al. 1987](#)). Nonclassical bipolar disorder ([Greil et al. 1998; Small et al. 1991](#)) and stable or decreasing episode frequency ([Post et al. 1990](#)) may be associated with CBZ response. Patients with a history of affective illness in first-degree relatives may preferentially respond to lithium, whereas the converse may be the case for CBZ ([Ballenger and Post 1978; Post et al. 1987](#)). Patients with comorbid neurological or substance abuse problems and inadequate lithium responses may respond to CBZ or valproate ([Himmelhoch 1987; Himmelhoch and Garfinkel 1986](#)). Preliminary observations indicate that baseline cerebral (left insula) hypermetabolism may be a marker of CBZ response ([Ketter et al. 1999](#)).

Reports vary with respect to the relationships between CBZ response and dysphoric manic presentations ([Lusznat et al. 1988; Post et al. 1989](#)) and illness severity ([Post et al. 1987; Small et al. 1991](#)). Antidepressant responses to CBZ may be seen in patients with more severe depression, more discrete depressive episodes, less chronicity, and greater decreases in serum thyroxine concentrations with CBZ ([Post et al. 1986, 1991](#)).

Although the initial studies of [Post et al. \(1987\)](#) and [Okuma et al. \(1981; Okuma 1983\)](#) indicated that some rapid-cycling patients were responsive to CBZ, other investigators found less robust results ([Dilsaver et al. 1993; Joyce 1988](#)). As with lithium, later studies by Okuma and associates reported a lower CBZ maintenance response rate in rapid cycling compared with non-rapid-cycling illness ([Okuma 1993](#)). However, even these rapid-cycling patients had a CBZ response rate (40%) that was higher than rates reported with other agents in other studies. [Denicoff et al. \(1997\)](#) also observed that patients with a history of rapid cycling had a lower response rate to maintenance CBZ (as with maintenance lithium) compared with those without such as history (19% vs. 54%), but rapid cyclers did well on the combination of lithium and CBZ.

---

## Side Effects and Toxicology

---

Baseline evaluation of patients with bipolar disorder includes not only psychosocial assessment but also a general medical evaluation in view of the risk of medical processes, which could confound diagnosis or influence management decisions, and the risk of adverse effects, which may occur with treatment. Assessment commonly includes history; physical examination; complete blood count with differential and platelets; renal, hepatic, and thyroid function; toxicology; pregnancy tests; and other chemistries and electrocardiogram as clinically indicated ([American Psychiatric Association 2002](#)). Such evaluation provides baseline values for parameters that influence decisions about choice of medication and intensity of clinical and laboratory monitoring.

## Carbamazepine

Adverse effects appear to have substantial impact on the utility of CBZ in the treatment of bipolar disorder. In a pooled analysis of two multicenter acute mania FDA registration studies of a proprietary extended-release capsule formulation of carbamazepine (Equetro), the number needed to harm for somnolence was 6, and for at least 7% weight gain, the number was 23 ([Ketter et al. 2011](#)), suggesting that neurocognitive adverse effects more than weight gain might limit CBZ utility ([Ketter 2015](#)). Some patients may tolerate CBZ better than other agents, particularly during longer-term treatment, because CBZ appears to have a low propensity to cause adverse effects such as weight gain and metabolic disturbance that can limit the utility of some other agents ([Akiskal et al. 2005](#); [Ketter 2015](#)).

CBZ has several common dose-related adverse effects that generally can be minimized by attention to drug-drug interactions and gradual titration of dosage or reversed by decreasing dosage. At high dosages, patients can develop neurotoxicity with sedation, ataxia, diplopia, and nystagmus, particularly early in therapy, before the autoinduction process is complete and tolerance develops to the CNS adverse effects of CBZ. Because there is wide interindividual variation in susceptibility to adverse effects at any given concentration, it is most useful clinically to titrate doses against each patient's adverse effects rather than targeting a fixed dosage or serum concentration range.

Neurotoxic effects that emerge 1–2 hours after an individual dose often signal that the adverse-effect threshold has been exceeded and that dose redistribution (spreading out the doses or giving more of the dose at bedtime) or dosage reduction may be required. Use of extended-release formulations may attenuate CBZ peak serum concentrations, enhancing tolerability.

CBZ commonly causes benign hematological (leukopenia, thrombocytopenia), dermatological (rash), electrolyte (asymptomatic hyponatremia), and hepatic (transaminase elevations) problems. Analogous serious problems are much less common. For example, mild leukopenia and benign rash occur in up to 1 in 10 patients, with the slight possibility that these usually benign phenomena are heralding malignant aplastic anemia and Stevens-Johnson syndrome, seen in about 1 in 100,000 patients ([Kramlinger et al. 1994](#); [Tohen et al. 1995](#)).

In view of the risk of rare but serious decreases in blood counts, which warrant a black box warning in the CBZ prescribing information, it is important to alert patients to seek immediate medical evaluation if they develop signs and symptoms of possible hematological reactions, such as fever, sore throat, oral ulcers, petechiae, and easy bruising or bleeding. Hematological monitoring needs to be intensified in patients with low or marginal leukocyte counts, and CBZ is generally discontinued if the leukocyte count falls below 3,000/ $\mu$ L or the granulocyte count below 1,000/ $\mu$ L. In the instance of benign

leukopenia, the addition of lithium can increase the neutrophil count back toward normal ([Kramlinger and Post 1990](#)), but this strategy is not likely to be helpful for the suppression of red cells or platelets, which is likely to indicate a more problematic process.

Serious rash may occur in about 1 in 100,000 patients. The risk of serious and sometimes fatal dermatological reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, may be increased tenfold in certain Asian populations and has been strongly linked to the human leukocyte antigen (HLA) *B\*1502* allele ([Physicians' Desk Reference 2015](#)). Thus, the U.S. prescribing information includes a black box warning that individuals of Asian ancestry should be genetically tested for *HLA-B\*1502* and that carriers of this allele should not be treated with CBZ. A twelvefold increased risk of drug-induced hypersensitivity syndrome (DIHS; also called drug rash with eosinophilia and systemic symptoms [DRESS]) has also been linked to *HLA-A\*3101* in whites of northern European descent ([McCormack et al. 2011](#)). Given the risk of serious rash, patients should be alerted to seek medical attention immediately if a rash develops. In particular, rash in patients presenting with systemic illness or involvement of the eyes, mouth, or bladder (dysuria) constitutes a medical emergency: carbamazepine should be immediately discontinued, and the patient should be assessed emergently ([Scaparrotta et al. 2011](#)). For more benign presentations, CBZ is generally discontinued, because there is little ability to predict which cases will progress to more severe, potentially life-threatening problems. However, in rare instances of resistance to all medications except CBZ, a repeat trial of CBZ with a course of prednisone has usually been well tolerated ([Murphy et al. 1991](#); [Vick 1983](#)). A substantial number of patients with CBZ-induced rash may not develop a rash on reexposure (even without prednisone coverage), but if a rash develops again, it usually appears more rapidly than the first occurrence. Only 25%–30% of patients who develop a rash with CBZ also develop a rash (cross-sensitivity) with OXC.

CBZ, in common with multiple other anticonvulsant medications (including OXC and ESL), may increase the risk of suicidality, including suicidal behavior or ideation. Data from controlled trials of anticonvulsant medications compared with placebo found a 1.5-fold increased risk from 0.57% to 0.85% for psychiatric patients ([Physicians' Desk Reference 2015](#)).

Because of the risk of rare hepatitis, patients should be advised to seek medical evaluation immediately if they develop malaise or abdominal pain or other marked gastrointestinal symptoms. In general, CBZ (like other anticonvulsants) should be discontinued if liver function values exceed three times the upper limit of the normal range ([Martínez et al. 1993](#)).

CBZ may affect cardiac conduction and should be used with caution in patients with cardiac disorders such as heart block. A baseline electrocardiogram is worth considering if there is a positive cardiac history.

Conservative laboratory monitoring during CBZ therapy includes baseline studies and evaluation of complete blood count, differential, platelets, and hepatic indices initially and at 2, 4, 6, and 8 weeks and then every 3 months ([American Psychiatric Association 1994, 2002](#)). Most of the serious hematological reactions occur within the first 3 months of therapy ([Tohen et al. 1995](#)). In contemporary clinical practice, clinically indicated monitoring (e.g., when a patient becomes ill with a fever) is emphasized over scheduled monitoring. Patients who have abnormal or marginal indices at any point merit careful scheduled and clinically indicated monitoring. The U.S. prescribing information for the beaded extended-release capsule CBZ formulation recommends a baseline complete blood count including platelets, possibly reticulocytes, possibly serum iron, and hepatic function tests; closely monitoring patients with low or decreased white blood cell counts or



platelets; and considering discontinuation of CBZ if evidence indicates bone marrow depression ([Physicians' Desk Reference 2015](#)). Serum CBZ concentrations are typically assessed at steady state and then as indicated by inefficacy or adverse effects. An important clinical note is that because of autoinduction, CBZ concentrations may decrease during the first 2–3 weeks after treatment initiation ([Eichelbaum et al. 1975](#)), thus potentially requiring readjustment of steady-state dosing.

Dividing or reducing dosages, rescheduling individual doses in relation to mealtimes, and changing formulations can attenuate CBZ-induced gastrointestinal disturbance. The CBZ oral suspension formulation may have more proximal absorption and thus may exacerbate upper gastrointestinal adverse effects (nausea and vomiting) or attenuate lower gastrointestinal effects (diarrhea). The reverse holds for extended-release preparations.

Weight gain and obesity are important clinical concerns in the management of bipolar disorder. Medications and the hyperphagia, hypersomnia, and anergy commonly seen in bipolar depression can contribute to this important obstacle to optimal outcomes. CBZ is less likely than lithium ([Coxhead et al. 1992](#); [Denicoff et al. 1997](#)) or valproate ([Mattson et al. 1992](#)) to cause weight gain. In one study, CBZ caused weight gain in depressed (but not manic) patients, which seemed to be related to the degree of relief of depression ([Joffe et al. 1986](#)). Nevertheless, in view of its relatively benign effect on weight, CBZ may provide an important alternative to other mood stabilizers for patients who struggle with weight gain and obesity.

CBZ can induce hyponatremia, which may be tolerated well by some younger patients but can be particularly problematic in the elderly. If confusion develops in an elderly patient, serum sodium should be assessed. In rare instances, water intoxication and seizures can occur. In some cases, hyponatremia can be effectively counteracted with the addition of lithium or the antibiotic demeclocycline ([Ringel and Brick 1986](#)).

CBZ increases plasma high-density lipoprotein (HDL; [O'Neill et al. 1982](#)) and total cholesterol ([Brown et al. 1992](#)) concentrations. However, the HDL-to-total cholesterol ratio does not change ([O'Neill et al. 1982](#)), and thus, CBZ-induced increases in total cholesterol are not likely to be clinically problematic in relation to atherosclerosis ([Brown et al. 1992](#)).

CBZ appears to reduce serum concentrations of both female and male sex hormones ([Verrotti et al. 2011](#)). In common with several other anticonvulsants, CBZ may adversely affect bone density ([Verrotti et al. 2010](#)).

CBZ is teratogenic (former FDA pregnancy category D) and is associated with low birth weight, craniofacial deformities, digital hypoplasia, and, in approximately 3% of births, spina bifida ([Jones et al. 1989](#); [Rosa 1991](#)). Folate supplementation may attenuate the risk of spina bifida, and fetal ultrasound studies may allow early detection. In one study of children born to women with epilepsy, in utero exposure to CBZ or valproate, but not to lamotrigine, had a detrimental effect on child neurodevelopment, although CBZ appeared less likely than valproate to cause major developmental delays ([Cummings et al. 2011](#)).

CBZ is present in breast milk at concentrations about half those in maternal blood, but it may not accumulate in fetal blood ([Froescher et al. 1984](#); [Kuhn et al. 1983](#); [Pynnönen et al. 1977](#); [Shimoyama et al. 2000](#)). Clinicians may prefer to avoid the risk of exposing infants to CBZ in breast milk ([Frey et al. 2002](#)) and may wish to discourage breast feeding in women taking CBZ ([Physicians' Desk Reference 2015](#)).

## Oxcarbazepine

As with CBZ, adverse effects may limit OXC therapy. However, OXC may have tolerability advantages compared with CBZ ([Dam et al. 1989](#)), in part perhaps related to the absence of the CBZ-E metabolite. Of note, OXC lacks black box warnings regarding serious rash, blood dyscrasias, or tissue typing, although OXC still has the class warning regarding increased risk of suicidality. Compared with CBZ, OXC appears to have a lower propensity to cause neurotoxicity and rash. About 75% of patients who develop a rash with CBZ will tolerate OXC. OXC does not appear to require hematological monitoring.

OXC, like CBZ, may cause transaminase elevations and gastrointestinal adverse effects, but there is less weight gain than with valproate ([Rättyä et al. 1999](#)) and less impact on lipids than with CBZ ([Isojärvi et al. 1994](#)). Hyponatremia occurs more commonly with OXC ([Friis et al. 1993](#)) than with CBZ ([Isojärvi et al. 2001a](#)). However, clinically significant hyponatremia is less common than asymptomatic hyponatremia ([Reinstein et al. 2002](#)).

Compared with CBZ, OXC has less impact on female hormone blood concentrations, likely due to its less marked hepatic enzyme induction. However, OXC induction of female hormone metabolism may still decrease the efficacy of hormonal contraceptives ([Fattore et al. 1999](#); [Krämer et al. 1992](#)). OXC, in common with CBZ and several other anticonvulsants, may adversely affect bone density ([Verrotti et al. 2010](#)).

OXC, in contrast to CBZ, has not to date been associated with congenital malformations in humans (former FDA pregnancy category C). Whether this is due to fewer OXC exposures or the absence of the CBZ-E metabolite (rendering OXC less teratogenic) is unknown. OXC is present in breast milk; therefore, as with CBZ, clinicians may prefer to avoid the risk of exposing infants to OXC in breast milk and may wish to discourage breast feeding in women taking OXC ([Physicians' Desk Reference 2015](#)).

## Eslicarbazepine Acetate

Adverse effects may limit OXC therapy, as with CBZ, but owing to structural advantages, tolerability may be better with ESL ([Almeida and Soares-da-Silva 2007](#)). The most commonly reported adverse effects from two epilepsy registration studies included somnolence, dizziness, vertigo, ataxia, abnormal coordination, diplopia, fatigue, and headache ([Physicians' Desk Reference 2015](#)). The risk of rash was low (about 1%). The risk of hyponatremia with ESL is unknown, with rates ranging from 0.6% to 1.3% in premarketing trials ([Zaccara et al. 2015](#)) and rates as high as 3% in postmarketing studies ([Massot et al. 2014](#)). Significant decreases in sodium levels ( $\geq 10$  mEq/L) were more common with ESL than with placebo ([Physicians' Desk Reference 2015](#)). ESL may increase QT interval on electrocardiogram ([Vaz-Da-Silva et al. 2012](#)).

Importantly, ESL, similar to OXC, lacks black box warnings for serious rash, blood dyscrasias, or tissue typing, although ESL still has the (non-black box) class warning regarding increased risk of suicidality.

ESL, like OXC, has not to date been associated with congenital malformations in humans (former FDA pregnancy category C), and ESL is excreted in breast milk ([Physicians' Desk Reference 2015](#)).

---

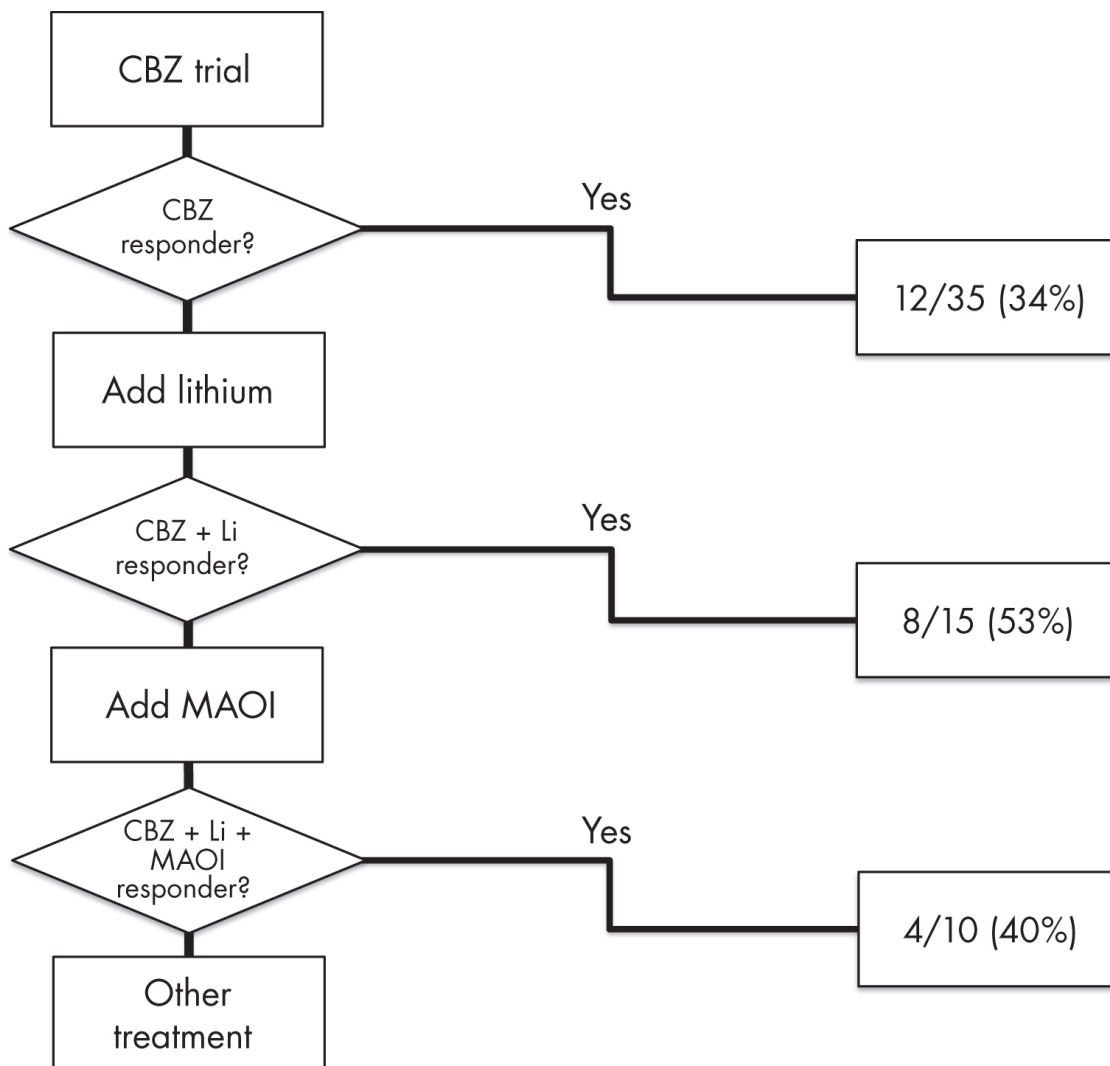
## Drug-Drug Interactions

---

Combination therapy is common in bipolar disorder, with up to two-thirds of patients taking more than one medication concurrently ([Kupfer et al. 2002](#)). Patients with treatment-resistant illness may require a stepped-care approach ([Figure 38-3](#)), and they



appear to be receiving increasingly complex medication regimens ([Frye et al. 2000](#)). CBZ, and to a lesser extent OXC, has clinically significant drug–drug interactions that increase the complexity of managing patients with bipolar disorder.



**FIGURE 38-3.** Stepped-care approach to bipolar depression.

Composite schema of results from three different studies in which patients with bipolar depression received carbamazepine (CBZ) monotherapy ([Post et al. 1986](#)), lithium (Li) added to CBZ ([Kramlinger and Post 1989b](#)), or a monoamine oxidase inhibitor (MAOI) added to CBZ±Li ([Ketter et al. 1995b](#)). Each successive intervention resulted in additional efficacy.

## Carbamazepine

The pharmacokinetic properties of CBZ are typical of older enzyme-inducing anticonvulsants but are atypical among medications prescribed by psychiatrists. CBZ necessitates special care when treating patients concurrently with other medications ([Ketter et al. 1991a, 1991b](#)). Three major principles appear to make important contributions to CBZ drug–drug interactions:

1. **CBZ is a robust inducer of catabolic enzymes (including CYP3A3/4) and decreases the serum concentrations of many medications, including CBZ itself (Table 38-4).** CBZ induces not only CYP3A3/4 and conjugates but also presumably other uncharacterized CYP isoforms. Thus, CBZ decreases the serum concentrations of CBZ itself (autoinduction) (Eichelbaum et al. 1975) and of other medications (heteroinduction). If CBZ is taken concurrently with certain medications, CBZ-induced decreases in serum concentrations can render these medications ineffective (Table 38-4). Moreover, if CBZ is discontinued, serum concentrations of these other medications can increase, potentially leading to adverse effects.

**TABLE 38-4. Selected drugs whose serum concentrations are DECREASED by carbamazepine (and oxcarbazepine)**

<b>Antidepressants</b>	<b>Anticonvulsants</b>	<b>Dihydropyridine CCBs</b>
Bupropion	Carbamazepine	<i>Felodipine</i>
Citalopram	Ethosuximide	Nimodipine
Mirtazapine	Felbamate	
Sertraline	<i>Lamotrigine</i>	<b>Immunosuppressants</b>
Tricyclics	Levetiracetam (?)	Cyclosporine (?)
	Oxcarbazepine	Sirolimus
<b>Antipsychotics</b>	Phenytoin	Tacrolimus
Aripiprazole	Primidone	
Chlorpromazine (?)	Tiagabine	<b>Muscle relaxants</b>
Clozapine	Topiramate	Atracurium
Fluphenazine (?)	Valproate	Cisatracurium
Haloperidol	Zonisamide	Doxacurium
Olanzapine		Mivacurium
Quetiapine (?)	<b>Analgesics</b>	Pancuronium
Risperidone	Alfentanil	Pipercuronium
Thiothixene (?)	<i>Buprenorphine</i>	Rocuronium
Ziprasidone (?)	Fentanyl (?)	Vecuronium
	Levobupivacaine	
<b>Anxiolytics/sedatives</b>	Methadone	<b>Steroids</b>
<i>Alprazolam (?)</i>	Tramadol	Dexamethasone
Buspirone		<i>Hormonal contraceptives</i>
<i>Clonazepam</i>	<b>Anticoagulants</b>	Mifepristone
Eszopiclone (?)	Warfarin	Prednisolone
Midazolam		

*Note. Italic type indicates that serum concentrations of the medication may decrease to a clinically significant extent not only with carbamazepine but also with oxcarbazepine, hindering efficacy of the agent. (?)=unclear clinical significance; CCBs=calcium channel blockers.*

	<b>Anti-infectives</b>	<b>Others</b>
<b>Stimulants</b>	Caspofungin	<i>Paclitaxel</i>
Methylphenidate	Delavirdine	Quinidine
Modafinil	Doxycycline	<i>Repaglinide</i>
	Praziquantel	Theophylline (?)
	Protease inhibitors	Thyroid hormones

*Note.* *Italic type* indicates that serum concentrations of the medication may decrease to a clinically significant extent not only with carbamazepine but also with oxcarbazepine, hindering efficacy of the agent. (?)=unclear clinical significance; CCBs=calcium channel blockers.

- CBZ metabolism (primarily CYP3A3/4) can be inhibited by certain enzyme inhibitors, yielding increases in serum CBZ concentrations and CBZ intoxication** (Table 38-5 and Figure 38-1, top). Autoinduction makes CBZ particularly vulnerable to the effects of enzyme inhibitors. Thus, a variety of agents that inhibit CYP3A3/4 can yield increased serum CBZ concentrations and intoxication (Table 38-5 and Figure 38-1, top).

**TABLE 38-5. Selected drugs that INCREASE serum concentrations of carbamazepine (but not oxcarbazepine)**

<b>Antidepressants</b>	<b>Calcium channel blockers</b>
Fluoxetine	Diltiazem
Fluvoxamine	Verapamil
Nefazodone	
	<b>Hypolipidemics</b>
<b>Anti-infectives</b>	Gemfibrozil
Isoniazid	Nicotinamide
Quinupristin/dalfopristin	
	<b>Others</b>
<b>Azole antifungals</b>	Acetazolamide
Fluconazole	Cimetidine
Itraconazole	Danazol
Ketoconazole	Grapefruit juice
	Omeprazole
<b>Macrolide antibiotics</b>	<i>d</i> -Propoxyphene
Clarithromycin	Ritonavir
Erythromycin	Ticlopidine (?)
Troleandomycin	Valproate (increases CBZ-E)

*Note.* (?)=unclear clinical significance; CBZ-E=carbamazepine-10,11-epoxide.

- CBZ has an active epoxide (CBZ-E) metabolite** (Figure 38-1, top). Valproate inhibits epoxide hydrolase, yielding increased serum CBZ-E (but not CBZ) concentrations (Table

38-5). Free CBZ may also increase because of valproate-induced displacement of CBZ protein binding.

CBZ has a wide variety of pharmacokinetic drug-drug interactions, in excess of and different from those seen with lithium or valproate. In the following subsections, we review CBZ drug interactions with other medications, with agents of particular interest in the management of mood disorders indicated in **boldface** type. The reader interested in detailed reviews of CBZ drug-drug interactions is referred to the review by [Ketter et al. \(1991a, 1991b\)](#).

### Interactions With Mood Stabilizers and Anticonvulsants

The combination of CBZ plus lithium is frequently used in bipolar disorder, and it may provide additive or synergistic antimanic ([Kramlinger and Post 1989a](#)) and antidepressant ([Kramlinger and Post 1989b](#)) effects. The combination is generally well tolerated, with merely additive (as opposed to synergistic or antagonistic) neurotoxicity ([McGinness et al. 1990](#)), which can be minimized by gradual dosage escalation. Pharmacokinetic interactions between these drugs do not occur because lithium has no hepatic metabolism. Adverse effects of lithium and CBZ can be either additive or complementary, so combination therapy decreases the serum concentrations of thyroid hormones in an additive fashion ([Kramlinger and Post 1990](#)), whereas lithium-induced increases in leukocytes and neutrophils override the common benign decreases in these indices seen with CBZ ([Kramlinger and Post 1990](#)). It is important to note that lithium cannot alter the course of the rare severe bone marrow suppression caused by CBZ ([Joffe and Post 1989](#)). Also, the diuretic effect of lithium overrides the antidiuretic effect of CBZ ([Klein 1987](#)). Thus, CBZ will not reverse lithium-induced diabetes insipidus, although lithium can attenuate CBZ-induced hyponatremia ([Klein 1987](#); [Vieweg et al. 1987](#)).

Reports suggest that the combination of CBZ plus **valproate** only is not tolerated but also shows psychotropic synergy ([Keck et al. 1992](#); [Ketter et al. 1992](#); [Tohen et al. 1994](#)). Effective combination treatment with these two medications requires a thorough knowledge of their drug interactions, which can be simplified with the general principle that usual dosages of CBZ should be reduced. Valproate inhibits CBZ metabolism ([Macphée et al. 1988](#)) and also displaces CBZ from plasma proteins, increasing the free CBZ fraction that is active and available to be metabolized ([Macphée et al. 1988](#); [Moreland et al. 1984](#)). Depending on which effect predominates, total serum CBZ concentrations can vary ([Brodie et al. 1983](#); [Kutt et al. 1985](#); [Macphée et al. 1988](#); [Moreland et al. 1984](#); [Rambeck et al. 1987](#)). Valproate inhibits epoxide hydrolase, increasing the serum CBZ-E concentration, at times without altering the total serum CBZ concentration ([Brodie et al. 1983](#); [Rambeck et al. 1987](#)).

These interactions can potentially confuse clinicians, because patients can experience neurotoxicity from elevated serum CBZ-E or free CBZ concentrations even if their serum total CBZ concentrations are at therapeutic levels ([Kutt et al. 1985](#)). CBZ decreases serum valproate concentrations ([Kondo et al. 1990](#)), and its discontinuation can result in increased serum valproate concentrations and toxicity ([Jann et al. 1988](#)). CBZ enzyme induction also increases the formation of the active valproic acid metabolite, 2-propyl-4-pentenoic acid (4-ene-valproic acid; [Kondo et al. 1990](#)), which may be hepatotoxic and may add to teratogenicity ([Nau and Löscher 1986](#); [Scheffner et al. 1988](#)). The risk of fatal hepatitis is of great concern in infants treated with combinations of valproate with other anticonvulsants ([Scheffner et al. 1988](#)), but this risk is much lower in adults ([Dreifuss et al. 1989](#)). As a general rule, clinicians should clinically monitor patients receiving the CBZ-

plus-valproate combination for adverse effects and should consider decreasing the CBZ dosage in advance of adding valproate, and possibly increasing the valproate dosage.

CBZ increases **lamotrigine** metabolism and approximately halves blood lamotrigine concentrations. Thus, lamotrigine dosages can be doubled with this combination. CBZ combined with lamotrigine may have additive neurotoxic effects, probably due to a pharmacodynamic interaction. CBZ even appears to affect **OXC** metabolism; in epilepsy patients, CBZ yielded decreased serum MHD concentrations (McKee et al. 1994).

CBZ induces the metabolism of **CBZ** (autoinduction) and **OXC** (McKee et al. 1994), as well as the metabolism of several older (e.g., ethosuximide, phenytoin, primidone) and newer (e.g., felbamate, **topiramate**) anticonvulsants (Sachdeo et al. 1996), tiagabine (Samara et al. 1998), and **zonisamide** (Ojemann et al. 1986), but not gabapentin (Radulovic et al. 1994) or pregabalin (Brodie et al. 2005). The enzyme-inducing anticonvulsants phenytoin, phenobarbital, primidone, methsuximide, and felbamate decrease serum CBZ levels.

## Interactions With Antidepressants

Antidepressants are commonly combined with mood stabilizers in the treatment of bipolar disorder. These drug-drug interactions may be bidirectional.

**Fluoxetine** (Grimsley et al. 1991; Pearson 1990), **fluvoxamine** (Fritze et al. 1991), and **nefazodone** (Ashton and Wolin 1996; Laroudie et al. 2000; Roth and Bertsch 2001) have been reported to inhibit CBZ metabolism, causing increased CBZ concentrations and toxicity. In addition, parkinsonian symptoms have been reported after adding fluoxetine to CBZ (Gernaat et al. 1991). In contrast, sertraline (Rapeport et al. 1996), paroxetine (Andersen et al. 1991), citalopram (Møller et al. 2001), and mirtazapine (Sitsen et al. 2001) do not appear to alter CBZ metabolism. CBZ appears to decrease serum concentrations of racemic **citalopram** and **escitalopram** (Steinacher et al. 2002). CBZ also appears to induce the metabolism of **mirtazapine** (Sitsen et al. 2001), **mianserin** (Eap et al. 1999), and **sertraline** (Khan et al. 2000; Pihlgård and Eliasson 2002), and (to some extent) that of trazodone (Otani et al. 1996), as well as (most likely) that of vilazodone (Physicians' Desk Reference 2015). Coadministration of CBZ with mirtazapine is of potential concern because mirtazapine has been associated with rare agranulocytosis.

Patients receiving CBZ and **bupropion** have extremely low serum bupropion concentrations and high hydroxybupropion (metabolite) concentrations (Ketter et al. 1995a). Because hydroxybupropion is active, this dramatic decrease in the ratio of bupropion to hydroxybupropion is unlikely to be clinically problematic, and the combination of CBZ and bupropion may often be effective and well tolerated.

CBZ may increase rather than decrease serum levels of transdermal selegiline and its metabolites (Physicians' Desk Reference 2015). Theoretical grounds have been stated for concern about combining CBZ with monoamine oxidase inhibitors (MAOIs; Thweatt 1986), but case reports (Joffe et al. 1985; Yatham et al. 1990) and series (Ketter et al. 1995b) suggest that the addition of phenelzine or tranylcypromine to CBZ may be well tolerated. However, the anti-tuberculosis drug isoniazid, which is also an MAOI, increases CBZ levels.

CBZ appears to induce the metabolism of **tricyclic antidepressants** (TCAs), including amitriptyline (Leinonen et al. 1991), nortriptyline ( ), imipramine (C.S. Brown et al. 1990), desipramine (Baldessarini et al. 1988), doxepin (Leinonen et al. 1991), and clomipramine (De la Fuente and Mendlewicz 1992). Therefore, if patients do not respond to standard dosages of TCAs, TCA and metabolite concentrations should be checked.

## Interactions With Antipsychotics

Combinations of antipsychotics with mood stabilizers are commonly required in severe mania ([American Psychiatric Association 2002](#)) and are increasingly used in bipolar maintenance treatment ([Ketter 2015](#); [Physicians' Desk Reference 2015](#)).

CBZ increases **haloperidol** metabolism ([Ereshefsky et al. 1986](#); [Jann et al. 1989](#); [Kahn et al. 1990](#)), dramatically lowering its blood concentrations, but clinical responses with this combination are varied ([Jann et al. 1989](#); [Kahn et al. 1990](#)). Weaker evidence suggests that CBZ may increase the metabolism of other first-generation antipsychotic agents, including fluphenazine ([Ereshefsky et al. 1986](#); [Jann et al. 1989](#)), chlorpromazine ([Raitasuo et al. 1994](#)), and thiothixene ([Ereshefsky et al. 1986](#)), but not thioridazine ([Tiihonen et al. 1995](#)), and that loxapine, chlorpromazine, and amoxapine may increase CBZ-E concentrations ([Pitterle and Collins 1988](#)). In view of these interactions, serum antipsychotic medication concentrations should be checked if patients fail to respond to standard dosages of antipsychotic agents during combined therapy with CBZ.

Coadministration of **clozapine** with CBZ is not recommended in view of the potential for synergistic bone marrow suppression ([Physicians' Desk Reference 2015](#)). European centers that have used this drug combination report that CBZ decreases clozapine concentrations ([Raitasuo et al. 1993](#)). Thus, clinicians considering the adjunctive use of a psychotropic anticonvulsant with clozapine should use valproate or another anticonvulsant rather than CBZ, except under unusual circumstances.

CBZ increases the metabolism of **olanzapine** ([Linnet and Olesen 2002](#); [Lucas et al. 1998](#)), **risperidone** ([Ono et al. 2002](#); [Spina et al. 2000](#); [Yatham et al. 2003](#)), **quetiapine** ([Grimm et al. 2006](#)), **aripiprazole** ([Physicians' Desk Reference 2015](#)), **ziprasidone** ([Miceli et al. 2000](#)), and possibly lurasidone. CBZ-related decreases in antipsychotic serum levels may interfere with the efficacy of risperidone ([Yatham et al. 2003](#)) and olanzapine ([Tohen et al. 2008](#)) for acute mania.

## Interactions With Anxiolytics and Sedatives

CBZ is commonly coadministered with **benzodiazepines**, with merely additive CNS adverse effects (e.g., sedation, ataxia). CBZ may decrease serum levels of clonazepam ([Lai et al. 1978](#); [Yukawa et al. 2001](#)), alprazolam ([Arana et al. 1988](#); [Furukori et al. 1998](#)), clobazam ([Levy et al. 1983](#)), and midazolam ([Backman et al. 1996](#)), potentially decreasing the efficacy of these agents. The newer hypnotics eszopiclone and zolpidem, which are susceptible to drug interactions involving induction of CYP3A4, may have drug interactions with carbamazepine ([Drover 2004](#)). On the other hand, clonazepam ([Lander et al. 1975](#); [Lehtovaara et al. 1978](#)) and clobazam ([Goggins and Callaghan 1985](#); [Muñoz et al. 1990](#)) appear to have variable effects on CBZ metabolism. Of interest, CBZ may be effective in ameliorating benzodiazepine withdrawal symptoms ([Ries et al. 1989](#)).

## Interactions With Stimulants

Armodafinil and CBZ combination treatment may decrease armodafinil levels by 37% and CBZ levels by 25% ([Darwish et al. 2015](#)). Methylphenidate is metabolized by nonmicrosomal hydrolytic esterases, without involvement of CYP isoenzymes; thus, interactions with CBZ are not expected. However, case reports have suggested that CBZ may decrease methylphenidate serum concentrations in some patients ([Behar et al. 1998](#)).

## Interactions With Calcium Channel Blockers

Of clear clinical importance, elevated serum CBZ concentrations and neurotoxic effects have been reported during concurrent treatment with the nondihydropyridines **verapamil** and **diltiazem** but not with the dihydropyridines nifedipine ([Brodie and](#)



MacPhee 1986; Price and DiMarzio 1988) and nimodipine. These observations are consistent with the finding that verapamil and diltiazem but not nifedipine inhibit the hepatic oxidative metabolism of various drugs (Hunt et al. 1989). Enzyme-inducing anticonvulsants such as CBZ appear to decrease serum concentrations of **dihydropyridines** such as nimodipine (Tartara et al. 1991) and felodipine (Capewell et al. 1988; Zaccara et al. 1993).

### Interactions With Substances of Abuse

Ethanol and CBZ do not interact pharmacokinetically (Dar et al. 1989; Pynnönen et al. 1978). However, CBZ attenuates alcohol withdrawal symptoms (Malcolm et al. 1989). Disulfiram combined with CBZ is well tolerated and does not cause clinically significant changes in serum CBZ and CBZ-E concentrations (Krag et al. 1981). Cigarette smoking does not alter CBZ metabolism (Bachmann et al. 1990), and CBZ does not alter caffeine pharmacokinetics (Wietholtz et al. 1989).

### Interactions With Nonpsychotropic Drugs

CBZ induces the metabolism of diverse medications, raising the possibility of undermining the efficacy of **steroids** (contraceptives, dexamethasone, mifepristone), **methylxanthines** (theophylline, aminophylline), antibiotics (**doxycycline**), **protease inhibitors**, **neuromuscular blockers** (pancuronium, vecuronium, doxacurium), analgesics such as **methadone**, **immunosuppressants** such as sirolimus and tacrolimus, the anticoagulant **warfarin**, and possibly dicumarol (see Table 38-4). In women taking CBZ, dosages of oral contraceptive preparations may need to be adjusted to ensure continued efficacy (Crawford 2002).

Similarly, a variety of medications can increase serum CBZ concentrations and cause clinical toxicity; such medications include **isoniazid**, **azole antifungals** such as ketoconazole, **macrolide antibiotics** such as erythromycin and clarithromycin, **protease inhibitors** such as ritonavir and nelfinavir, **hypolipidemics** such as gemfibrozil and nicotinamide, and the carbonic anhydrase inhibitor **acetazolamide** (see Table 38-5). In addition, other medications such as cisplatin and doxorubicin may decrease serum CBZ levels, potentially leading to inefficacy.

## Oxcarbazepine

In comparison with CBZ, OXC has fewer clinically significant drug-drug interactions. Differences in three major areas appear to contribute importantly to differences between OXC and CBZ with regard to drug-drug interactions:

1. **OXC is only a modest to moderate enzyme (CYP3A4) inducer, which yields clinically significant decreases in serum concentrations of some medications** (see Table 38-4). OXC yields minor enzyme heteroinduction (but not autoinduction), which is clearly less robust than that seen with CBZ, but the effect may be clinically significant for some medications (in *italics* in Table 38-4). In some instances, OXC induction is substantially less robust than CBZ induction, so switching from OXC to CBZ (or vice versa) will make adjustments of doses of other medications necessary.
2. **OXC metabolism (which is primarily by arylketone reductase) is not generally susceptible to enzyme inhibitors.** The absence of autoinduction and the robust actions of cytosol reductases that mediate conversion to the MHD appear to render OXC metabolism not susceptible to the common phenomenon of inhibition by other agents

seen with CBZ. Thus, the medications listed in [Table 38-5](#) that can elevate serum CBZ concentrations and cause neurotoxicity do *not* appear to have such interactions with OXC.

3. **OXC has an active (MHD) metabolite** ([Figure 38-1](#), bottom middle). MHD metabolism, unlike CBZ-E catabolism, is not inhibited by valproate, presumably because of the lack of involvement of epoxide hydrolase in MHD's disposition. Thus, coadministration of valproate with OXC does *not* result in toxicity related to increased MHD.

### Interactions With Mood Stabilizers and Anticonvulsants

OXC, in contrast to CBZ, does not induce valproate metabolism and appears to have less robust effects on **lamotrigine** metabolism ([May et al. 1999](#)). OXC may modestly decrease serum concentrations of topiramate ([May et al. 2002](#)) and levetiracetam ([May et al. 2003](#)). OXC can increase serum phenytoin concentrations, presumably by inhibiting the activity of CYP2C19. The anticonvulsants phenytoin, phenobarbital, primidone, and CBZ may induce OXC metabolism, yielding decreased serum MHD concentrations ([McKee et al. 1994](#)).

### Interactions With Antidepressants

OXC, in contrast to CBZ, does not robustly induce citalopram metabolism.

### Interactions With Antipsychotics

OXC, unlike CBZ, does not robustly induce antipsychotic metabolism.

### Interactions With Anxiolytics and Sedatives

OXC may decrease serum concentrations of **benzodiazepines**.

### Interactions With Calcium Channel Blockers

OXC appears to decrease serum concentrations of **dihydropyridine** calcium channel blockers (which are CYP3A4 substrates) to some extent.

### Interactions With Nonpsychotropic Drugs

OXC, compared with CBZ, also appears to have fewer interactions with nonpsychotropic drugs. Thus, neither the CYP3A4 inhibitor erythromycin ([Keränen et al. 1992a](#)) nor the heteroinhibitor cimetidine ([Keränen et al. 1992b](#)) appears to alter OXC pharmacokinetics in healthy volunteers. In a study in healthy volunteers taking steady-state warfarin, OXC did not significantly alter prothrombin time ([Krämer et al. 1992](#)); therefore, OXC does not appear to robustly induce warfarin metabolism.

However, OXC appears to have a clinically significant interaction with **hormonal contraceptives**. In healthy female volunteers, OXC appeared to decrease ethinylestradiol and levonorgestrel derived from hormonal contraceptives by as much as 50% ([Fattore et al. 1999](#); [Krämer et al. 1992](#)), such that use of higher-dosage forms of estrogen-related oral contraceptives may be indicated.

OXC, like CBZ, may decrease serum concentrations of the analgesic buprenorphine, the anticancer agent paclitaxel, and the antidiabetic agent repaglinide. OXC also yields decreases in serum concentrations of the dihydropyridine calcium channel blocker felodipine (which is also a CYP3A4 substrate). In contrast to the case with CBZ, the CYP3A4 inhibitor erythromycin and the antidepressant viloxazine do not yield clinically significant increases in serum OXC concentrations.



# Eslicarbazepine Acetate

ESL, which shares the same active metabolite as OXC, also has fewer clinically significant drug-drug interactions compared with CBZ. ESL is modestly protein bound, without significant related interactions. ESL does not have significant effects on most CYP enzyme pathways, including 1A2, 2A6, 2B6, 2C9, 2D6, 2E1, and 4A9/11 ([Almeida and Soares-da-Silva 2007](#)). Its three main pharmacokinetic effects are weak induction of CYP3A4, weak induction of UDP-glucuronyl transferases, and weak inhibition of CYP2C19 ([Zaccara et al. 2015](#)).

## Interactions With Mood Stabilizers

Similar to OXC and in contrast to CBZ, ESL does not significantly induce valproate metabolism. Moreover, ESL does not have significant interactions with lamotrigine or topiramate metabolism ([Bialer and Soares-da-Silva 2012](#)). ESL may increase phenytoin levels by up to 35%, presumably because of CYP2C19 inhibition ([Bialer and Soares-da-Silva 2012](#)). When used concurrently with CBZ, however, ESL levels may be decreased by up to 33%, presumably because of CBZ-induced glucuronidation, potentially requiring ESL dosage adjustments ([Bialer and Soares-da-Silva 2012](#)).

## Interactions With Nonpsychotropic Drugs

Because of its modest induction of CYP3A4 activity, ESL may induce moderate reductions in estradiol (up to 42%) in a possibly dose-dependent interaction, potentially reducing the effectiveness of oral contraceptives ([Bialer and Soares-da-Silva 2012](#)). Simvastatin levels may be decreased by up to 40% with ESL coadministration, presumably as a function of CYP3A4 induction ([Zaccara et al. 2015](#)). Effects on warfarin levels are small and within the range of interindividual variability of warfarin pharmacokinetics; therefore, warfarin dosing should be individually optimized to a stable prothrombin international normalized ratio (INR) ([Bialer and Soares-da-Silva 2012](#)). Digoxin and metformin levels are not affected by ESL.

---

## Conclusion

---

In the past, because of the lack of an FDA indication, complexity of use, and methodological concerns regarding earlier efficacy studies, CBZ was generally considered an alternative rather than a first-line intervention in bipolar disorder. However, the approval of a proprietary CBZ beaded extended-release capsule formulation (Equetro) for the treatment of acute manic and mixed episodes in patients with bipolar disorder and the low propensity of CBZ to cause the weight gain and metabolic problems seen with some other agents may lead clinicians to reassess the role of CBZ in the management of bipolar disorder ([Ketter 2015](#)).

OXC, compared with CBZ, has more limited evidence of efficacy in bipolar disorder, but it has enhanced tolerability and fewer drug-drug interactions. MHD (the active metabolite of OXC) and ESL (the prodrug to the *S*-enantiomer of MHD) likewise have enhanced tolerability and fewer drug-drug interactions, but their efficacy in bipolar disorder remains to be established. Thus, with CBZ (but not OXC), common benign leukopenia needs to be distinguished from rare serious aplastic anemia, and patients and caregivers need to be alert to symptoms of this adverse effect. In addition, CBZ (and to a lesser extent OXC) in combination therapy induces the metabolism of other drugs, potentially

undermining their efficacy if the dosage is not adjusted for this lowering effect. Also, other drugs (e.g., erythromycin, verapamil) can inhibit CBZ (but not OXC) metabolism, causing CBZ toxicity. Instructing patients to alert their other caregivers and their pharmacist that they are receiving CBZ may help avoid drug interactions. Informing patients of several of the common interactions can further assist in the warning process, because other practitioners may inadvertently introduce commonly used drugs such as erythromycin with the attendant risk of CBZ toxicity.

CBZ is an important treatment option for patients with bipolar disorder who experience inadequate response or unacceptable adverse effects with lithium and valproate. Awareness of CBZ and OXC pharmacology and potential drug-drug interactions will enable clinicians to provide the safest and most effective care for their patients with bipolar disorder.

---

## References

---

- Akiskal HS, Fuller MA, Hirschfeld RM, et al: Reassessing carbamazepine in the treatment of bipolar disorder: clinical implications of new data. *CNS Spectr* 10 (6 suppl 5):1-11, 12-13, quiz 14-15, 2005 16041864
- Almeida L, Soares-da-Silva P: Eslicarbazepine acetate (BIA 2-093). *Neurotherapeutics* 4(1):88-96, 2007 17199020
- Almeida L, Potgieter JH, Maia J, et al: Pharmacokinetics of eslicarbazepine acetate in patients with moderate hepatic impairment. *Eur J Clin Pharmacol* 64(3):267-273, 2008 18157705
- Ambrósio AF, Silva AP, Malva JO, et al: Inhibition of glutamate release by BIA 2-093 and BIA 2-024, two novel derivatives of carbamazepine, due to blockade of sodium but not calcium channels. *Biochem Pharmacol* 61(10):1271-1275, 2001 11322931
- Ambrósio AF, Soares-Da-Silva P, Carvalho CM, et al: Mechanisms of action of carbamazepine and its derivatives, oxcarbazepine, BIA 2-093, and BIA 2-024. *Neurochem Res* 27(1-2):121-130, 2002 11926264
- American Psychiatric Association: Practice guideline for the treatment of patients with bipolar disorder. *Am J Psychiatry* 151 (12 suppl):1-36, 1994 7977902
- American Psychiatric Association: Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 159 (4 suppl):1-50, 2002 11958165
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Andersen BB, Mikkelsen M, Vesterager A, et al: No influence of the antidepressant paroxetine on carbamazepine, valproate and phenytoin. *Epilepsy Res* 10(2-3): 201-204, 1991 1840138
- Arana GW, Epstein S, Molloy M, et al: Carbamazepine-induced reduction of plasma alprazolam concentrations: a clinical case report. *J Clin Psychiatry* 49(11):448-449, 1988 3182735
- Ashton AK, Wolin RE: Nefazodone-induced carbamazepine toxicity. *Am J Psychiatry* 153(5):733, 1996 8615427
- Bachmann KA, Nunlee M, Martin M, et al: The use of single sample clearance estimates to probe hepatic drug metabolism: handprinting the influence of cigarette smoking on human hepatic drug metabolism. *Xenobiotica* 20(5):537-547, 1990 2112290
- Backman JT, Olkkola KT, Ojala M, et al: Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. *Epilepsia* 37(3):253-257, 1996 8598183
- Baldessarini RJ, Teicher MH, Cassidy JW, et al: Anticonvulsant cotreatment may increase toxic metabolites of antidepressants and other psychotropic drugs. *J Clin*

- Psychopharmacol 8(5):381-382, 1988 3183079
- Ballenger JC, Post RM: Therapeutic effects of carbamazepine in affective illness: a preliminary report. *Commun Psychopharmacol* 2(2):159-175, 1978 352607
- Barcs G, Walker EB, Elger CE, et al: Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. *Epilepsia* 41(12):1597-1607, 2000 11114219
- Baruzzi A, Albani F, Riva R: Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. *Epilepsia* 35 (suppl 3): S14-S19, 1994 8156974
- Behar D, Schaller J, Spreat S: Extreme reduction of methylphenidate levels by carbamazepine. *J Am Acad Child Adolesc Psychiatry* 37(11):1128-1129, 1998 9808919
- Bellaire W, Demish K, Stoll KD: Carbamazepine versus lithium in prophylaxis of recurrent affective disorder (abstract). *Psychopharmacology (Berl)* 96 (suppl):287, 1988
- Benes J, Parada A, Figueiredo AA, et al: Anticonvulsant and sodium channel-blocking properties of novel 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide derivatives. *J Med Chem* 42(14):2582-2587, 1999 10411478
- Berky MW, Kovacs G: Carbamazepine versus lithium in bipolar affective disorders (abstract P174). *Eur Arch Psychiatry Clin Neurosci* 248(S119), 1998
- Beydoun A, Sachdeo RC, Rosenfeld WE, et al: Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. *Neurology* 54(12): 2245-2251, 2000 10881247
- Bialer M: New antiepileptic drugs that are second generation to existing antiepileptic drugs. *Expert Opin Investig Drugs* 15(6):637-647, 2006 16732716
- Bialer M, Soares-da-Silva P: Pharmacokinetics and drug interactions of eslicarbazepine acetate. *Epilepsia* 53(6):935-946, 2012 22612290
- Booker SA, Pires N, Cobb S, et al: Carbamazepine and oxcarbazepine, but not eslicarbazepine, enhance excitatory synaptic transmission onto hippocampal CA1 pyramidal cells through an antagonist action at adenosine A1 receptors. *Neuropharmacology* 93:103-115, 2015 25656478
- Bowden CL, Calabrese JR, McElroy SL, et al; Divalproex Maintenance Study Group: A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry* 57(5):481-489, 2000 10807488
- Brodie MJ, MacPhee GJ: Carbamazepine neurotoxicity precipitated by diltiazem. *Br Med J (Clin Res Ed)* 292(6529):1170-1171, 1986 3085769
- Brodie MJ, Forrest G, Rapeport WG: Carbamazepine 10, 11 epoxide concentrations in epileptics on carbamazepine alone and in combination with other anticonvulsants. *Br J Clin Pharmacol* 16(6):747-749, 1983 6661364
- Brodie MJ, Wilson EA, Wesche DL, et al: Pregabalin drug interaction studies: lack of effect on the pharmacokinetics of carbamazepine, phenytoin, lamotrigine, and valproate in patients with partial epilepsy. *Epilepsia* 46(9):1407-1413, 2005 16146435
- Brøsen K, Kragh-Sørensen P: Concomitant intake of nortriptyline and carbamazepine. *Ther Drug Monit* 15(3):258-260, 1993 8333008
- Brown CS, Wells BG, Cold JA, et al: Possible influence of carbamazepine on plasma imipramine concentrations in children with attention deficit hyperactivity disorder. *J Clin Psychopharmacol* 10(5):359-362, 1990 2258453
- Brown D, Silverstone T, Cookson J: Carbamazepine compared to haloperidol in acute mania. *Int Clin Psychopharmacol* 4(3):229-238, 1989 2794470
- Brown DW, Ketter TA, Crumlish J, et al: Carbamazepine-induced increases in total serum cholesterol: clinical and theoretical implications. *J Clin Psychopharmacol* 12(6):431-437, 1992 1474180
- Cabrera JF, Muhlbauer HD, Schley J, et al: Long-term randomized clinical trial of oxcarbazepine vs lithium in bipolar and schizoaffective disorders: preliminary results. *Pharmacopsychiatry* 19:282-283, 1986
- Capewell S, Freestone S, Critchley JA, et al: Reduced felodipine bioavailability in patients taking anticonvulsants. *Lancet* 2(8609):480-482, 1988 2900404

- Cereghino JJ: Serum carbamazepine concentration and clinical control, in *Advances in Neurology*, Vol 11. Edited by Penry JK, Daly DD. New York, Raven, 1975, pp 309-330
- Ceron-Litvoc D, Soares BG, Geddes J, et al: Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. *Hum Psychopharmacol* 24(1):19-28, 2009 19053079
- Chung SS, Johnson JK, Brittain ST, Baroldi P: Long-term efficacy and safety of adjunctive extended-release oxcarbazepine (Oxtellar XR®) in adults with partial-onset seizures. *Acta Psychiatr Scand* 133(2): 124-130, 2016 26248506
- Coxhead N, Silverstone T, Cookson J: Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder. *Acta Psychiatr Scand* 85(2):114-118, 1992 1543034
- Crawford P: Interactions between antiepileptic drugs and hormonal contraception. *CNS Drugs* 16(4):263-272, 2002 11945109
- Cummings C, Stewart M, Stevenson M, et al: Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 96(7):643-647, 2011 21415043
- Dam M, Ekberg R, Løyning Y, et al: A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 3(1):70-76, 1989 2645120
- Dar MS, Hardee M, Ganey T: Brain adenosine modulation of behavioral interactions between ethanol and carbamazepine in mice. *Alcohol* 6(4):297-301, 1989 2765198
- Dardennes R, Even C, Bange F, et al: Comparison of carbamazepine and lithium in the prophylaxis of bipolar disorders. A meta-analysis. *Br J Psychiatry* 166(3):378-381, 1995 7788131
- Darwish M, Bond M, Yang R, et al: Evaluation of the potential for pharmacokinetic drug-drug interaction between armodafinil and carbamazepine in healthy adults. *Clin Ther* 37(2):325-337, 2015 25438721
- Davis JM, Janicak PG, Hogan DM: Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. *Acta Psychiatr Scand* 100(6):406-417, 1999 10626918
- De la Fuente JM, Mendlewicz J: Carbamazepine addition in tricyclic antidepressant-resistant unipolar depression. *Biol Psychiatry* 32(4):369-374, 1992 1420651
- Deckert J, Berger W, Kleopa K, et al: Adenosine A1 receptors in human hippocampus: inhibition of [3H]8-cyclopentyl-1,3-dipropylxanthine binding by antagonist drugs. *Neurosci Lett* 150(2):191-194, 1993 8469419
- Degen PH, Flesch G, Cardot JM, et al: The influence of food on the disposition of the antiepileptic oxcarbazepine and its major metabolites in healthy volunteers. *Biopharm Drug Dispos* 15(6):519-526, 1994 7993989
- Denicoff KD, Smith-Jackson EE, Disney ER, et al: Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 58(11):470-478, 1997 9413412
- Di Costanzo E, Schifano F: Lithium alone or in combination with carbamazepine for the treatment of rapid-cycling bipolar affective disorder. *Acta Psychiatr Scand* 83(6):456-459, 1991 1882698
- Dilsaver SC, Swann AC, Shoaib AM, et al: The manic syndrome: factors which may predict a patient's response to lithium, carbamazepine and valproate. *J Psychiatry Neurosci* 18(2):61-66, 1993 8461283
- Dreifuss FE, Langer DH, Moline KA, et al: Valproic acid hepatic fatalities. II. US experience since 1984. *Neurology* 39(2 Pt 1):201-207, 1989 2492646
- Drover DR: Comparative pharmacokinetics and pharmacodynamics of short-acting hypnotics: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 43(4):227-238, 2004 15005637
- Eap CB, Yasui N, Kaneko S, et al: Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. *Ther Drug Monit* 21(2):166-170, 1999 10217335

- Eichelbaum M, Ekbom K, Bertilsson L, et al: Plasma kinetics of carbamazepine and its epoxide metabolite in man after single and multiple doses. *Eur J Clin Pharmacol* 8(5):337-341, 1975 1233232
- Eichelbaum M, Tomson T, Tybring G, et al: Carbamazepine metabolism in man. Induction and pharmacogenetic aspects. *Clin Pharmacokinet* 10(1):80-90, 1985 3971637
- Elphick M, Lyons F, Cowen PJ: Low tolerability of carbamazepine in psychiatric patients may restrict its clinical usefulness. *J Psychopharmacol* 2(1):1-4, 1988 22159662
- Emrich HM: Studies with oxcarbazepine (Trileptal) in acute mania. *Int Clin Psychopharmacol* 5 (suppl 1):83-88, 1990
- Emrich HM, Altmann H, Dose M, et al: Therapeutic effects of GABA-ergic drugs in affective disorders. A preliminary report. *Pharmacol Biochem Behav* 19(2):369-372, 1983 6415677
- Emrich HM, Dose M, von Zerssen D: The use of sodium valproate, carbamazepine and oxcarbazepine in patients with affective disorders. *J Affect Disord* 8(3):243-250, 1985 3160736
- Ereshefsky L, Jann MW, Saklad SR, et al: Bioavailability of psychotropic drugs: historical perspective and pharmacokinetic overview. *J Clin Psychiatry* 47 (9 suppl): 6-15, 1986 3528134
- Faigle JW, Feldmann KF: Carbamazepine: chemistry and biotransformation, in *Antiepileptic Drugs*, 4th Edition. Edited by Levy RH, Mattson RH, Meldrum BS. New York, Raven, 1995, pp 499-513
- Fattore C, Cipolla G, Gatti G, et al: Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. *Epilepsia* 40(6):783-787, 1999 10368079
- Frankenburg FR, Tohen M, Cohen BM, et al: Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 8(2):130-132, 1988 3372707
- Frey B, Braegger CP, Ghelfi D: Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 36(4):644-647, 2002 11918515
- Friis ML, Kristensen O, Boas J, et al: Therapeutic experiences with 947 epileptic out-patients in oxcarbazepine treatment. *Acta Neurol Scand* 87(3):224-227, 1993 8475694
- Fritze J, Unsorg B, Lanczik M: Interaction between carbamazepine and fluvoxamine. *Acta Psychiatr Scand* 84(6):583-584, 1991 1792934
- Froescher W, Eichelbaum M, Niesen M, et al: Carbamazepine levels in breast milk. *Ther Drug Monit* 6(3):266-271, 1984 6390794
- Frye MA, Ketter TA, Leverich GS, et al: The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *J Clin Psychiatry* 61(1):9-15, 2000 10695639
- Furukori H, Otani K, Yasui N, et al: Effect of carbamazepine on the single oral dose pharmacokinetics of alprazolam. *Neuropsychopharmacology* 18(5):364-369, 1998 9536449
- Gangadhar BN, Desai NG, Channabasavanna SM: Potentiation of lithium with carbamazepine in acute mania. *Indian J Psychiatry* 29(1):73-75, 1987 21927212
- Garnett WR, Levy B, McLean AM, et al: Pharmacokinetic evaluation of twice-daily extended-release carbamazepine (CBZ) and four-times-daily immediate-release CBZ in patients with epilepsy. *Epilepsia* 39(3):274-279, 1998 9578044
- Gernaat HB, Van de Woude J, Touw DJ: Fluoxetine and parkinsonism in patients taking carbamazepine. *Am J Psychiatry* 148(11):1604-1605, 1991 1928486
- Glauser TA, Nigro M, Sachdeo R, et al; The Oxcarbazepine Pediatric Study Group: Adjunctive therapy with oxcarbazepine in children with partial seizures. *Neurology* 54(12):2237-2244, 2000 10881246
- Goggin T, Callaghan N: Blood levels of clobazam and its metabolites and therapeutic effect, in *Clobazam: Human Psychopharmacology and Clinical Applications*. International

- Congress and Symposium Series, No 74. Edited by Hindmarch I, Stonier PD, Trimble MR. London, Royal Society of Medicine, 1985, pp 149-153
- Gonçalves N, Stoll KD: [Carbamazepine in manic syndromes. A controlled double-blind study]. *Nervenarzt* 56(1):43-47, 1985 3883202
- Greil W, Ludwig-Mayerhofer W, Erazo N, et al: Lithium versus carbamazepine in the maintenance treatment of bipolar disorders—a randomised study. *J Affect Disord* 43(2):151-161, 1997 9165384
- Greil W, Kleindienst N, Erazo N, et al: Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *J Clin Psychopharmacol* 18(6): 455-460, 1998 9864077
- Grimm SW, Richtand NM, Winter HR, et al: Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. *Br J Clin Pharmacol* 61(1):58-69, 2006 16390352
- Grimsley SR, Jann MW, Carter JG, et al: Increased carbamazepine plasma concentrations after fluoxetine coadministration. *Clin Pharmacol Ther* 50(1):10-15, 1991 1855347
- Grossi E, Sacchetti E, Vita A, et al: Carbamazepine versus chlorpromazine in mania: a double-blind trial, in *Anticonvulsants in Affective Disorders*. Edited by Emrich HM, Okuma T, Müller AA. Amsterdam, Elsevier Science Publishers, 1984, pp 177-187
- Grunze H, Kotlik E, Costa R, et al: Assessment of the efficacy and safety of eslicarbazepine acetate in acute mania and prevention of recurrence: experience from multicentre, double-blind, randomised phase II clinical studies in patients with bipolar disorder I. *J Affect Disord* 174:70-82, 2015 25484179
- Hartong EG, Moleman P, Hoogduin CA, et al; LitCar Group: Prophylactic efficacy of lithium versus carbamazepine in treatment-naïve bipolar patients. *J Clin Psychiatry* 64(2):144-151, 2003 12633122
- Hebeisen S, Pires N, Loureiro AI, et al: Eslicarbazepine and the enhancement of slow inactivation of voltage-gated sodium channels: a comparison with carbamazepine, oxcarbazepine and lacosamide. *Neuropharmacology* 89:122-135, 2015 25242737
- Himmelhoch JM: Cerebral dysrhythmia, substance abuse, and the nature of secondary affective illness. *Psychiatric Annals* 17: 710-727, 1987
- Himmelhoch JM, Garfinkel ME: Sources of lithium resistance in mixed mania. *Psychopharmacol Bull* 22(3):613-620, 1986 3797567
- Hirschfeld RM, Kasper S: A review of the evidence for carbamazepine and oxcarbazepine in the treatment of bipolar disorder. *Int J Neuropsychopharmacol* 7(4):507-522, 2004 15458610
- Hunt BA, Self TH, Lalonde RL, et al: Calcium channel blockers as inhibitors of drug metabolism. *Chest* 96(2):393-399, 1989 2568899
- Isojärvi JI, Pakarinen AJ, Rautio A, et al: Liver enzyme induction and serum lipid levels after replacement of carbamazepine with oxcarbazepine. *Epilepsia* 35(6):1217-1220, 1994 7988514
- Isojärvi JI, Huuskonen UE, Pakarinen AJ, et al: The regulation of serum sodium after replacing carbamazepine with oxcarbazepine. *Epilepsia* 42(6):741-745, 2001a 11422328
- Isojärvi JI, Turkka J, Pakarinen AJ, et al: Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. *Epilepsia* 42(7):930-934, 2001b 11488894
- Jann MW, Fidone GS, Israel MK, et al: Increased valproate serum concentrations upon carbamazepine cessation. *Epilepsia* 29(5):578-581, 1988 3137021
- Jann MW, Fidone GS, Hernandez JM, et al: Clinical implications of increased antipsychotic plasma concentrations upon anticonvulsant cessation. *Psychiatry Res* 28(2):153-159, 1989 2568651
- Joca SR, Skalisz LL, Beijamini V, et al: The antidepressive-like effect of oxcarbazepine: possible role of dopaminergic neurotransmission. *Eur Neuropsychopharmacol* 10(4):223-228, 2000 10871703

- Joffe RT, Post RM: Lithium and carbamazepine-induced agranulocytosis. *Am J Psychiatry* 146(3):404, 1989 2493199
- Joffe RT, Post RM, Uhde TW: Lack of pharmacokinetic interaction of carbamazepine with tranylcypromine. *Arch Gen Psychiatry* 42(7):738, 1985 4015316
- Joffe RT, Post RM, Uhde TW: Effect of carbamazepine on body weight in affectively ill patients. *J Clin Psychiatry* 47(6):313-314, 1986 3711029
- Jones KL, Lacro RV, Johnson KA, et al: Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med* 320(25): 1661-1666, 1989 2725616
- Joyce PR: Carbamazepine in rapid cycling bipolar affective disorder. *Int Clin Psychopharmacol* 3(2):123-129, 1988 3397520
- Kahn EM, Schulz SC, Perel JM, et al: Change in haloperidol level due to carbamazepine—a complicating factor in combined medication for schizophrenia. *J Clin Psychopharmacol* 10(1):54-57, 1990 2106534
- Kakkar AK, Rehan HS, Unni KE, et al: Comparative efficacy and safety of oxcarbazepine versus divalproex sodium in the treatment of acute mania: a pilot study. *Eur Psychiatry* 24(3):178-182, 2009 19324530
- Keating GM: Eslicarbazepine acetate: a review of its use as adjunctive therapy in refractory partial-onset seizures. *CNS Drugs* 28(7):583-600, 2014 24972948
- Keck PE Jr, McElroy SL, Vuckovic A, et al: Combined valproate and carbamazepine treatment of bipolar disorder. *J Neuropsychiatry Clin Neurosci* 4(3):319-322, 1992 1498585
- Keck PE Jr, McElroy SL, Tugrul KC, et al: Valproate oral loading in the treatment of acute mania. *J Clin Psychiatry* 54(8):305-308, 1993 8253698
- Keränen T, Jolkkonen J, Jensen PK, et al: Absence of interaction between oxcarbazepine and erythromycin. *Acta Neurol Scand* 86(2):120-123, 1992a 1414219
- Keränen T, Jolkkonen J, Klosterskov-Jensen P, et al: Oxcarbazepine does not interact with cimetidine in healthy volunteers. *Acta Neurol Scand* 85(4):239-242, 1992b 1585795
- Kerr BM, Thummel KE, Wurden CJ, et al: Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. *Biochem Pharmacol* 47(11):1969-1979, 1994 8010982
- Ketter TA: *Advances in the Treatment of Bipolar Disorder*. Washington, DC, American Psychiatric Publishing, 2005
- Ketter TA: *Handbook of Diagnosis and Treatment of Bipolar Disorder*. Washington, DC, American Psychiatric Publishing, 2010
- Ketter TA: *Advances in Treatment of Bipolar Disorders*. Washington, DC, American Psychiatric Publishing, 2015
- Ketter TA, Wang PW: Predictors of treatment response in bipolar disorders: evidence from clinical and brain imaging studies. *J Clin Psychiatry* 63 (suppl 3):21-25, 2002 11908918
- Ketter TA, Post RM, Worthington K: Principles of clinically important drug interactions with carbamazepine. Part I. *J Clin Psychopharmacol* 11(3):198-203, 1991a 2066459
- Ketter TA, Post RM, Worthington K: Principles of clinically important drug interactions with carbamazepine. Part II. *J Clin Psychopharmacol* 11(5):306-313, 1991b 1765573
- Ketter TA, Pazzaglia PJ, Post RM: Synergy of carbamazepine and valproic acid in affective illness: case report and review of the literature. *J Clin Psychopharmacol* 12(4):276-281, 1992 1527232
- Ketter TA, Jenkins JB, Schroeder DH, et al: Carbamazepine but not valproate induces bupropion metabolism. *J Clin Psychopharmacol* 15(5):327-333, 1995a 8830063
- Ketter TA, Post RM, Parekh PI, Worthington K: Addition of monoamine oxidase inhibitors to carbamazepine: preliminary evidence of safety and antidepressant efficacy in treatment-resistant depression. *J Clin Psychiatry* 56(10):471-475, 1995b 7559374
- Ketter TA, Kimbrell TA, George MS, et al: Baseline cerebral hypermetabolism associated with carbamazepine response, and hypometabolism with nimodipine response in mood disorders. *Biol Psychiatry* 46(10):1364-1374, 1999 10578451

- Ketter TA, Wang PW, Becker OV, et al: The diverse roles of anticonvulsants in bipolar disorders. *Ann Clin Psychiatry* 15(2):95-108, 2003 12938867
- Ketter TA, Kalali AH, Weisler RH; SPD417 Study Group: A 6-month, multicenter, open-label evaluation of beaded, extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry* 65(5):668-673, 2004 15163253
- Ketter TA, Citrome L, Wang PW, et al: Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions? *Acta Psychiatr Scand* 123(3): 175-189, 2011 21133854
- Khan A, Shad MU, Preskorn SH: Lack of sertraline efficacy probably due to an interaction with carbamazepine. *J Clin Psychiatry* 61(7):526-527, 2000 10937612
- Kishimoto A, Okuma T: Antimanic and prophylactic effects of carbamazepine in affective disorders (abstract 506.4), in 4th World Congress of Biological Psychiatry, Philadelphia, PA, September 8-13, 1985, p 363
- Klein EM: Lithium and carbamazepine therapy in a patient with manic depressive illness: clinical effects, interactions and side effects. *Isr J Psychiatry Relat Sci* 24(4):295-298, 1987 3505519
- Klein E, Bental E, Lerer B, et al: Carbamazepine and haloperidol v placebo and haloperidol in excited psychoses. A controlled study. *Arch Gen Psychiatry* 41(2):165-170, 1984 6365015
- Kondo T, Otani K, Hirano T, et al: The effects of phenytoin and carbamazepine on serum concentrations of mono-unsaturated metabolites of valproic acid. *Br J Clin Pharmacol* 29(1):116-119, 1990 2105099
- Krag B, Dam M, Angelo H, et al: Influence of disulfiram on the serum concentration of carbamazepine in patients with epilepsy. *Acta Neurol Scand* 63(6):395-398, 1981 7324869
- Krämer G, Tettenborn B, Klosterskov Jensen P, et al: Oxcarbazepine does not affect the anticoagulant activity of warfarin. *Epilepsia* 33(6):1145-1148, 1992 1464277
- Kramlinger KG, Post RM: Adding lithium carbonate to carbamazepine: antimanic efficacy in treatment-resistant mania. *Acta Psychiatr Scand* 79(4):378-385, 1989a 2500006
- Kramlinger KG, Post RM: The addition of lithium to carbamazepine. Antidepressant efficacy in treatment-resistant depression. *Arch Gen Psychiatry* 46(9):794-800, 1989b 2505730
- Kramlinger KG, Post RM: Addition of lithium carbonate to carbamazepine: hematological and thyroid effects. *Am J Psychiatry* 147(5):615-620, 1990 2109539
- Kramlinger KG, Phillips KA, Post RM: Rash complicating carbamazepine treatment. *J Clin Psychopharmacol* 14(6):408-413, 1994 7884021
- Kuhn W, Jäger-Roman E, Rating D, et al: Carbamazepine and carbamazepine-10,11-epoxide during pregnancy and postnatal period in epileptic mother and their nursed infants: pharmacokinetics and clinical effects. *Pediatr Pharmacol (New York)* 3(3-4):199-208, 1983 6677873
- Kupfer DJ, Frank E, Grochocinski VJ, et al: Demographic and clinical characteristics of individuals in a bipolar disorder case registry. *J Clin Psychiatry* 63(2):120-125, 2002 11874212
- Kutt H, Solomon G, Peterson H, et al: Accumulation of carbamazepine epoxide caused by valproate contributing to intoxication syndromes. *Neurology* 35 (suppl 1):286-287, 1985
- Lai AA, Levy RH, Cutler RE: Time-course of interaction between carbamazepine and clonazepam in normal man. *Clin Pharmacol Ther* 24(3):316-323, 1978 688725
- Lander CM, Eadie MJ, Tyrer JH: Interactions between anticonvulsants. *Proc Aust Assoc Neurol* 12:111-116, 1975 2912
- Laroudie C, Salazar DE, Cosson JP, et al: Carbamazepine-nefazodone interaction in healthy subjects. *J Clin Psychopharmacol* 20(1):46-53, 2000 10653208



- Lehtovaara R, Bardy A, Hari R, et al: Sodium valproate and clonazepam interactions with phenytoin and carbamazepine, in *Advances in Epileptology*. Edited by Meinardi H, Rowan AJ. Amsterdam, Swets & Zeitlinger, 1978, pp 269-270
- Leinonen E, Lillsunde P, Laukkanen V, et al: Effects of carbamazepine on serum antidepressant concentrations in psychiatric patients. *J Clin Psychopharmacol* 11(5):313-318, 1991 1765574
- Lenzi A, Lazzerini F, Grossi E, et al: Use of carbamazepine in acute psychosis: a controlled study. *J Int Med Res* 14(2):78-84, 1986 3084316
- Lerer B, Moore N, Meyendorff E, et al: Carbamazepine versus lithium in mania: a double-blind study. *J Clin Psychiatry* 48(3):89-93, 1987 3546274
- Levy RH, Lane EA, Guyot M, et al: Analysis of parent drug-metabolite relationship in the presence of an inducer. Application to the carbamazepine-clobazam interaction in normal man. *Drug Metab Dispos* 11(4):286-292, 1983 6137332
- Linnet K, Olesen OV: Free and glucuronidated olanzapine serum concentrations in psychiatric patients: influence of carbamazepine comedication. *Ther Drug Monit* 24(4):512-517, 2002 12142636
- Lucas RA, Gilfillan DJ, Bergstrom RF: A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanism. *Eur J Clin Pharmacol* 54(8):639-643, 1998 9860152
- Lusznat RM, Murphy DP, Nunn CM: Carbamazepine vs lithium in the treatment and prophylaxis of mania. *Br J Psychiatry* 153:198-204, 1988 3151275
- Macphee GJ, Mitchell JR, Wiseman L, et al: Effect of sodium valproate on carbamazepine disposition and psychomotor profile in man. *Br J Clin Pharmacol* 25(1):59-66, 1988 3130892
- Malcolm R, Ballenger JC, Sturgis ET, et al: Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. *Am J Psychiatry* 146(5):617-621, 1989 2653057
- Martínez P, González de Etxabarri S, Ereño C, et al: [Acute severe hepatic insufficiency caused by carbamazepine]. *Rev Esp Enferm Dig* 84(2):124-126, 1993 8398372
- Massot A, Vivanco R, Principe A, et al: Post-authorisation study of eslicarbazepine as treatment for drug-resistant epilepsy: preliminary results. *Neurologia* 29(2):94-101, 2014 23623701
- Mattson RH, Cramer JA, Collins JF: A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *N Engl J Med* 327(11): 765-771, 1992 1298221
- May TW, Rambeck B, Jürgens U: Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a retrospective study. *Ther Drug Monit* 21(2):175-181, 1999 10217337
- May TW, Rambeck B, Jürgens U: Serum concentrations of topiramate in patients with epilepsy: influence of dose, age, and comedication. *Ther Drug Monit* 24(3):366-374, 2002 12021627
- May TW, Rambeck B, Jürgens U: Serum concentrations of Levetiracetam in epileptic patients: the influence of dose and co-medication. *Ther Drug Monit* 25(6):690-699, 2003 14639055
- McCormack M, Alfrevic A, Bourgeois S, et al: HLA-A\*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med* 364(12):1134-1143, 2011 21428769
- McGinness J, Kishimoto A, Hollister LE: Avoiding neurotoxicity with lithium-carbamazepine combinations. *Psychopharmacol Bull* 26(2):181-184, 1990 2236454
- McKee PJ, Blacklaw J, Forrest G, et al: A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. *Br J Clin Pharmacol* 37(1):27-32, 1994 8148215

- McLean MJ, Schmutz M, Wamil AW, et al: Oxcarbazepine: mechanisms of action. *Epilepsia* 35 (3 suppl 3):S5-S9, 1994 8156978
- Miceli JJ, Anziano RJ, Robarge L, et al: The effect of carbamazepine on the steady-state pharmacokinetics of ziprasidone in healthy volunteers. *Br J Clin Pharmacol* 49 (suppl 1):65S-70S, 2000 10771457
- Mishory A, Yaroslavsky Y, Bersudsky Y, et al: Phenytoin as an antimanic anticonvulsant: a controlled study. *Am J Psychiatry* 157(3):463-465, 2000 10698828
- Möller HJ, Kissling W, Riehl T, et al: Doubleblind evaluation of the antimanic properties of carbamazepine as a comedication to haloperidol. *Prog Neuropsychopharmacol Biol Psychiatry* 13(1-2):127-136, 1989 2664882
- Møller SE, Larsen F, Khant AZ, et al: Lack of effect of citalopram on the steady-state pharmacokinetics of carbamazepine in healthy male subjects. *J Clin Psychopharmacol* 21(5):493-499, 2001 11593075
- Moreland TA, Chang SL, Levy RH: Mechanisms of interaction between sodium valproate and carbamazepine in the rhesus monkey and in the isolated perfused rat liver, in *Metabolism of Antiepileptic Drugs*. Edited by Levy RH, Pitlick WH, Eichelbaim M, et al. New York, Raven, 1984, pp 53-60
- Mosolov SN: [Comparative effectiveness of preventive use of lithium carbonate, carbamazepine and sodium valproate in affective and schizoaffective psychoses]. *Zh Nevropatol Psikhiatr Im S S Korsakova* 91(4):78-83, 1991 1650105
- Müller AA, Stoll KD: Carbamazepine and oxcarbazepine in the treatment of manic syndromes: studies in Germany, in *Anticonvulsants in Affective Disorders*. Edited by Emrich HM, Okuma T, Müller AA. Amsterdam, Elsevier Science Publishers, 1984, pp 139-147
- Muñoz JJ, De Salamanca RE, Diaz-Obregón C, et al: The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 29(6):763-765, 1990 2378792
- Murphy DJ, Gannon MA, McGennis A: Carbamazepine in bipolar affective disorder. *Lancet* 2(8672):1151-1152, 1989 2572865
- Murphy JM, Mashman J, Miller JD, et al: Suppression of carbamazepine-induced rash with prednisone. *Neurology* 41(1):144-145, 1991 1824644
- Nau H, Löscher W: Pharmacologic evaluation of various metabolites and analogs of valproic acid: teratogenic potencies in mice. *Fundam Appl Toxicol* 6(4):669-676, 1986 3086174
- Neumann J, Seidel K, Wunderlich HP: Comparative studies of the effect of carbamazepine and trimipramine in depression in Anticonvulsants in Affective Disorders. Edited by Emrich HM, Okuma T, Müller AA. Amsterdam, Elsevier Science Publishers, 1984, pp 160-166
- Nightingale SL: From the Food and Drug Administration. *JAMA* 263(14):1896, 1990 2313862
- O'Neill B, Callaghan N, Stapleton M, et al: Serum elevation of high density lipoprotein (HDL) cholesterol in epileptic patients taking carbamazepine or phenytoin. *Acta Neurol Scand* 65(2):104-109, 1982 7072480
- Ojemann LM, Shastri RA, Wilensky AJ, et al: Comparative pharmacokinetics of zonisamide (CI-912) in epileptic patients on carbamazepine or phenytoin monotherapy. *Ther Drug Monit* 8(3):293-296, 1986 3750373
- Okuma T: Therapeutic and prophylactic effects of carbamazepine in bipolar disorders. *Psychiatr Clin North Am* 6(1):157-174, 1983 6351033
- Okuma T: Effects of carbamazepine and lithium on affective disorders. *Neuropsychobiology* 27(3):138-145, 1993 8232828
- Okuma T, Inanaga K, Otsuki S, et al: Comparison of the antimanic efficacy of carbamazepine and chlorpromazine: a double-blind controlled study. *Psychopharmacology (Berl)* 66(3):211-217, 1979 119267

- Okuma T, Inanaga K, Otsuki S, et al: A preliminary double-blind study on the efficacy of carbamazepine in prophylaxis of manic-depressive illness. *Psychopharmacology (Berl)* 73(1):95-96, 1981 6785799
- Okuma T, Yamashita I, Takahashi R, et al: A double-blind study of adjunctive carbamazepine versus placebo on excited states of schizophrenic and schizoaffective disorders. *Acta Psychiatr Scand* 80(3):250-259, 1989 2573234
- Okuma T, Yamashita I, Takahashi R, et al: Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study. *Pharmacopsychiatry* 23(3):143-150, 1990 1973844
- Ono S, Mihara K, Suzuki A, et al: Significant pharmacokinetic interaction between risperidone and carbamazepine: its relationship with CYP2D6 genotypes. *Psychopharmacology (Berl)* 162(1):50-54, 2002 12107617
- Otani K, Ishida M, Kaneko S, et al: Effects of carbamazepine coadministration on plasma concentrations of trazodone and its active metabolite, m-chlorophenylpiperazine. *Ther Drug Monit* 18(2):164-167, 1996 8721280
- Pearson HJ: Interaction of fluoxetine with carbamazepine. *J Clin Psychiatry* 51(3):126, 1990 2353956
- Peltola J, Holtkamp M, Rocamora R, et al: Practical guidance and considerations for transitioning patients from oxcarbazepine or carbamazepine to eslicarbazepine acetate—Expert opinion. *Epilepsy Behav* 50:46-49, 2015 26114438
- Physicians' Desk Reference, 69th Edition. Montvale, NJ, PDR Network, 2015
- Pihlgård M, Eliasson E: Significant reduction of sertraline plasma levels by carbamazepine and phenytoin. *Eur J Clin Pharmacol* 57(12):915-916, 2002 11936714
- Pitterle ME, Collins DM: Carbamazepine-10,11-epoxide evaluation associated with coadministration of loxapine or amoxapine (abstract). *Epilepsia* 29:654, 1988
- Placidi GF, Lenzi A, Lazzerini F, et al: The comparative efficacy and safety of carbamazepine versus lithium: a randomized, double-blind 3-year trial in 83 patients. *J Clin Psychiatry* 47(10):490-494, 1986 3093468
- Post RM: Time course of clinical effects of carbamazepine: implications for mechanisms of action. *J Clin Psychiatry* 49 (4 suppl):35-48, 1988 3280560
- Post RM: Carbamazepine treatment of bipolar affective disorder, in *Directions in Psychiatry*, Vol 9, Lesson 19. New York, Hatherleigh, 1989, pp 1-12
- Post RM, Weiss SR: Tolerance to the prophylactic effects of carbamazepine and related mood stabilizers in the treatment of bipolar disorders. *CNS Neurosci Ther* 17(6):649-660, 2011 21159150
- Post RM, Uhde TW, Ballenger JC, et al: Carbamazepine and its -10,11-epoxide metabolite in plasma and CSF. Relationship to antidepressant response. *Arch Gen Psychiatry* 40(6):673-676, 1983 6847334
- Post RM, Ballenger JC, Uhde TW, et al: Efficacy of carbamazepine in manic-depressive illness: implications for underlying mechanisms, in *Neurobiology of Mood Disorders*. Edited by Post RM, Ballenger JC. Baltimore, Williams & Wilkins, 1984a, pp 777-816
- Post RM, Berrettini W, Uhde TW, et al: Selective response to the anticonvulsant carbamazepine in manic-depressive illness: a case study. *J Clin Psychopharmacol* 4(4):178-185, 1984b 6432857
- Post RM, Uhde TW, Roy-Byrne PP, et al: Antidepressant effects of carbamazepine. *Am J Psychiatry* 143(1):29-34, 1986 3510572
- Post RM, Uhde TW, Roy-Byrne PP, et al: Correlates of antimanic response to carbamazepine. *Psychiatry Res* 21(1):71-83, 1987 2885878
- Post RM, Rubinow DR, Uhde TW, et al: Dysphoric mania. Clinical and biological correlates. *Arch Gen Psychiatry* 46(4):353-358, 1989 2930331
- Post RM, Leverich GS, Rosoff AS, et al: Carbamazepine prophylaxis in refractory affective disorders: a focus on long-term follow-up. *J Clin Psychopharmacol* 10(5): 318-327, 1990 2124216

- Post RM, Altshuler LL, Ketter TA, et al: Antiepileptic drugs in affective illness. Clinical and theoretical implications. *Adv Neurol* 55:239-277, 1991 2003410
- Post RM, Ketter TA, Uhde T, et al: Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and practice. *CNS Drugs* 21(1):47-71, 2007 17190529
- Price WA, DiMarzio LR: Verapamil-carbamazepine neurotoxicity. *J Clin Psychiatry* 49(2):80, 1988 3338983
- Prien RF, Gelenberg AJ: Alternatives to lithium for preventive treatment of bipolar disorder. *Am J Psychiatry* 146(7):840-848, 1989 2568092
- Pynnönen S, Kanto J, Sillanpää M, et al: Carbamazepine: placental transport, tissue concentrations in foetus and newborn, and level in milk. *Acta Pharmacol Toxicol (Copenh)* 41(3):244-253, 1977 578653
- Pynnönen S, Björkquist SE, Pekkarinen A: The pharmacokinetics of carbamazepine in alcoholics, in *Advances in Epileptology*. Edited by Meinardi H, Rowan AJ. Amsterdam, Swets & Zeitlinger, 1978, pp 285-290
- Radulovic LL, Wilder BJ, Leppik IE, et al: Lack of interaction of gabapentin with carbamazepine or valproate. *Epilepsia* 35(1):155-161, 1994 8112239
- Raitasuo V, Lehtovaara R, Huttunen MO: Carbamazepine and plasma levels of clozapine. *Am J Psychiatry* 150(1):169, 1993 8417568
- Raitasuo V, Lehtovaara R, Huttunen MO: Effect of switching carbamazepine to oxcarbazepine on the plasma levels of neuroleptics. A case report. *Psychopharmacology (Berl)* 116(1):115-116, 1994 7862923
- Rambeck B, May T, Juergens U: Serum concentrations of carbamazepine and its epoxide and diol metabolites in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* 9(3):298-303, 1987 3672573
- Rapeport WG, Williams SA, Muirhead DC, et al: Absence of a sertraline-mediated effect on the pharmacokinetics and pharmacodynamics of carbamazepine. *J Clin Psychiatry* 57 (suppl 1):20-23, 1996 8617707
- Rättyä J, Vainionpää L, Knip M, et al: The effects of valproate, carbamazepine, and oxcarbazepine on growth and sexual maturation in girls with epilepsy. *Pediatrics* 103(3):588-593, 1999 10049961
- Reinstein MD, Sonnenberg JG, Mohan SC, et al: Oxcarbazepine: review of 200 subjects treated for mania in a hospital setting. Paper presented at the 155th Annual Meeting of the American Psychiatric Association, Philadelphia, PA, May 18-23, 2002
- Ries RK, Roy-Byrne PP, Ward NG, et al: Carbamazepine treatment for benzodiazepine withdrawal. *Am J Psychiatry* 146(4):536-537, 1989 2929759
- Ringel RA, Brick JF: Perspective on carbamazepine-induced water intoxication: reversal by demeclocycline. *Neurology* 36(11):1506-1507, 1986 3093919
- Rosa FW: Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 324(10):674-677, 1991 1994251
- Roth L, Bertschy G: Nefazodone may inhibit the metabolism of carbamazepine: three case reports. *Eur Psychiatry* 16(5):320-321, 2001 11514137
- Sachdeo RC, Sachdeo SK, Walker SA, et al: Steady-state pharmacokinetics of topiramate and carbamazepine in patients with epilepsy during monotherapy and concomitant therapy. *Epilepsia* 37(8):774-780, 1996 8764818
- Samara EE, Gustavson LE, El-Shourbagy T, et al: Population analysis of the pharmacokinetics of tiagabine in patients with epilepsy. *Epilepsia* 39(8):868-873, 1998 9701378
- Scaparrotta A, Verrotti A, Consilvio NP, et al: Pathogenesis and clinical approaches to anticonvulsant hypersensitivity syndrome: current state of knowledge. *Int J Immunopathol Pharmacol* 24(2):277-284, 2011 21658302
- Scheffner D, König S, Rauterberg-Ruland I, et al: Fatal liver failure in 16 children with valproate therapy. *Epilepsia* 29(5):530-542, 1988 3137017

- Schmutz M, Brugger F, Gentsch C, et al: Oxcarbazepine: preclinical anticonvulsant profile and putative mechanisms of action. *Epilepsia* 35 (suppl 5):S47-S50, 1994 8039471
- Schütz H, Feldmann KF, Faigle JW, et al: The metabolism of <sup>14</sup>C-oxcarbazepine in man. *Xenobiotica* 16(8):769-778, 1986 3765657
- Shimoyama R, Ohkubo T, Sugawara K: Monitoring of carbamazepine and carbamazepine 10,11-epoxide in breast milk and plasma by high-performance liquid chromatography. *Ann Clin Biochem* 37(Pt 2):210-215, 2000 10735366
- Sitsen J, Maris F, Timmer C: Drug-drug interaction studies with mirtazapine and carbamazepine in healthy male subjects. *Eur J Drug Metab Pharmacokinet* 26(1-2):109-121, 2001 11554425
- Small JG: Anticonvulsants in affective disorders. *Psychopharmacol Bull* 26(1):25-36, 1990 2196624
- Small JG, Klapper MH, Milstein V, et al: Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry* 48(10):915-921, 1991 1929761
- Smith LA, Cornelius V, Warnock A, et al: Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord* 9(4):394-412, 2007 17547586
- Spina E, Avenoso A, Facciola G, et al: Plasma concentrations of risperidone and 9-hydroxyrisperidone: effect of comedication with carbamazepine or valproate. *Ther Drug Monit* 22(4):481-485, 2000 10942191
- Staines AG, Coughtrie MW, Burchell B: N-glucuronidation of carbamazepine in human tissues is mediated by UGT2B7. *J Pharmacol Exp Ther* 311(3):1131-1137, 2004 15292462
- Stefani A, Pisani A, De Murtas M, et al: Action of GP 47779, the active metabolite of oxcarbazepine, on the corticostriatal system. II. Modulation of high-voltage-activated calcium currents. *Epilepsia* 36(10):997-1002, 1995 7555964
- Stefani A, Spadoni F, Bernardi G: Voltage-activated calcium channels: targets of antiepileptic drug therapy? *Epilepsia* 38(9):959-965, 1997 9579933
- Steinacher L, Vandel P, Zullino DF, et al: Carbamazepine augmentation in depressive patients non-responding to citalopram: a pharmacokinetic and clinical pilot study. *Eur Neuropsychopharmacol* 12(3):255-260, 2002 12007677
- Stoll KD, Bisson HE, Fischer E, et al: Carbamazepine versus haloperidol in manic syndromes—first report of a multicentric study in Germany, in *Biological Psychiatry* 1985. Edited by Shagass C. Amsterdam, Elsevier, 1986, pp 332-334
- Suppes T, Dennehy EB, Hirschfeld RM, et al; Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder: The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry* 66(7):870-886, 2005 16013903
- Takezaki H, Hanaoka M: The use of carbamazepine (Tegretol) in the control of manic-depressive psychosis and other manic-depressive states. *Seishin Igaku* 13:173-183, 1971
- Tartara A, Galimberti CA, Manni R, et al: Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 32(3):335-340, 1991 1777370
- Thakker KM, Mangat S, Garnett WR, et al: Comparative bioavailability and steady state fluctuations of Tegretol commercial and carbamazepine OROS tablets in adult and pediatric epileptic patients. *Biopharm Drug Dispos* 13(8):559-569, 1992 1421050
- Thweatt RE: Carbamazepine/MAOI interaction. *Psychosomatics* 27(7):538, 1986 3737846
- Tiihonen J, Vartiainen H, Hakola P: Carbamazepine-induced changes in plasma levels of neuroleptics. *Pharmacopsychiatry* 28(1):26-28, 1995 7746842
- Tohen M, Castillo J, Pope HG Jr, et al: Concomitant use of valproate and carbamazepine in bipolar and schizoaffective disorders. *J Clin Psychopharmacol* 14(1):67-70, 1994 8151006

- Tohen M, Castillo J, Baldessarini RJ, et al: Blood dyscrasias with carbamazepine and valproate: a pharmacoepidemiological study of 2,228 patients at risk. *Am J Psychiatry* 152(3):413-418, 1995 7864268
- Tohen M, Bowden CL, Smulevich AB, et al: Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. *Br J Psychiatry* 192(2):135-143, 2008 18245032
- Van Parys JA, Meinardi H: Survey of 260 epileptic patients treated with oxcarbazepine (Trileptal) on a named-patient basis. *Epilepsy Res* 19(1):79-85, 1994 7813417
- Vasudev A, Macritchie K, Watson S, et al: Oxcarbazepine in the maintenance treatment of bipolar disorder. *Cochrane Database Syst Rev* (1):CD005171, 2008 18254071
- Vaz-Da-Silva M, Nunes T, Almeida L, et al: Evaluation of Eslicarbazepine acetate on cardiac repolarization in a thorough QT/QTc study. *J Clin Pharmacol* 52(2):222-233, 2012 21415284
- Verrotti A, Coppola G, Parisi P, et al: Bone and calcium metabolism and antiepileptic drugs. *Clin Neurol Neurosurg* 112(1):1-10, 2010 19913352
- Verrotti A, D'Egidio C, Mohn A, et al: Antiepileptic drugs, sex hormones, and PCOS. *Epilepsia* 52(2):199-211, 2011 21204821
- Vick NA: Suppression of carbamazepine-induced skin rash with prednisone. *N Engl J Med* 309(19):1193-1194, 1983 6225950
- Vieta E, Cruz N, García-Campayo J, et al: A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. *Int J Neuropsychopharmacol* 11(4):445-452, 2008 18346292
- Vieweg V, Glick JL, Herring S, et al: Absence of carbamazepine-induced hyponatremia among patients also given lithium. *Am J Psychiatry* 144(7):943-947, 1987 3605408
- Wagner KD, Kowatch RA, Emslie GJ, et al: A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry* 163(7):1179-1186, 2006 16816222
- Wamil AW, Schmutz M, Portet C, et al: Effects of oxcarbazepine and 10-hydroxycarbamazepine on action potential firing and generalized seizures. *Eur J Pharmacol* 271(2-3):301-308, 1994 7705430
- Watkins SE, Callender K, Thomas DR, et al: The effect of carbamazepine and lithium on remission from affective illness. *Br J Psychiatry* 150:180-182, 1987 3115347
- Weisler RH, Kalali AH, Ketter TA; SPD417 Study Group: A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry* 65(4):478-484, 2004 15119909
- Weisler RH, Keck PE Jr, Swann AC, et al; SPD417 Study Group: Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 66(3):323-330, 2005 15766298
- Wietholtz H, Zysset T, Kreiten K, et al: Effect of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* 36(4):401-406, 1989 2500346
- Wildgrube C: Case studies on prophylactic long-term effects of oxcarbazepine in recurrent affective disorders. *Int Clin Psychopharmacol* 5 (suppl 1):89S-94S, 1990
- Yatham LN, Barry S, Mobayed M, et al: Is the carbamazepine-phenelzine combination safe? *Am J Psychiatry* 147(3):367, 1990 2309956
- Yatham LN, Grossman F, Augustyns I, et al: Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. *Br J Psychiatry* 182:141-147, 2003 12562742
- Yukawa E, Nonaka T, Yukawa M, et al: Pharmacoepidemiologic investigation of a clonazepam-carbamazepine interaction by mixed effect modeling using routine clinical pharmacokinetic data in Japanese patients. *J Clin Psychopharmacol* 21(6):588-593, 2001 11763006

- Zaccara G, Gangemi PF, Bondoni L, et al: Influence of single and repeated doses of oxcarbazepine on the pharmacokinetic profile of felodipine. *Ther Drug Monit* 15(1):39-42, 1993 8451779
- Zaccara G, Giovannelli F, Cincotta M, et al: Clinical utility of eslicarbazepine: current evidence. *Drug Des Devel Ther* 9:781-789, 2015 25709402
- Zhang ZJ, Kang WH, Tan QR, et al: Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. *J Psychiatr Res* 41(3-4):360-369, 2007 16081106

## CHAPTER 39

# Gabapentin and Pregabalin

Mark A. Frye, M.D.

Katherine Marshall Moore, M.D.

Alan F. Schatzberg, M.D.

---

## Gabapentin

---

Early observations of enhanced general well-being in epileptic patients treated with anticonvulsants, as well as various early hypotheses of kindling and sensitization proposed as models of affective illness progression ([Weiss and Post 1998](#)), have promoted controlled investigations of anticonvulsant drugs as potential mood-stabilizing agents.

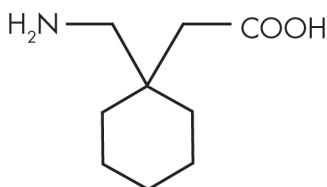
Gabapentin is U.S. Food and Drug Administration (FDA)-approved for the adjunctive treatment of complex partial epilepsy in pediatric patients ages 3-12 years and in patients older than 12 years (with and without secondary generalization) and for the management of postherpetic



neuralgia in adults. A retrospective review of five placebo-controlled trials of gabapentin in more than 700 patients with refractory partial seizure disorder additionally supported the concept of improvement in general well-being, prompting controlled investigation of the drug in primary psychiatric conditions ([Dimond et al. 1996](#)).

## Structure–Activity Relations

Gabapentin, 2-[1-(aminomethyl)cyclohexyl]acetic acid, is a synthetic analog of  $\gamma$ -aminobutyric acid (GABA) ([Figure 39-1](#)).



---

**FIGURE 39-1.** Chemical structure of gabapentin.

## Pharmacological Profile and Mechanism of Action

The mechanism of gabapentin's anticonvulsant and psychotropic action is not fully understood. Gabapentin was originally developed as a GABA analog. As reviewed by [Taylor et al. \(1998\)](#), GABA is the major inhibitory neurotransmitter in the cerebral cortex. Preclinical studies have suggested that gabapentin increases brain and intracellular GABA by an amino acid active transporter at the blood-brain barrier and multiple enzymatic regulatory mechanisms, respectively. In vitro, gabapentin increases the

activity of glutamic acid decarboxylase, the enzyme that converts glutamate to GABA ([Taylor et al. 1992](#)). Conversely, gabapentin has been shown to inhibit GABA transaminase (GABA-T), the enzyme primarily responsible for GABA catabolism ([Löscher et al. 1991](#)). Glutamate metabolism is also modulated by gabapentin. In vitro, gabapentin inhibits branched-chain amino acid aminotransferase (BCAA-T), which is responsible for glutamate synthesis ([Hutson et al. 1998](#)), and activates glutamate dehydrogenase, which is involved in glutamate catabolism ([Goldlust et al. 1995](#)).

These enzymatic regulatory mechanisms that suggest an increased synthesis and decreased degradation of GABA are clinically relevant. Several, but not all, studies have reported decreased levels of cerebrospinal fluid ([Goddard et al. 1996](#); [Gold et al. 1980](#); [Roy et al. 1991](#)), plasma ([Petty et al. 1990](#)), and magnetic resonance (MR) spectroscopic GABA ([Sanacora et al. 1999](#)) in patients with affective illness in comparison with healthy control subjects. Furthermore, increased MR spectroscopic occipital GABA concentrations have been reported with serotonin reuptake inhibitor treatment in depressed patients ([Sanacora et al. 2002](#)) and gabapentin treatment in patients with complex partial epilepsy ([Petroff et al. 1996](#)).

Gabapentin also has been shown to bind to the  $\alpha_2$  subunit receptor of brain voltage-dependent calcium channels, an effect that may relate to the subsequent inhibition of monoaminergic transmission ([Schlicker et al. 1985](#)). There is no known direct activity at the dopamine, serotonin, benzodiazepine, or histamine receptors. However, gabapentin has been reported to increase whole-blood levels of serotonin in healthy control subjects ([Rao et al. 1988](#)).

# Pharmacokinetics and Disposition

All bioavailability, distribution, and elimination parameters are based on the gabapentin molecule itself, as there is no active metabolite. Gabapentin exhibits nonlinear bioavailability most likely related to an active saturable l-amino acid transport carrier present in gut and blood-brain barrier ([McLean 1999](#)). There is no evidence of plasma protein binding, hepatic metabolism, or cytochrome P450 (CYP) autoinduction. Elimination half-life is 6–8 hours, with a recommended three-times-a-day dosing strategy. Gabapentin is eliminated from systemic circulation unchanged by renal excretion. Patients with compromised renal function will show evidence of reduced gabapentin clearance.

## Indications and Efficacy

### **Epilepsy**

Gabapentin currently is FDA approved for use in the adjunctive treatment of partial seizures with and without secondary generalization in adults with epilepsy ([Medical Economics Company 2006](#)). Approval for this indication was based on controlled evaluations of gabapentin at daily dosages of 600–1,800 mg. Additional research has reported efficacy and tolerability for gabapentin monotherapy at daily dosages up to 4,800 mg in patients with refractory epilepsy ([Beydoun et al. 1998](#)). There is no established therapeutic plasma level for seizure control. Gabapentin has a highly favorable side-effect profile, with only mild side effects (sedation, dizziness, and ataxia) commonly reported.

## Nonepilepsy Neurological Conditions

**Neuropathic pain.** Gabapentin received FDA approval for use in the management of postherpetic neuralgia in adults on the basis of two placebo-controlled studies ([Rice et al. 2001](#); [Rowbotham et al. 1998](#)). Gabapentin also has been systemically evaluated in diabetic neuropathy ([Backonja et al. 1998](#)).

The initial postherpetic neuralgia ([Rowbotham et al. 1998](#)) and diabetic neuropathy ([Backonja et al. 1998](#)) studies were randomized, double-blind, placebo-controlled, parallel-group multicenter investigations with three phases of evaluation. The first phase identified the subject population (patients with diabetic neuropathy of 1–5 years' duration [[Backonja et al. 1998](#)] or postherpetic neuralgia of 3 months' duration [[Rowbotham et al. 1998](#)]). The 8-week double-blind phases consisted of a 4-week step titration (week 1, 900 mg; week 2, 1,800 mg; week 3, 2,400 mg; and week 4, 3,600 mg) and a 4-week fixed-dosage period wherein the dosage that was effective and tolerable from the titration phase was held constant. There were no differences in demographics or rates of dropout due to inefficacy or adverse events between the gabapentin group and the placebo group.

Among the 229 postherpetic neuralgia patients ([Rowbotham et al. 1998](#)), greater pain reduction occurred with gabapentin, noted as early as week 2 and maintained throughout the entire study period. Similarly, secondary measures of mood, such as depression, anger-hostility, fatigue-inertia, and physical functioning, were more effectively treated with gabapentin than with placebo. Eighty-three percent of the patients receiving gabapentin

were maintained on the 2,400-mg daily dosage, and 65% were maintained on the 3,600-mg daily dosage.

Among the 165 diabetic neuropathy patients ([Backonja et al. 1998](#)), greater pain reduction (as measured with an 11-point Likert scale) occurred with gabapentin than with placebo; this difference was statistically significant as early as week 2 of the blind titration phase and remained significant for the duration of the 8-week study. Significant reductions in sleep interference related to pain were also reported, as well as improved quality of life. Gabapentin appeared to be well tolerated, with 67% of the patient group being maintained at a maximum daily dosage of 3,600 mg.

Finally, a 7-week placebo-controlled study evaluated gabapentin (1,800 or 2,400 mg/day in three divided doses) in 334 patients with postherpetic neuralgia ([Rice et al. 2001](#)). Pain was significantly reduced with both gabapentin dosages, with similar improvements in sleep. The improvement in pain score was noted as early as week 1 and was maintained throughout the study.

These findings contrast with findings of additional studies that have investigated gabapentin's utility in the management of perioperative pain ([Zhang et al. 2015](#)). In a reanalysis of two randomized controlled trials of adjunctive gabapentin versus adjunctive placebo in patients undergoing total knee ( $n=102$ ) or total hip arthroplasty ( $n=101$ ), gabapentin did not significantly reduce the primary outcome measure of morphine consumption immediately postprocedure, and 24, 48, and 72 hours postsurgery.

**Movement disorders.** Controlled investigations of gabapentin have been conducted in several movement

disorders. These studies were much smaller than the neuropathic pain studies mentioned in the prior section but included amyotrophic lateral sclerosis (ALS) ([Miller et al. 1996](#)), essential tremor ([Ondo et al. 2000](#); [Pahwa et al. 1998](#)), and parkinsonism ([Olson et al. 1997](#)).

In a study of 152 patients with ALS, patients were randomly assigned to receive a 2,400-mg daily dosage of gabapentin or placebo for 6 months. Decline in muscle strength, the primary outcome measure, was slower in the gabapentin-treated patients than in the placebo-treated patients ([Miller et al. 1996](#)).

Controlled studies of gabapentin for essential tremor have reported mixed results. The first 2-week controlled study showed no difference between gabapentin 1,800 mg/day and placebo for treatment of essential tremor ([Pahwa et al. 1998](#)). A second 6-week controlled study evaluating two gabapentin dosages—1,800 mg/day and 3,600 mg/day—in patients with essential tremor found significant improvements in self-report scores, observed tremor scores, and activities of daily living scores in patients who were randomly assigned to receive gabapentin compared with patients who received placebo ([Ondo et al. 2000](#)).

In a 1-month double-blind, placebo-controlled evaluation of gabapentin in 19 patients with advanced parkinsonism, gabapentin at a mean total daily dosage of 1,200 mg was superior to placebo in reducing rigidity, bradykinesia, and tremor, as measured by the United Parkinson's Disease Rating Scale ([Olson et al. 1997](#)). The rigidity and bradykinesia improvements were independent of tremor improvement.

**Migraine headache.** The comorbidity of migraine headache and bipolar disorder is highly prevalent and clinically significant ([Mahmood et al. 1999](#)). Anticonvulsants, for their mood-stabilizing effects and migraine prophylactic properties, appear to be ideal in this patient population. [Mathew et al. \(2001\)](#) suggested that gabapentin is an effective agent for migraine prophylaxis. One hundred forty-three patients with migraine (with and without aura) participated in this three-phase controlled evaluation of gabapentin. Phase 1 was a 4-week single-blind placebo period during which baseline migraine headache frequency was established. Phase 2 was a 4-week double-blind, placebo-controlled, flexible-dosage titration period during which patients received gabapentin at dosages of up to 2,400 mg/day. Phase 3 was an 8-week double-blind, placebo-controlled period during which the dosage of gabapentin was held constant. Patients randomly assigned to receive gabapentin at 2,400 mg/day had significant reductions in migraine attacks in comparison with placebo-treated patients. Dropout rates were higher with gabapentin and were primarily related to drowsiness and somnolence.

## **Anxiety Disorders**

Gabapentin produces a dose-dependent anxiolytic response in animal models ([Singh et al. 1996](#)). Open-trial investigations have reported positive results with add-on gabapentin in the treatment of generalized anxiety disorder (GAD) ([Pollack et al. 1998](#)) and panic disorder ([Pollack et al. 1998](#)), as well as in refractory obsessive-compulsive disorder ([Corá-Locatelli et al. 1998](#)). Findings from controlled investigations of gabapentin in social phobia

([Pande et al. 1999](#)) and in panic disorder ([Pande et al. 2000b](#)) suggested that gabapentin has anxiolytic activity.

The first study was a 14-week randomized, double-blind, placebo-controlled two-site study of 69 outpatients with DSM-IV ([American Psychiatric Association 1994](#))-confirmed social phobia ([Pande et al. 1999](#)). All patients were required to have a score of 50 or greater on the Liebowitz Social Anxiety Scale (LSAS) at baseline. Reductions in the LSAS score served as the primary outcome measure. In the intent-to-treat analysis, gabapentin was more effective than placebo in reducing social anxiety symptoms. The dosage range for gabapentin was 900–3,600 mg/day, with 56% of patients responding to and tolerating the maximum daily dosage of 3,600 mg. Dizziness and dry mouth were significantly more common in patients treated with gabapentin.

The second study was an 8-week randomized, placebo-controlled six-site monotherapy study of 103 patients with DSM-IV-confirmed panic disorder with or without agoraphobia ([Pande et al. 2000b](#)). Gabapentin was dosed flexibly between 600 and 3,600 mg/day. The primary outcome measure was a decrease in the Panic and Agoraphobia Scale (PAS) score. There were no differences in dropout rate. In the intent-to-treat analysis, no difference in PAS score reduction was seen between patients randomly assigned to receive gabapentin and those receiving placebo. In a post hoc stratification between high ( $\geq 20$ ) and low ( $< 20$ ) PAS symptom severity, patients with high symptom severity who were randomly assigned to receive gabapentin had a greater baseline-to-endpoint decrease in PAS score than did those who were randomly assigned to receive placebo. Somnolence, headache, dizziness,



infection, asthenia, and ataxia were more common with gabapentin than with placebo.

## **Bipolar Disorder**

Numerous case reports on and open trials of gabapentin as a mood stabilizer, encompassing more than 400 patients with a pooled response rate between 65% and 70%, have been reviewed elsewhere ([Frye et al. 2000](#); [Yatham et al. 2002](#)).

One double-blind, placebo-controlled outpatient study evaluated add-on gabapentin for the treatment of bipolar I disorder with manic, hypomanic, or mixed symptoms ([Pande et al. 2000a](#)). The first phase of the study involved a 2-week single-blind, placebo lead-in wherein dosages of the subject's primary mood stabilizer (lithium or valproate) could be adjusted to maximal clinical benefit and minimum threshold of therapeutic level (i.e., lithium level of 0.5 mmol/L, valproate level of >50 µg/mL). The second phase was a 10-week double-blind trial in which subjects were randomly assigned to receive gabapentin, at flexible dosages between 600 and 3,600 mg/day (three-times-a-day dosing), or placebo. In the intent-to-treat population, 117 subjects were randomized; no differences in demographic profile or dropout rate were found between the two groups. The primary outcome measure—total decreased score on the Young Mania Rating Scale—was significantly different between groups in favor of add-on placebo. In a post hoc analysis, lithium adjustments in the single-blind placebo lead-in phase were made more frequently in the placebo group than in the gabapentin group; most of these adjustments (9 of 12; 75%) consisted of a dosage increase. This fact suggests either a strong placebo response or the effect of maximizing lithium blood levels to achieve a

greater antimanic response. Of the gabapentin-treated patients who had drug levels measured, nearly 20% had plasma gabapentin levels that were undetectable.

The second controlled study was a 6-week double-blind, placebo-controlled crossover comparative trial of gabapentin monotherapy, lamotrigine monotherapy, and placebo in 35 inpatients with refractory mood disorder ([Frye et al. 2000](#); [Obrocea et al. 2002](#)). In the preliminary analysis ([Frye et al. 2000](#)) and final analysis ([Obrocea et al. 2002](#)), gabapentin demonstrated no better treatment response than placebo in a group of patients with highly refractory bipolar (primarily rapid-cycling) disorder.

There appears to be a marked contrast between the pooled results of the uncontrolled observations (generally positive) and the results of the controlled studies (generally negative). Important limitations of the controlled investigations included maximizing lithium response in the single-blind placebo run-in phase, lack of rigorous compliance assessment, and use of a monotherapy study design in a cohort of patients with primarily rapid-cycling, treatment-refractory illness.

## **Substance-Related Disorders**

Mood-stabilizing anticonvulsants such as divalproex sodium and carbamazepine may be useful in the treatment of alcohol abuse in bipolar disorder ([Malcolm et al. 2001](#)). Gabapentin has been shown to reduce excitability and convulsions in animal models of alcohol withdrawal ([Watson et al. 1997](#)). Its lack of hepatic metabolism, CYP enzyme induction, protein binding, and addictive potential makes gabapentin a potentially useful compound in this patient population.

Gabapentin's potential utility in the treatment of alcohol withdrawal was examined after initial positive reports emerged ([Bozikas et al. 2002](#)). One study demonstrated that gabapentin had efficacy comparable to that of phenobarbital in treating alcohol withdrawal ([Mariani et al. 2006](#)), although another controlled trial did not substantiate gabapentin's benefit over placebo ([Bonnet et al. 2003](#)). In a post hoc analysis ([Bonnet et al. 2007](#)), there was a significant increase in the Profile of Mood States (POMS) vigor subscore in the gabapentin group versus the placebo group; this response was particularly robust in patients with comorbid mild depression.

Despite the conflicting findings regarding gabapentin's efficacy in alcohol withdrawal, its therapeutic benefit in the sleep-disturbance component of alcohol withdrawal syndrome is now recognized. In outpatients with DSM-IV alcohol dependence experiencing persistent insomnia, low-dose gabapentin (mean dose=900 mg at bedtime), in comparison with trazodone, was associated with greater improvement in sleep problems, as assessed with the Sleep Problems Questionnaire ([Karam-Hage and Brower 2003](#)). In another study, gabapentin, in comparison with lorazepam, was associated with significant reductions in self-reported sleep disturbances and daytime sleepiness in outpatients being treated for alcohol withdrawal ([Malcolm et al. 2007](#)).

A 4-week randomized, placebo-controlled, double-blind study evaluated gabapentin's utility in the prevention of relapse to alcohol use ([Furieri and Nakamura-Palacios 2007](#)). After detoxification, 60 men with DSM-IV alcohol dependence who had been consuming, on average, 17 drinks per day for the preceding 3 months were randomly assigned to receive gabapentin (300 mg twice daily) or

placebo. The gabapentin group showed significant reductions in number of drinks per day, percentage of heavy drinking days, and craving for alcohol (specifically automaticity of drinking) as well as an increase in percentage of days abstinent. In a more recent study in 150 individuals with DSM-IV alcohol dependence, the addition of gabapentin to naltrexone was reported to significantly improve drinking outcomes in comparison with naltrexone alone or placebo ([Anton et al. 2011](#)). The largest clinical trial to date examined linear dose effects of gabapentin on alcohol-related insomnia, dysphoria, and craving in patients with DSM-IV alcohol dependence ([Mason et al. 2014](#)). In this 12-week randomized, double-blind trial ( $n=150$ ), evidence of a linear dose response (1,800 mg gabapentin > 900 mg gabapentin > placebo) was found for abstinence, absence of heavy drinking (defined as  $\geq 4$  and  $\geq 5$  drinks/day for women and men, respectively), mood (i.e., improvement), sleep (i.e., sleep quality), and craving (i.e., reduction).

Finally, in a proof-of-concept randomized controlled study in 50 treatment-seeking outpatients with DSM-IV cannabis dependence, gabapentin at 1,200 mg/day was significantly more effective than placebo in reducing cannabis use and decreasing withdrawal symptoms ([Mason et al. 2012](#)).

## Side Effects and Toxicology

Gabapentin has a highly favorable side-effect profile that has been remarkably consistent across controlled studies of diverse disease states. Sedation, drowsiness, and dizziness always have been reported, and ataxia, dry mouth,

infection, and asthenia have been reported in at least one placebo-controlled study.

Adverse events caused by gabapentin are uncommon but can have serious psychiatric implications. Gabapentin-induced hypomania and mania have been reported ([Leweke et al. 1999](#); [Short and Cooke 1995](#)). The controlled study in mania did not report data on the percentage of patients experiencing exacerbation of mania secondary to gabapentin treatment ([Pande et al. 2000a](#)). Gabapentin also has been associated with aggression, both in pediatric epilepsy ([Wolf et al. 1995](#)) and in adult mania ([Pinninti and Mahajan 2001](#)).

Gabapentin has a broad therapeutic index and appears to be safe in overdose. The broadness of the therapeutic index is most likely related to its nonlinear bioavailability secondary to a saturable transport carrier ([McLean 1999](#)).

## Drug-Drug Interactions

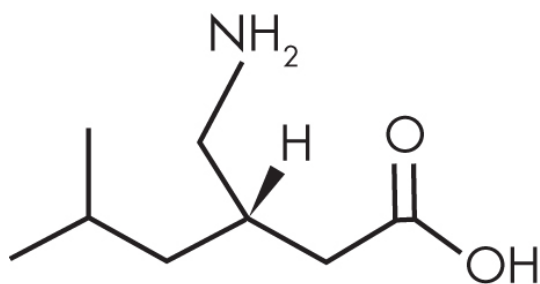
Given its lack of hepatic metabolism, absence of CYP autoinduction, and minimal plasma protein binding, gabapentin does not affect levels of anticonvulsant drugs; similarly, gabapentin's pharmacokinetic characteristics do not change when the drug is coadministered with hepatically metabolized anticonvulsants ([Medical Economics Company 2006](#)). However, gabapentin's renal excretion does pose a potential risk when the drug is used concomitantly with lithium.

Although the therapeutic index for gabapentin is large, the safety window for lithium is not. In a pharmacokinetic study examining the effect of gabapentin versus placebo on a single 600-mg dose of lithium, there was no difference in

maximal lithium concentration ( $Li\ C_{max}$ ), time to reach  $C_{max}$ , or area under the curve in 13 patients receiving steady-state gabapentin (mean dose= $3,645.15 \pm 931.5$  mg) compared with those receiving steady-state placebo ([Frye et al. 1998](#)). It is important to emphasize that this study was in a patient population with normal renal function; cases of reversible renal impairment associated with gabapentin have been reported ([Grunze et al. 1998](#)).

## Summary for Gabapentin

Results of controlled studies of gabapentin clearly suggest its efficacy in several medical conditions, including complex partial epilepsy, postherpetic neuropathy, diabetic neuropathy, and migraine headache. Data also clearly suggest gabapentin's benefit in several off-label psychiatric uses, such as alcohol-related abstinence, craving, and mood/anxiety. Conclusions regarding gabapentin's efficacy in ALS, essential tremor, parkinsonism, social phobia, or panic disorder are less clear, either because of positive controlled studies with small sample sizes or because of negative studies. Gabapentin's role as a mood stabilizer is not clearly established. Gabapentin has a favorable pharmacokinetic profile, and its lack of hepatic metabolism is a particular advantage in patients with compromised liver function. Its minimal drug-drug interactions, low risk of toxicity, and benign side-effect profile make it a useful addition to the pharmacopoeia.



**FIGURE 39-2.** Chemical structure of pregabalin

## Pregabalin

Pregabalin is an anticonvulsant drug approved by the FDA for the adjunctive treatment of partial-onset seizures in adults. It is also approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. Like many of the newer anticonvulsant agents, pregabalin has been evaluated in carefully controlled studies for possible utility in neurological and psychiatric conditions other than primary epilepsy.

## Structure–Activity Relations

Pregabalin, (3S)-3-(aminomethyl)-5-methylhexanoic acid, is a synthetic analog of GABA ([Figure 39-2](#)).

## Pharmacological Profile and Mechanism of Action

Pregabalin, like gabapentin, is a structural analog of the inhibitory neurotransmitter GABA. Pregabalin showed greater potency than gabapentin in preclinical models of epilepsy, pain, and anxiety ([Hamandi and Sander 2006](#)). Despite being a GABA structural analog, pregabalin has no clinically significant effect at either the GABA<sub>A</sub> or the GABA<sub>B</sub> receptor and is not converted metabolically into GABA or a GABA agonist ([Kavoussi 2006](#)). Furthermore, pregabalin does not bind to any serotonergic, dopaminergic, or glutamatergic receptors. It does bind to the  $\alpha_2\delta$  subunit of the presynaptic voltage-gated calcium channel, modulating the release of excitatory neurotransmitters ([Dooley et al. 2002](#); [Kavoussi 2006](#)). In contrast to GABA reuptake inhibitory anticonvulsants (e.g., tiagabine) or anticonvulsants that modulate enzymatic activity related to GABA production (e.g., vigabatrin), pregabalin has no direct GABA reuptake-inhibitory effects or GABA transaminase-inhibiting effects.

## Pharmacokinetics and Disposition

Pregabalin exhibits linear pharmacokinetics and is not associated with any significant protein binding or hepatic metabolism. Its oral bioavailability is greater than 90% and independent of dose. Steady-state plasma levels are generally achieved within 24–48 hours. Administration with food has no clinically significant effect on the extent of absorption or on elimination. The elimination half-life of the drug is approximately 6.5 hours ([Montgomery 2006](#)). Highly lipophilic but not bound to plasma proteins, pregabalin readily crosses the blood-brain barrier. It is primarily renally excreted, with no active metabolites.



Dosage adjustment is required in patients with renal impairment.

Pregabalin does not induce or inhibit CYP enzymes, nor do CYP enzyme inhibitors alter its pharmacokinetics as a consequence.

## Indications and Efficacy

### **Epilepsy**

Several placebo-controlled studies have evaluated pregabalin in the treatment of patients with refractory partial epilepsy ([Elger et al. 2005](#); [Hamandi and Sander 2006](#)). Response rates for pregabalin dosed at 600 mg/day were similar to those reported in other trials of antiepileptic drugs in refractory epilepsy. The study by [Elger et al. \(2005\)](#) showed that pregabalin administered in either fixed or flexible dosages was highly effective and generally well tolerated as an add-on therapy for partial seizures with or without secondary generalization.

### **Nonepilepsy Neurological Conditions**

Four placebo-controlled studies have evaluated pregabalin's efficacy in neuropathic pain ([Dworkin et al. 2003](#); [Freyenhagen et al. 2005](#); [Sabatowski et al. 2004](#); [van Seventer et al. 2006](#)). In the first study ([Dworkin et al. 2003](#)), an 8-week parallel-group, double-blind, placebo-controlled, randomized multicenter trial, patients with postherpetic neuralgia were randomly assigned to receive either pregabalin 600 mg/day (300 mg/day if they had reduced creatinine clearance) or placebo. At study endpoint, a significant decrease in mean pain scores was found for patients treated with pregabalin compared with

those receiving placebo, and this improvement was identified as early as day 2 and maintained throughout the 8 weeks of double-blind treatment. In the second study ([Freynhagen et al. 2005](#)), patients with chronic postherpetic neuralgia or diabetic peripheral neuropathy were randomly assigned to receive placebo, flexible-dosage pregabalin titrated upward to a maximum dosage of 600 mg/day, or fixed-dosage pregabalin at 300 mg/day for the first week followed by 600 mg/day for the remaining 11 weeks. Both flexible- and fixed-dosage pregabalin significantly reduced endpoint mean pain scores and were significantly superior to placebo in improving pain-related sleep interference.

In the third study, [van Seventer et al. \(2006\)](#) evaluated pregabalin (150, 300, or 600 mg/day in twice-daily doses) or placebo in 370 patients with postherpetic neuralgia. At endpoint, significant dose-proportional pain relief was evident among patients who received pregabalin versus placebo. Sleep interference in all pregabalin groups was significantly improved at endpoint. Similar results were obtained in the fourth study ([Sabatowski et al. 2004](#)), which reported improvement in sleep and mood disturbance in patients treated with pregabalin. In total, these four studies showed benefit in pain reduction, sleep improvement, and mood associated with pregabalin treatment. The most common side effects were dizziness, peripheral edema, weight gain, and somnolence.

[Freeman et al. \(2008\)](#) conducted a pooled analysis of data from seven published randomized, placebo-controlled trials encompassing 400 patients with diabetic peripheral neuropathy. The primary outcome measure was change from baseline to endpoint in mean pain score from patients' daily pain diaries. With three-times-daily administration, all

pregabalin dosages (150, 300, and 600 mg/day) significantly reduced pain and pain-related sleep interference in comparison with placebo. With twice-daily administration, only the 600-mg/day dosage showed efficacy. Pregabalin's pain-reducing and sleep-improving properties appeared to be positively correlated with dosage, with the greatest effect observed in patients treated with 600 mg/day.

## **Fibromyalgia**

Pregabalin is the first medication to receive an FDA indication for the treatment of fibromyalgia. Fibromyalgia is a common chronic pain disorder characterized by widespread diffuse musculoskeletal pain and tenderness frequently accompanied by significant psychiatric comorbidity, including fatigue, sleep disturbance, and mood and anxiety disorders. Classifications of disease severity for fibromyalgia have been published by the American College of Rheumatology ([Wolfe et al. 1990](#)). The prevalence of fibromyalgia in the U.S. population is estimated at 2%, with rates higher in adult women than in men ([Arnold et al. 2007](#)).

Three placebo-controlled studies—two focused on acute treatment ([Crofford et al. 2005](#); [Mease et al. 2008](#)) and one focused on relapse prevention ([Crofford et al. 2008](#))—have evaluated pregabalin's efficacy in the treatment of patients with fibromyalgia. In the first study, an 8-week double-blind, randomized, placebo-controlled investigation of pregabalin (150, 300, and 450 mg/day) versus placebo, pregabalin at the 450-mg daily dosage significantly reduced the average severity of pain in comparison with placebo ([Crofford et al. 2005](#)). Sleep improvement was noted at both the 300-mg and the 450-mg daily dosages. Dizziness and somnolence

were the most frequent adverse events. [Arnold et al. \(2007\)](#), in recognition of the large overlap of psychiatric comorbidity in fibromyalgia, conducted a post hoc analysis of the [Crofford et al. \(2005\)](#) study to assess symptoms of anxiety and depression and their impact on pregabalin treatment. Of 529 patients who had enrolled in pregabalin treatment for fibromyalgia, significantly more patients endorsed anxiety symptoms (71%) than endorsed depressive symptoms (56%). Improvement in pain symptoms with pregabalin versus placebo did not depend on baseline anxiety or depression; in fact, 75% of the pain reduction was not explained by improvements in mood and/or anxiety.

In the second study, a 13-week double-blind, placebo-controlled multicenter trial, 748 patients with fibromyalgia were randomly assigned to receive either placebo or pregabalin at dosages of 300, 450, or 600 mg/day (twice-daily dosing) ([Mease et al. 2008](#)). The primary outcome measure was symptomatic relief of pain associated with fibromyalgia, as measured by a mean pain score from an 11-point numeric rating scale (0=no pain; 10=worst possible pain) from patients' daily diaries. Patients in all pregabalin groups showed statistically significant improvement in endpoint mean pain scores as well as in sleep.

In the third study, the Fibromyalgia Relapse Evaluation and Efficacy for Durability Of Meaningful Relief (FREEDOM) trial, pregabalin was evaluated in nearly 600 patients with fibromyalgia ([Crofford et al. 2008](#)). This study included an initial 6-week open-label phase followed by 26 weeks of double-blind treatment with pregabalin or blind substitution with placebo. The primary outcome measure was time to loss of therapeutic response, defined as less

than a 30% reduction in pain or worsening of symptoms of fibromyalgia. Time to loss of therapeutic response was significantly greater for the pregabalin group than for the placebo group, with Kaplan-Meier estimates of time to event showing that half of the placebo group had relapsed by day 19, whereas half of the pregabalin group had still not lost response by trial end.

Finally, pregabalin was investigated as an adjunct to antidepressant medication in fibromyalgia patients with comorbid depression ([Arnold et al. 2015](#)). In this randomized, placebo-controlled, double-blind crossover study, patients on stable treatment with selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants were randomly assigned to adjunctive pregabalin or placebo for 6 weeks, followed by a 2-week taper/washout phase and a crossover to the opposite adjunctive condition for another 6 weeks. Mean scores on measures of pain, anxiety, depression, and fibromyalgia impact all significantly improved with adjunctive pregabalin compared with placebo.

## Anxiety Disorders

**Generalized anxiety disorder.** Findings from four placebo-controlled studies contributed to the approval of pregabalin in Europe for GAD ([Montgomery et al. 2006](#); [Pande et al. 2003](#); [Pohl et al. 2005](#); [Rickels et al. 2005](#)). In the first study ([Pande et al. 2003](#)), 276 patients with GAD were randomly assigned to receive pregabalin 150 or 600 mg/day, lorazepam 6 mg/day, or placebo. The 6-week trial included a 1-week placebo lead-in, 4 weeks of blind treatment, and a 1-week taper. The primary efficacy outcome measure was the endpoint Hamilton Anxiety Scale

(Ham-A) score. The mean baseline-to-endpoint decrease in Ham-A total score in all three active-treatment groups (pregabalin 150 mg/day, pregabalin 600 mg/day, and lorazepam 6 mg/day) was significantly greater than the decrease in the placebo group. Percentages of subjects who met a secondary outcome measure, a reduction of 50% or greater in Ham-A score, were significantly higher in the pregabalin 600-mg/day group (46%) and the lorazepam group (61%) than in the placebo group (27%). There were no significant differences in response rates by either definition between patients receiving pregabalin 150 mg/day and patients receiving placebo.

In the second study by [Pohl et al. \(2005\)](#), twice-daily versus three-times-daily dosing of pregabalin was evaluated in a 6-week double-blind, placebo-controlled study. In this study, 250 patients with GAD were randomly assigned to receive pregabalin 100 mg twice daily, 200 mg twice daily, 150 mg three times daily, or placebo. Mean improvement in the Ham-A total score was significantly greater with pregabalin at all three dosages than with placebo. Pairwise comparisons of twice-daily versus three-times-daily dosing found no significant differences in outcome. All three pregabalin groups showed significantly greater improvement in comparison with placebo at endpoint.

In the third study by [Rickels et al. \(2005\)](#), 454 patients with GAD were randomly assigned in a 4-week design to receive pregabalin 300 mg/day, 450 mg/day, or 600 mg/day; alprazolam 1.5 mg/day; or placebo. The primary outcome measure was change from baseline to endpoint in the total Ham-A score. In comparison with the placebo group, all treatment groups showed significantly greater reductions in mean Ham-A total score at last-observation-carried-forward (LOCF) analysis. A significantly higher proportion

of patients in the pregabalin (all dosages) and alprazolam groups than in the placebo group met the endpoint response criterion of 50% or greater reduction in Ham-A total score. The response rate for the 300-mg/day pregabalin group (61%) was significantly higher than that for the alprazolam group (43%).

In the only pregabalin study with an active antidepressant comparator, [Montgomery et al. \(2006\)](#) randomly assigned 421 patients with GAD to 6 weeks of double-blind treatment with pregabalin (400 or 600 mg/day), venlafaxine (75 mg/day), or placebo. The primary outcome measure was change in the Ham-A total score from baseline to LOCF analysis. Pregabalin (both dosages) and venlafaxine produced significantly greater improvement in the Ham-A total score than did placebo. Patients receiving pregabalin 400 mg/day experienced significant improvement in all primary and secondary outcome measures in comparison with those receiving placebo. Rates of discontinuation associated with adverse events were highest in the venlafaxine group (20.4%), followed by the pregabalin 600 mg/day (13.6%), pregabalin 400 mg/day (6.2%), and placebo (9.9%) groups.

Other trials have followed in the wake of these earlier studies, and a recent meta-analysis of seven trials still points to pregabalin's greater efficacy versus placebo in GAD, although the effect sizes are relatively small (approximately 0.35 for psychic anxiety symptoms) ([Boschen 2011](#)). Pregabalin has also been reported to be an effective adjunctive treatment in patients whose GAD symptoms are nonresponsive to SSRI or SNRI therapy ([Rickels et al. 2012](#)).



**Social anxiety disorder.** In a study by [Pande et al. \(2004\)](#), 135 patients with social anxiety disorder were randomly assigned to 10 weeks of double-blind treatment with either pregabalin (low dosage: 150 mg/day; high dosage: 600 mg/day) or placebo. The primary outcome measure was change from baseline to endpoint in the LSAS total score. Patients randomly assigned to receive pregabalin 600 mg/day showed significant decreases in LSAS total score compared with those receiving placebo. Significant differences between high-dosage pregabalin and placebo were also noted on several secondary measures, including the LSAS subscales Total Fear, Avoidance, Social Fear, and Social Avoidance. Low-dosage pregabalin (150 mg/day) was not significantly better than placebo. Somnolence and dizziness were the most frequently reported adverse events. In a more recent study in 329 patients, pregabalin at 600 mg/day—but not at 300 mg/day or 450 mg/day—separated from placebo ([Feltner et al. 2011](#)), a finding consistent with the dosage recommendation of 600 mg/day for efficacy in this disorder. Finally, a long-term study in 153 patients who had responded to an initial course of pregabalin therapy indicated that 450 mg/day was effective as a maintenance treatment in social anxiety disorder ([Greist et al. 2011](#)).

## **Substance-Related Disorders**

As previously noted, pregabalin has no hepatic metabolism and is excreted essentially unchanged in the urine. This pharmacokinetic profile is ideal for patients with alcohol abuse or dependence who have elevated transaminases but need safe, efficacious treatment for symptoms of alcohol withdrawal. Pregabalin's anticonvulsant, analgesic, and anxiolytic properties and potential utility in alcohol-related



disorders were examined in a preclinical study using a mouse model of alcohol dependence ([Becker et al. 2006](#)). Controlled clinical studies of pregabalin in alcohol-dependent patients are needed.

A study in patients with GAD indicated that pregabalin was efficacious in facilitating discontinuation of long-term benzodiazepine therapy ([Hadley et al. 2012](#)).

## Side Effects and Toxicology

In general, the side effects commonly occurring with pregabalin treatment have been mild and not associated with a severity sufficient to warrant drug discontinuation. The most frequently reported symptoms have been dizziness, sedation, dry mouth, edema, blurred vision, weight gain, and concentration difficulty. In controlled clinical trials with pregabalin, significant weight gain (a gain of 7% or more over baseline) was observed in 9% of patients treated with pregabalin, compared with 2% of patients receiving placebo. Pregabalin treatment does not appear to be associated with significant changes in heart rate, blood pressure, respirations, or electrocardiogram measures. Peripheral edema has occurred in a small percentage of patients, but only in rare circumstances has it been identified as severe.

Available preclinical and clinical data suggest that pregabalin has very low abuse liability and is unlikely to produce significant physical dependence. There have been postmarketing reports of angioedema and hypersensitivity in patients treated with pregabalin ([Pfizer 2006](#)).

# Drug-Drug Interactions

Pregabalin does not induce or inhibit CYP enzymes, nor do CYP enzyme inhibitors alter its pharmacokinetics as a consequence. Therefore, hepatic and CYP drug-drug interactions are not relevant when pregabalin is part of a complex polypharmacotherapy regimen. Because of the drug's renal elimination, dosage adjustment is required for patients with renal impairment. To date, no pharmacokinetic drug-drug interactions have been identified. There is some literature to suggest that there can be an additive cognitive impairment when pregabalin is taken in conjunction with oxycodone and that pregabalin may potentiate the effects of lorazepam and alcohol ([Pfizer 2006](#)).

## Summary for Pregabalin

Controlled studies of pregabalin clearly indicate its efficacy in complex partial epilepsy, postherpetic neuropathy, diabetic neuropathy, fibromyalgia, generalized anxiety disorder, and social anxiety disorder. Like gabapentin, pregabalin has a favorable pharmacokinetic profile, with particular advantages in patients with compromised hepatic function. Its minimal drug-drug interactions, low risk of toxicity, and favorable side-effect profile make it a useful addition to the pharmacopoeia.

---

## Conclusion

---

There is increasing interest in the use of anticonvulsant drugs in mood and anxiety disorders. Both gabapentin and pregabalin have demonstrated efficacy for pain, fibromyalgia, and specific anxiety disorders. Gabapentin also appears to have potential use in cannabis and alcohol use disorders. Gabapentin's and pregabalin's use in bipolar disorder have not been demonstrated in controlled clinical trials.

---

## References

---

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Anton RF, Myrick H, Wright TM, et al: Gabapentin combined with naltrexone for the treatment of alcohol dependence. *Am J Psychiatry* 168(7):709-717, 2011 21454917
- Arnold LM, Crofford LJ, Martin SA, et al: The effect of anxiety and depression on improvements in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. *Pain Med* 8(8):633-638, 2007 18028041
- Arnold LM, Sarzi-Puttini P, Arsenault P, et al: Efficacy and safety of pregabalin in patients with fibromyalgia and comorbid depression taking concurrent antidepressant medication: a randomized, placebo-controlled study. *J Rheumatol* 42(7):1237-1244, 2015 26034150
- Backonja M, Beydoun A, Edwards KR, et al: Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 280(21):1831-1836, 1998 9846777
- Becker HC, Myrick H, Veatch LM: Pregabalin is effective against behavioral and electrographic seizures during

alcohol withdrawal. *Alcohol Alcohol* 41(4):399–406, 2006 16636010

Beydoun A, Fakhoury T, Nasreddine W, et al: Conversion to high dose gabapentin monotherapy in patients with medically refractory partial epilepsy. *Epilepsia* 39(2):188–193, 1998 9577999

Bonnet U, Banger M, Leweke FM, et al: Treatment of acute alcohol withdrawal with gabapentin: results from a controlled two-center trial. *J Clin Psychopharmacol* 23(5):514–519, 2003 14520131

Bonnet U, Specka M, Leweke FM, et al: Gabapentin's acute effect on mood profile—a controlled study on patients with alcohol withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry* 31(2):434–438, 2007 17178181

Boschen MJ: A meta-analysis of the efficacy of pregabalin in the treatment of generalized anxiety disorder. *Can J Psychiatry* 56(9):558–566, 2011 21959031

Bozikas V, Petrikis P, Gamvrula K, et al: Treatment of alcohol withdrawal with gabapentin. *Prog Neuropsychopharmacol Biol Psychiatry* 26(1):197–199, 2002 11853112

Corá-Locatelli G, Greenberg BD, Martin J, et al: Gabapentin augmentation for fluoxetine-treated patients with obsessive-compulsive disorder. *J Clin Psychiatry* 59(9):480–481, 1998 9771822

Crofford LJ, Rowbotham MC, Mease PJ, et al; Pregabalin 1008–105 Study Group: Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 52(4):1264–1273, 2005 15818684

Crofford LJ, Mease PJ, Simpson SL, et al: Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 136(3):419–431, 2008 18400400

- Dimond KR, Pande AC, Lamoreaux L, et al: Effect of gabapentin (Neurontin) [corrected] on mood and well-being in patients with epilepsy. *Prog Neuropsychopharmacol Biol Psychiatry* 20(3):407-417, 1996 8771597
- Dooley DJ, Donovan CM, Meder WP, et al: Preferential action of gabapentin and pregabalin at P/Q-type voltage-sensitive calcium channels: inhibition of K<sup>+</sup>-evoked [3H]-norepinephrine release from rat neocortical slices. *Synapse* 45(3):171-190, 2002 12112396
- Dworkin RH, Corbin AE, Young JP Jr, et al: Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 60(8):1274-1283, 2003 12707429
- Elger CE, Brodie MJ, Anhut H, et al: Pregabalin add-on treatment in patients with partial seizures: a novel evaluation of flexible-dose and fixed-dose treatment in a double-blind, placebo-controlled study. *Epilepsia* 46(12):1926-1936, 2005 16393158
- Feltner DE, Liu-Dumaw M, Schweizer E, et al: Efficacy of pregabalin in generalized social anxiety disorder: results of a double-blind, placebo-controlled, fixed-dose study. *Int Clin Psychopharmacol* 26(4):213-220, 2011 21368587
- Freeman R, Durso-Decruz E, Emir B: Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 31(7):1448-1454, 2008 18356405
- Freyenhagen R, Strojek K, Griesing T, et al: Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 115(3):254-263, 2005 15911152
- Frye MA, Kimbrell TA, Dunn RT, et al: Gabapentin does not alter single-dose lithium pharmacokinetics. *J Clin*

- Psychopharmacol 18(6):461-464, 1998 9864078
- Frye MA, Ketter TA, Kimbrell TA, et al: A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 20(6):607-614, 2000 11106131
- Furieri FA, Nakamura-Palacios EM: Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 68(11):1691-1700, 2007 18052562
- Goddard AW, Narayan M, Woods SW, et al: Plasma levels of gamma-aminobutyric acid and panic disorder. Psychiatry Res 63(2-3):223-225, 1996 8878319
- Gold BI, Bowers MB Jr, Roth RH, et al: GABA levels in CSF of patients with psychiatric disorders. Am J Psychiatry 137(3):362-364, 1980 7356067
- Goldlust A, Su TZ, Welty DF, et al: Effects of anticonvulsant drug gabapentin on the enzymes in metabolic pathways of glutamate and GABA. Epilepsy Res 22(1):1-11, 1995 8565962
- Greist JH, Liu-Dumaw M, Schweizer E, et al: Efficacy of pregabalin in preventing relapse in patients with generalized social anxiety disorder: results of a double-blind, placebo-controlled 26-week study. Int Clin Psychopharmacol 26(5):243-251, 2011 21734588
- Grunze H, Dittert S, Bungert M, et al: Renal impairment as a possible side effect of gabapentin. A single case report. Neuropsychobiology 38(3):198-199, 1998 9778609
- Hadley SJ, Mandel FS, Schweizer E: Switching from long-term benzodiazepine therapy to pregabalin in patients with generalized anxiety disorder: a double-blind, placebo-controlled trial. J Psychopharmacol 26(4):461-470, 2012 21693549
- Hamandi K, Sander JW: Pregabalin: a new antiepileptic drug for refractory epilepsy. Seizure 15(2):73-78, 2006 16413993

- Hutson SM, Berkich D, Drown P, et al: Role of branched-chain aminotransferase isoenzymes and gabapentin in neurotransmitter metabolism. *J Neurochem* 71(2):863-874, 1998 9681479
- Karam-Hage M, Brower KJ: Open pilot study of gabapentin versus trazodone to treat insomnia in alcoholic outpatients. *Psychiatry Clin Neurosci* 57(5):542-544, 2003 12950711
- Kavoussi R: Pregabalin: From molecule to medicine. *Eur Neuropsychopharmacol* 16 (suppl 2):S128-S133, 2006 16765030
- Leweke FM, Bauer J, Elger CE: Manic episode due to gabapentin treatment. *Br J Psychiatry* 175:291, 1999 10645343
- Löscher W, Hönack D, Taylor CP: Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several regions of rat brain. *Neurosci Lett* 128(2):150-154, 1991 1945036
- Mahmood T, Romans S, Silverstone T: Prevalence of migraine in bipolar disorder. *J Affect Disord* 52(1-3):239-241, 1999 10357039
- Malcolm R, Myrick H, Brady KT, et al: Update on anticonvulsants for the treatment of alcohol withdrawal. *Am J Addict* 10 (suppl):16-23, 2001 11268817
- Malcolm R, Myrick LH, Veatch LM, et al: Self-reported sleep, sleepiness, and repeated alcohol withdrawals: a randomized, double blind, controlled comparison of lorazepam vs gabapentin. *J Clin Sleep Med* 3(1):24-32, 2007 17557449
- Mariani JJ, Rosenthal RN, Tross S, et al: A randomized, open-label, controlled trial of gabapentin and phenobarbital in the treatment of alcohol withdrawal. *Am J Addict* 15(1):76-84, 2006 16449096
- Mason BJ, Crean R, Goodell V, et al: A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits

in cannabis-dependent adults.  
Neuropsychopharmacology 37(7):1689-1698, 2012  
22373942

Mason BJ, Quello S, Goodell V, et al: Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med 174(1):70-77, 2014 24190578

Mathew NT, Rapoport A, Saper J, et al: Efficacy of gabapentin in migraine prophylaxis. Headache 41(2):119-128, 2001 11251695

McLean MJ: Gabapentin in the management of convulsive disorders. Epilepsia 40 (suppl 6):S39-S50, discussion S73-S74, 1999 10530682

Mease PJ, Russell IJ, Arnold LM, et al: A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 35(3):502-514, 2008  
18278830

Medical Economics Company: Neurontin (gabapentin). Package insert. Physicians' Desk Reference, 60th Edition. Montvale, NJ, Medical Economics Company, 2006

Miller RG, Moore D, Young LA, et al; WALS Study Group; Western Amyotrophic Lateral Sclerosis Study Group: Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. Neurology 47(6):1383-1388, 1996 8960715

Montgomery SA: Pregabalin for the treatment of generalised anxiety disorder. Expert Opin Pharmacother 7(15):2139-2154, 2006 17020438

Montgomery SA, Tobias K, Zornberg GL, et al: Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry 67(5):771-782, 2006 16841627



- Obrocea GV, Dunn RM, Frye MA, et al: Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry* 51(3):253-260, 2002 11839368
- Olson WL, Gruenthal M, Mueller ME, et al: Gabapentin for parkinsonism: a double-blind, placebo-controlled, crossover trial. *Am J Med* 102(1):60-66, 1997 9209202
- Ondo W, Hunter C, Vuong KD, et al: Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. *Mov Disord* 15(4):678-682, 2000 10928578
- Pahwa R, Lyons K, Hubble JP, et al: Double-blind controlled trial of gabapentin in essential tremor. *Mov Disord* 13(3):465-467, 1998 9613738
- Pande AC, Davidson JRT, Jefferson JW, et al: Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol* 19(4):341-348, 1999 10440462
- Pande AC, Crockatt JG, Janney CA, et al; Gabapentin Bipolar Disorder Study Group: Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disord* 2(3 Pt 2):249-255, 2000a 11249802
- Pande AC, Pollack MH, Crockatt J, et al: Placebo-controlled study of gabapentin treatment of panic disorder. *J Clin Psychopharmacol* 20(4):467-471, 2000b 10917408
- Pande AC, Crockatt JG, Feltner DE, et al: Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 160(3):533-540, 2003 12611835
- Pande AC, Feltner DE, Jefferson JW, et al: Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol* 24(2):141-149, 2004 15206660
- Petroff OA, Rothman DL, Behar KL, et al: The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. *Ann Neurol* 39(1):95-99, 1996 8572673

- Petty F, Kramer GL, Dunnam D, Rush AJ: Plasma GABA in mood disorders. *Psychopharmacol Bull* 26(2):157-161, 1990 2236451
- Pfizer: Lyrica (pregabalin) tablets: prescribing information. New York, Pfizer, 2006
- Pinninti NR, Mahajan DS: Gabapentin-associated aggression. *J Neuropsychiatry Clin Neurosci* 13(3):424-429, 2001 11514656
- Pohl RB, Feltner DE, Fieve RR, Pande AC: Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. *J Clin Psychopharmacol* 25(2):151-158, 2005 15738746
- Pollack MH, Matthews J, Scott EL: Gabapentin as a potential treatment for anxiety disorders. *Am J Psychiatry* 155(7):992-993, 1998 9659873
- Rao ML, Clarenbach P, Vahlensieck M, Krätzschar S: Gabapentin augments whole blood serotonin in healthy young men. *J Neural Transm* 73(2):129-134, 1988 3210005
- Rice AS, Maton S; Postherpetic Neuralgia Study Group: Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 94(2):215-224, 2001 11690735
- Rickels K, Pollack MH, Feltner DE, et al: Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry* 62(9):1022-1030, 2005 16143734
- Rickels K, Shiovitz TM, Ramey TS, et al: Adjunctive therapy with pregabalin in generalized anxiety disorder patients with partial response to SSRI or SNRI treatment. *Int Clin Psychopharmacol* 27(3): 142-150, 2012 22302014
- Rowbotham M, Harden N, Stacey B, et al: Gabapentin for the treatment of postherpetic neuralgia: a randomized

controlled trial. JAMA 280(21):1837-1842, 1998 9846778

Roy A, Dejong J, Ferraro T: CSF GABA in depressed patients and normal controls. Psychol Med 21(3):613-618, 1991 1719577

Sabatowski R, Gálvez R, Cherry DA, et al; 1008-045 Study Group: Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 109(1-2):26-35, 2004 15082123

Sanacora G, Mason GF, Rothman DL, et al: Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. Arch Gen Psychiatry 56(11):1043-1047, 1999 10565505

Sanacora G, Mason GF, Rothman DL, et al: Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. Am J Psychiatry 159(4):663-665, 2002 11925309

Schlicker E, Reimann W, Göthert M: Gabapentin decreases monoamine release without affecting acetylcholine release in the brain. Arzneimittelforschung 35(9): 1347-1349, 1985 4084337

Short C, Cooke L: Hypomania induced by gabapentin. Br J Psychiatry 166(5):679-680, 1995 7620760

Singh L, Field MJ, Ferris P, et al: The antiepileptic agent gabapentin (Neurontin) possesses anxiolytic-like and antinociceptive actions that are reversed by D-serine. Psychopharmacology (Berl) 127(1):1-9, 1996 8880937

Taylor CP, Vartanian MG, Andruszkiewicz R, et al: 3-alkyl GABA and 3-alkylglutamic acid analogues: two new classes of anticonvulsant agents. Epilepsy Res 11(2): 103-110, 1992 1618176

Taylor CP, Gee NS, Su TZ, et al: A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res 29(3):233-249, 1998 9551785

- van Seventer R, Feister HA, Young JP Jr, et al: Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Curr Med Res Opin* 22(2):375-384, 2006 16466610
- Watson WP, Robinson E, Little HJ: The novel anticonvulsant, gabapentin, protects against both convulsant and anxiogenic aspects of the ethanol withdrawal syndrome. *Neuropharmacology* 36(10):1369-1375, 1997 9423924
- Weiss SR, Post RM: Kindling: separate vs. shared mechanisms in affective disorders and epilepsy. *Neuropsychobiology* 38(3):167-180, 1998 9778605
- Wolf SM, Shinnar S, Kang H, et al: Gabapentin toxicity in children manifesting as behavioral changes. *Epilepsia* 36(12):1203-1205, 1995 7489697
- Wolfe F, Smythe HA, Yunus MB, et al: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 33(2):160-172, 1990 2306288
- Yatham LN, Kusumakar V, Calabrese JR, et al: Third generation anticonvulsants in bipolar disorder: a review of efficacy and summary of clinical recommendations. *J Clin Psychiatry* 63(4):275-283, 2002 12000201
- Zhang S, Paul J, Nantha-Aree M, et al: Reanalysis of morphine consumption from two randomized controlled trials of gabapentin using longitudinal statistical methods. *J Pain Res* 8:79-85, 2015 25709496

# CHAPTER 40

## Lamotrigine

David E. Kemp, M.D., M.S.

Marc L. van der Loos, M.D., Ph.D.

Keming Gao, M.D., Ph.D.

Joseph R. Calabrese, M.D.

---

### History and Discovery

---

During the clinical development of lamotrigine as a treatment for intractable seizures, improved mood in lamotrigine-treated patients was anecdotally reported ([Jawad et al. 1989](#); [Smith et al. 1993](#)). In 1993, the addition of lamotrigine to an existing antiepileptic drug regimen was evaluated in a small study of 81 patients with epilepsy ([Smith et al. 1993](#)). Lamotrigine-treated patients reported significantly higher levels of happiness and an improvement in perceived internal locus of control. There was no correlation between perceived happiness and changes in seizure frequency or severity. Thus, the investigators

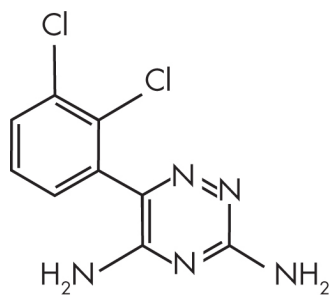
preliminarily concluded that lamotrigine may have an effect on mood independent of its antiepileptic effect.

---

## Structure-Activity Relations and Pharmacological Profile

---

Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine,  $C_9H_7Cl_2N_5$ ; [Figure 40-1](#)) is an antiepileptic drug of the phenyltriazine class that is chemically unrelated to hepatic enzyme inducers (e.g., carbamazepine) and enzyme inhibitors (e.g., valproic acid). Lamotrigine has not been shown to inhibit the reuptake of norepinephrine, dopamine, or serotonin. Although it exerts inhibitory effects at the serotonin 3 (5-HT<sub>3</sub>) receptor, this activity is weak and unlikely to contribute to its therapeutic profile. Lamotrigine does not have high binding affinity to adrenergic ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ ), dopamine (D<sub>1</sub>, D<sub>2</sub>),  $\gamma$ -aminobutyric acid (GABA), histamine (H<sub>1</sub>), kappa opioid ( $\kappa$ ), sigma ( $\sigma_1$ ,  $\sigma_2$ ), or muscarinic (M<sub>1</sub>, M<sub>2</sub>) acetylcholine receptors. Lamotrigine inhibits use-dependent sodium channels, allowing continued normal depolarizations while suppressing paroxysmal burst firing encountered in seizures and hypoxic insult.



---

**FIGURE 40-1.** Chemical structure of lamotrigine.

---

---

## Pharmacokinetics and Disposition

---

Oral lamotrigine is rapidly absorbed with negligible first-pass metabolism. Peak plasma concentrations are reached in approximately 2–4 hours, and its half-life is approximately 25 hours (GlaxoSmithKline [2011](#)). Lamotrigine is approximately 55% bound to plasma proteins and is unlikely to significantly interact with drugs that are highly protein bound. Metabolism is primarily achieved by competitive glucuronic acid conjugation. At steady-state concentrations, the pharmacokinetics of lamotrigine are linear within a dosage range of 100–700 mg/day (Leach et al. [1995](#)). The clearance of lamotrigine is reduced in the setting of renal insufficiency and hepatic disease.

During pregnancy, clinically significant perturbations in lamotrigine levels can occur. Estradiol, which rises during pregnancy, upregulates the expression of uridine diphosphate-glucuronosyltransferase (UGT) 1A4 (UGT1A4) (Chen et al. [2009](#)), an enzyme that catalyzes 90% of lamotrigine conjugation (Fotopoulou et al. [2009](#)). The rate of lamotrigine clearance increases during each trimester, reaching a peak of 330% of baseline clearance by week 32 gestational age (Pennell et al. [2004](#)). The American Academy of Neurology recommends active monitoring of lamotrigine levels during pregnancy (Harden et al. [2009b](#)). Although lamotrigine levels are not routinely obtained in psychiatry because of a lack of well-defined levels for

clinical response, a woman's preconception level could potentially be used as a guide for prophylactically increasing dosage during pregnancy ([Deligiannidis et al. 2014](#)). If lamotrigine dosing has been increased throughout pregnancy, the dosage should be decreased immediately after delivery by 20%-25% to prevent lamotrigine toxicity, as plasma levels are noted to rapidly return to normal during the first few postpartum weeks ([Clark et al. 2013](#)).

---

## Mechanism of Action

---

The mechanism by which lamotrigine achieves its therapeutic effect in the treatment of bipolar disorder is unknown. The inhibition of voltage-activated sodium channels ([Xie and Hagan 1998](#)) may best characterize lamotrigine's mechanism of action. In addition to sodium channel inhibition, lamotrigine antagonizes N-type calcium channels ([Stefani et al. 1996](#); [von Wegerer et al. 1997](#)). Interestingly, one of the most replicated susceptibility genes for bipolar disorder (*ANK3*) codes for a protein that regulates the assembly of voltage-gated sodium channels ([Schulze et al. 2009](#)). These genetic findings, coupled with the action of lamotrigine on sodium and calcium channels, suggest that channelopathies may be involved in the pathophysiology of bipolar disorder. Antiglutamatergic action is another means by which lamotrigine may affect mood. Presynaptic inhibition of voltage- and use-sensitive sodium channels, calcium channels, and potassium channels ([Grunze et al. 1998](#)) is believed to result in decreased release of the excitatory amino acid glutamate. The reduction of glutamate may occur through suppression of



postsynaptic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors ([Lee et al. 2008](#)). In addition, lamotrigine may increase brain levels of *N*-acetylaspartate, a mechanism believed to enhance neuronal viability, as deficits in *N*-acetylaspartate contribute to excessive glutamatergic tone and subsequent cell death ([Croarkin et al. 2015](#)).

---

## Indications and Efficacy

---

In 2003, lamotrigine was granted approval by the U.S. Food and Drug Administration (FDA) for use in the maintenance treatment of bipolar I disorder to delay the time to recurrence of new mood episodes. Lamotrigine is also indicated for adjunctive antiepileptic therapy in adults and pediatric patients ( $\geq 2$  years of age) with partial seizures, with generalized seizures secondary to Lennox-Gastaut syndrome, or with primary and generalized tonic-clonic seizures, as well as for antiepileptic monotherapy in patients ( $\geq 16$  years of age) with partial seizures (GlaxoSmithKline [2015](#)).

Although lamotrigine is not FDA-approved for acute bipolar depression, clinical evidence suggests that lamotrigine is effective for this indication. Inadequate data are available to recommend use of lamotrigine in unipolar depression. Other conditions in which lamotrigine has shown promising results in clinical trials include management of rapid-cycling bipolar disorder, borderline personality disorder, schizophrenia, and menstrually entrained mood cyclicity.

# Maintenance Therapy in Bipolar I Disorder

Two large randomized, double-blind, parallel-group, placebo-controlled multicenter studies led to the approval of lamotrigine as a maintenance therapy in bipolar I disorder ([Bowden et al. 2003](#); [Calabrese et al. 2003](#)). Both of these paired studies included a screening phase of up to 2 weeks; an 8- to 16-week open-label phase during which lamotrigine was initiated as an adjunctive agent or as monotherapy and other psychotropic drugs were discontinued; and an 18-month double-blind phase during which patients received lamotrigine, lithium, or placebo as maintenance monotherapy. The primary efficacy variable in both studies was time to intervention for any mood episode.

One of the studies ([Bowden et al. 2003](#)) evaluated subjects who were or had recently been in a manic, hypomanic, or mixed state. The other study ([Calabrese et al. 2003](#)) examined subjects who were or had recently been depressed. Both lamotrigine and lithium were superior to placebo in delaying the time to intervention for any mood episode ( $P=0.018$  for previously manic;  $P=0.029$  for previously depressed). Lamotrigine, but not lithium, was superior to placebo in prolonging the time to a depressive episode ( $P=0.015$  for previously manic;  $P=0.047$  for previously depressed). Lithium, but not lamotrigine, was superior to placebo in prolonging the time to a manic, hypomanic, or mixed episode ( $P=0.006$  for previously manic;  $P=0.026$  for previously depressed). In a post hoc analysis of these two studies, both lithium and lamotrigine were more effective than placebo in prolonging the time to any mood relapse and manic or hypomanic relapse, but only

lamotrigine was superior to placebo in delaying depressive relapse (Goodwin et al. 2004). An open-label study conducted in a clinical setting did not find a significant difference between lithium and lamotrigine in preventing any mood, manic or hypomanic, or depressive relapse (Licht et al. 2010).

In the interpretation of maintenance-phase data, it is important to distinguish between efficacy in relapse prevention and true prophylactic efficacy (Ghaemi et al. 2004). Mood episodes of the same polarity as the index episode that occur during the initial 2 months following recovery are generally regarded as *relapses*, and therefore are considered as being still part of the acute recovery period. Alternatively, mood episodes that occur beyond this time frame, during the period of remission, are regarded as *recurrences*. To test the true maintenance efficacy of lamotrigine, Calabrese et al. (2006) conducted a post hoc analysis of the two double-blind 18-month maintenance trials that compared lamotrigine and lithium against placebo. When all subjects who experienced a relapse to a mood episode of the same polarity as the index episode within 90 days of randomization were excluded, both lamotrigine and lithium were found to be more effective than placebo in delaying the time to intervention for a mood episode ( $P=0.02$  for lamotrigine;  $P=0.01$  for lithium). Similar results were found when patients who relapsed to a mood episode of the same polarity as the index episode within 180 days of randomization were excluded, suggesting that lamotrigine and lithium possess true maintenance efficacy.

# Acute Monotherapy and Adjunctive Therapy of Bipolar Depression

## Monotherapy of Bipolar Depression

A series of double-blind, placebo-controlled multicenter studies of lamotrigine was completed to replicate and extend preliminary open-label prospective findings suggesting moderate to marked efficacy in bipolar depression ([Calabrese et al. 1999a](#)). The first study in this series evaluated the efficacy and safety of two dosages of lamotrigine compared with placebo in the acute treatment of a major depressive episode in 195 patients with bipolar I disorder ([Calabrese et al. 1999b](#)). Outpatients received lamotrigine (50 or 200 mg/day) or placebo as monotherapy for 7 weeks. Assessments using the a priori primary outcome measure, the Hamilton Rating Scale for Depression (Ham-D), as well as several secondary outcome measures—including the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Severity of Illness and Improvement subscales of the Clinical Global Impression Scale (CGI-S and CGI-I, respectively)—were conducted at 4 days and then weekly. Lamotrigine at a dosage of 200 mg/day showed significant antidepressant efficacy on the MADRS, CGI-S, and CGI-I compared with placebo. However, lamotrigine did not separate from placebo on the overall Ham-D score. Despite the promising findings in this first study, four later monotherapy trials with randomized, parallel-group, placebo-controlled designs failed to find differences between lamotrigine and placebo, most likely because of a high placebo response rate (40%–50%) ([Calabrese et al. 2008](#)).

To clarify the effects of lamotrigine in acute bipolar depression, [Geddes et al. \(2009\)](#) conducted a systematic meta-analysis of individual patient data from 1,072 participants in five randomized controlled trials comparing lamotrigine with placebo. The pooled analysis found that a greater proportion of patients receiving lamotrigine than of those receiving placebo showed response on both the Ham-D and the MADRS ( $P=0.002$ ). However, the advantage of lamotrigine over placebo was larger in more severely depressed patients.

Because of the modest effect sizes when lamotrigine is prescribed as monotherapy, the *S3 Guideline for Diagnosis and Treatment of Bipolar Disorders* collaboratively developed by [the German Society for Bipolar Disorder and the German Society of Psychiatry, Psychotherapy and Nervous Diseases \(2012\)](#) stated that whereas lamotrigine may be used for bipolar depression, it is not considered a first-line treatment ([Köhler et al. 2014](#)). The *Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010* from the World Federation of Societies of Biological Psychiatry recommended use of lamotrigine for acute bipolar depression on the basis of the overall positive results of the meta-analysis by [Geddes et al. \(2009\)](#), the drug's effectiveness in severe depression, and the positive clinical experience associated with this agent ([Grunze et al. 2010](#)). The *Collaborative Update of CANMAT Guidelines for the Management of Patients With Bipolar Disorder* of the Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders also recommended lamotrigine as a first-line agent for the treatment of acute bipolar depression ([Yatham et al. 2013](#)). Although negative controlled studies outweigh positive studies of lamotrigine administered as monotherapy for

bipolar depression, the negative findings in individual trials may be more a reflection of the patient composition than of a property of the drug itself, given the lack of a comparator arm to determine assay sensitivity and the relatively high rates of placebo response ([Grunze et al. 2010](#)).

In an effort to identify the symptomatic dimensions that may be responsive or unresponsive to lamotrigine, [Mitchell et al. \(2013\)](#) applied factor analysis to a large sample of depressed patients recruited for two separate double-blind, placebo-controlled trials of lamotrigine. Results suggested that lamotrigine's beneficial effect in bipolar depression is largely limited to two core aspects of bipolar depressive symptomatology—namely, depressive cognitions and psychomotor disturbance. Lamotrigine was unlikely to provide benefits for weight gain, insomnia, anergia, or anxiety ([Mitchell et al. 2013](#)).

To date, only three compounds are FDA approved for the treatment of acute bipolar depression: an olanzapine-fluoxetine combination (OFC), quetiapine, and lurasidone. To compare lamotrigine's efficacy in managing bipolar depression with that of an established agent, a head-to-head randomized, double-blind, parallel-group study of lamotrigine and OFC was conducted over 7 weeks in patients with bipolar I disorder in an acute depressive phase ([Brown et al. 2006](#)). The study randomly assigned 410 subjects to either lamotrigine (titrated to 200 mg/day;  $n=205$ ) or OFC (6/25, 6/50, 12/25, or 12/50 mg/day;  $n=205$ ). Overall response and remission rates were comparable between the active agents, although differences did emerge in regard to tolerability profiles. The incidence of adverse events involving suicidal and self-injurious behavior was higher among patients taking lamotrigine (3.4%) than among those taking OFC (0.5%;

$P=0.037$ ). However, significant differences in mean change from baseline to endpoint for clinically relevant laboratory and physiological parameters favored treatment with lamotrigine, including measures such as hemoglobin A1c, prolactin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and body weight. This study was subsequently extended to 25 weeks. At study endpoint, no significant differences were found between OFC and lamotrigine in response, remission, or relapse as measured by change in MADRS total score, although OFC was superior to lamotrigine in reducing depressive and manic symptoms ([Brown et al. 2009](#)).

### **Adjunctive Therapy of Bipolar Depression**

In a trial comparing lamotrigine with placebo in the adjunctive treatment of bipolar I and II depression ([van der Loos et al. 2009](#)), all patients were required to be taking lithium maintained at a therapeutic blood level (0.6–1.2 mmol/L) prior to random assignment to lamotrigine ( $n=64$ ) or placebo ( $n=60$ ) for 8 weeks. Response was assessed at endpoint using the MADRS (primary outcome measure) and the CGI Scale–Bipolar Version (CGI-BP; [Spearing et al. 1997](#)). The change from baseline to endpoint on the MADRS was significantly greater in lamotrigine-treated subjects (15.4) compared with those receiving placebo (11.0;  $P=0.02$ ). A higher percentage of patients responded (as measured by a  $\geq 50\%$  reduction in MADRS score) to adjunctive lamotrigine (51.6%) compared with placebo (31.7%;  $P=0.030$ ), although no difference was observed in the response rate based on the CGI-BP (64.1% for lamotrigine vs. 48.3% for placebo;  $P=0.10$ ). Following the open-label addition of paroxetine for another 8 weeks in

nonresponders, the change in MADRS scores from baseline to week 16 between lithium plus lamotrigine (plus paroxetine in nonresponders) and lithium plus placebo (plus paroxetine in nonresponders) was not significantly different ( $-17.91$  vs.  $-15.40$ ;  $P=0.25$ ) ([van der Loos et al. 2010](#)). After 16 weeks, all responders in both groups were followed for 68 weeks or until a relapse or recurrence of a depressive or manic episode occurred. Time to relapse or recurrence was longer for the lamotrigine group (median time=10.0 months; 95% confidence interval [CI]=1.1-18.8) than for the placebo group (3.5 months; 95% CI=0.7-7.0]) ([van der Loos et al. 2011](#)).

## Additional Uses

### Maintenance Treatment of Rapid-Cycling Bipolar Disorder

[Calabrese et al. \(2000\)](#) conducted a maintenance study with lamotrigine in rapid-cycling bipolar disorder. The difference between the lamotrigine and placebo treatment groups in time to additional pharmacotherapy for a developing or fully developed mood episode did not achieve statistical significance. However, overall survival time in the study (i.e., time to dropout for any reason) was significantly different between the treatment groups in favor of lamotrigine ( $P=0.036$ ). When patients with bipolar I and II subtypes were compared, lamotrigine-treated bipolar II disorder patients had a significantly longer median survival of 17 weeks compared with a median of 7 weeks for placebo-treated patients ( $P=0.015$ ).



## **Menstrual Cycle-Related Mood Variability in Women With Bipolar Disorder**

Because lamotrigine is implicated in the modulation of glutamatergic and potentially GABAergic signaling, it has been hypothesized that lamotrigine may affect menstrual cycle-related alterations in neurotransmitter activity. Among women with bipolar disorder whose regimens included lamotrigine, less intraindividual variability in mood was evidenced across menstrual cycle phases ([Robakis et al. 2015](#)). Although the effect was small, it represents preliminary evidence for lamotrigine's potential utility in treating menstrually entrained mood cyclicity.

## **Acute Treatment of Bipolar Mania or Schizophrenia**

Lamotrigine does not appear to possess acute antimanic activity. In two placebo-controlled trials in patients with bipolar I disorder experiencing an acute manic or mixed episode, including a 3-week monotherapy trial and a 6-week add-on trial ([Bowden et al. 2000](#)), lamotrigine failed to separate from placebo on the primary outcome measure, change in symptom severity on the Mania Rating Scale (MRS). Similarly, in two placebo-controlled trials, lamotrigine used as an adjunct to antipsychotic treatment was not more effective than adjunctive placebo (i.e., antipsychotic monotherapy) as measured by change in mean Positive and Negative Syndrome Scale total scores, although in one trial, a cognitive composite score improved more with lamotrigine than with placebo ([Goff et al. 2007](#)).

## **Monotherapy or Adjunctive Therapy of Major Depressive Disorder**

Limited evidence suggests that lamotrigine may be effective in the treatment of unipolar major depressive disorder, either as monotherapy or as an adjunct to conventional antidepressants. Three double-blind, placebo-controlled multicenter trials of lamotrigine monotherapy for nonrefractory major depressive disorder did not detect a significant drug-placebo difference (GlaxoSmithKline 2008a, 2008b, 2011). Lamotrigine also did not separate from placebo in a small double-blind, fixed-dose study comparing the addition of lamotrigine versus placebo to paroxetine treatment (Normann et al. 2002). In two small prospective studies of lamotrigine augmentation of antidepressant treatment in refractory depression, the open-label trial reported improvement on the CGI-I and MADRS (Gabriel 2006), but the double-blind trial found no significant drug-placebo differences at study endpoint (Santos et al. 2008). A subsequent double-blind, placebo-controlled trial of lamotrigine in treatment-refractory depression by Barbee et al. (2011) also did not detect statistically significant differences between the lamotrigine and the placebo groups, although benefit was observed in study completers and those with more severe illness. A systematic review and meta-analysis examining response and remission rates in studies of lamotrigine augmentation of antidepressants in treatment-refractory unipolar depression concluded that lamotrigine was no more efficacious than placebo (Zhou et al. 2015). Thus, there is little evidence to recommend lamotrigine as a pharmacological option for treatment of major depressive disorder.

## **Borderline Personality Disorder**

Lamotrigine's potential utility in borderline personality disorder was investigated in two randomized, double-blind, placebo-controlled trials (total  $N=55$ ) ranging in duration from 8 to 12 weeks ([Reich et al. 2009](#); [Tritt et al. 2005](#)). Significant improvements in anger, impulsivity, and affective instability were reported.

---

## Dosing Recommendations

---

The recommended dosing schedule for lamotrigine in adults involves initiating therapy with 25 mg daily for the first 14 days and then advancing to 50 mg daily for the third and fourth weeks of treatment. During the fifth week of treatment, lamotrigine can be increased to 100 mg daily, followed by titration to 200 mg daily during the sixth and seventh weeks of treatment. When lamotrigine is used to augment valproate therapy in adult patients, the recommended titration schedule begins with 25 mg every other day for 14 days, advances to 25 mg daily for 14 days, and then increases to 50 mg daily and 100 mg daily beginning at each of the fifth and sixth weeks of treatment, respectively ([Table 40-1](#)). The titration process for lamotrigine used as an adjunct to treatment with an enzyme-inducing antiepileptic drug begins with 50 mg daily for 14 days, advances to 100 mg daily (taken in divided doses) for 14 days, and eventually increases to a target maintenance dosage of 400 mg/day ([Table 40-2](#)). No published data support improved efficacy for lamotrigine in the treatment of bipolar disorder at dosages greater than 200 mg/day in the absence of an enzyme inducer.

Additionally, there is no clear association between serum levels of lamotrigine and measures of affective response.

**TABLE 40-1. Recommended titration schedule for lamotrigine for patients with bipolar disorder taking valproate**

<b>Week</b>	<b>Dosage</b>
Weeks 1 and 2	25 mg every other day
Weeks 3 and 4	25 mg daily
Week 5	50 mg daily
Week 6	100 mg daily
Week 7	100 mg daily

*Note.* The usual maintenance dosage when lamotrigine is added to valproate is 100 mg/day.

*Source.* Adapted from [GlaxoSmithKline 2015](#).

**TABLE 40-2. Recommended titration schedule for lamotrigine when used as monotherapy and when added to an enzyme-inducing antiepileptic drug regimen\* (without valproate)**

	<b>For patients NOT TAKING an enzyme- inducing antiepileptic drug regimen* and not taking valproate</b>	<b>For patients TAKING an enzyme- inducing antiepileptic drug regimen* and not taking valproate</b>

---

Weeks 1 and 2	25 mg/day	50 mg/day
Weeks 3 and 4	50 mg/day	100 mg/day (in two divided doses)
Week 5	100 mg/day	200 mg/day (in two divided doses)
Week 6	200 mg/day	300 mg/day (in two divided doses)
Usual maintenance dosage	200 mg/day	400 mg/day (in two divided doses)

---

\*Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to increase the apparent clearance of lamotrigine.

*Source.* Adapted from [GlaxoSmithKline 2015](#).

---

## Side Effects and Toxicity

---

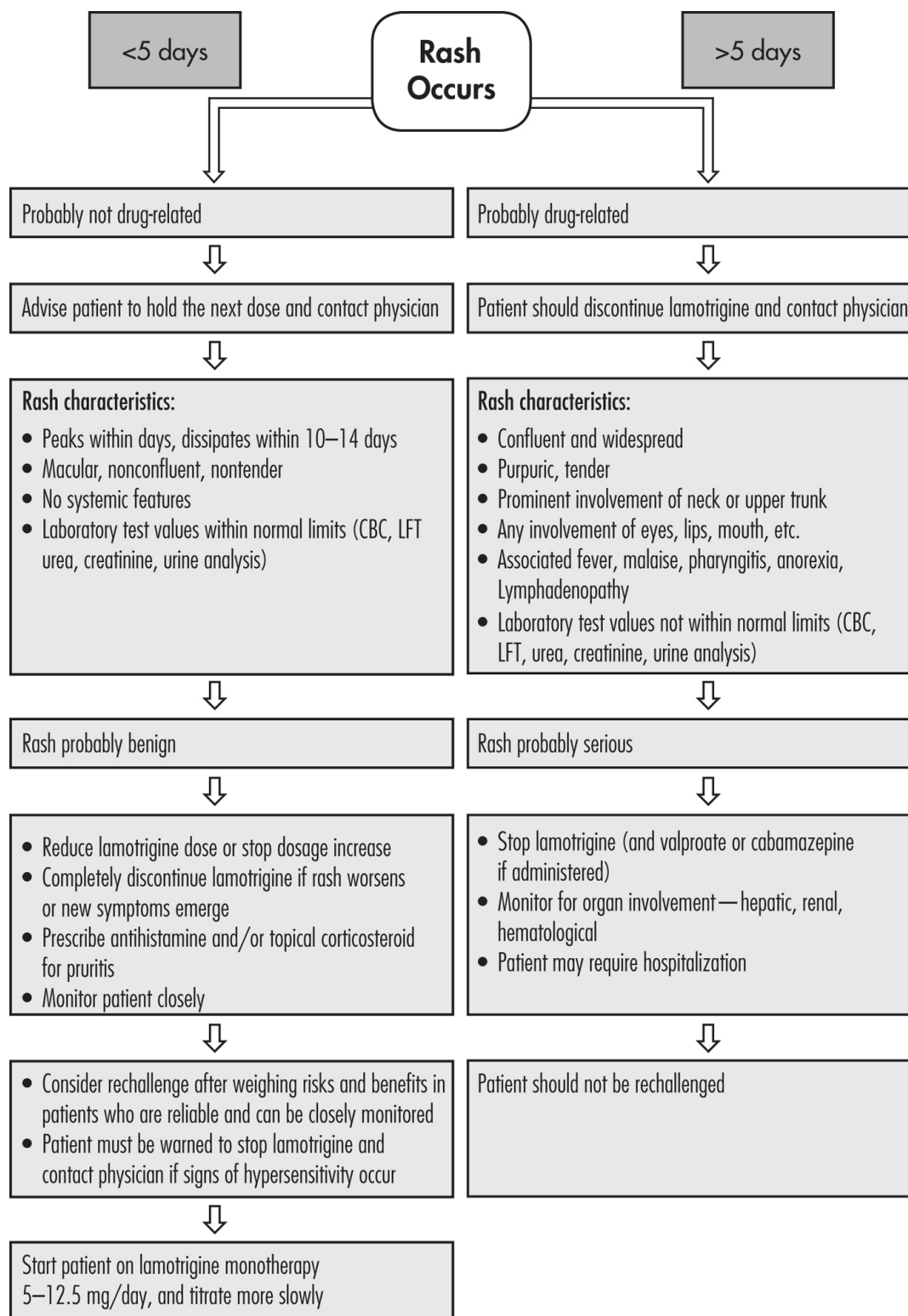
In controlled monotherapy trials of lamotrigine in the treatment of mood disorders, the drug was associated with headache, changes in sleep habits, nausea, and dizziness ([Bowden et al. 2004](#)). In randomized trials of lamotrigine in mood disorders, the prevalence of rash did not exceed that of placebo; however, rash is generally recognized as the side effect most likely to significantly complicate lamotrigine's clinical use.

# Skin Reactions

In early epilepsy trials, rash led to hospitalization and treatment discontinuation or Stevens-Johnson syndrome in 0.3% of the adults taking lamotrigine ([Calabrese et al. 2002](#)). The annual incidence of serious drug-based skin reactions associated with lamotrigine—such as Stevens-Johnson syndrome, DRESS (drug rash with eosinophilia and systemic symptoms), and toxic epidermal necrolysis—was highest in 1993 (4.2%) but steadily declined and had stabilized by 1998 (0.02%). This reduction in incidence was likely attributable to the manufacturer's dosage revision in 1994, which advised a more protracted titration schedule ([Calabrese et al. 2002](#); [Messenheimer et al. 1998](#)). It is well documented that the risk of rash is heightened by exceeding the recommended initial dosage or the rate of dosage escalation of lamotrigine, and by coadministering lamotrigine with valproic acid. The risk is also greater in children younger than 12 years. Nearly all cases of life-threatening rashes caused by lamotrigine have occurred within 2–8 weeks of treatment initiation (GlaxoSmithKline [2015](#)).

The most common lamotrigine-associated rash is an exanthematic maculopapular or morbilliform eruption that is benign. However, a clinically similar eruption may be associated with more rare and serious systemic hypersensitivity reactions ([Guberman et al. 1999](#)). [Figure 40-2](#) presents a decision-making algorithm for the management of benign and serious rashes ([Calabrese et al. 2002](#)). A serious lamotrigine rash is usually confluent with prominent facial and neck involvement. The rash may be tender or have a purpuric or hemorrhagic appearance. It may be accompanied or preceded by fever, malaise,

pharyngitis, anorexia, or lymphadenopathy ([Guberman et al. 1999](#)). Thus, all patients who develop a rash during the first few months of lamotrigine therapy should be instructed to hold the next dose and immediately seek medical consultation. The greatest risk of rash appears to be during the first 8 weeks of treatment. A rash during the first 5 days of therapy is usually due to a nondrug cause. Because immune tolerance to lamotrigine is lost following interruption of dosage for more than 1 week, patients should be instructed to resume lamotrigine at the prior initial start-up dose and to gradually titrate upward whenever therapy has been interrupted for more than a few days.



**FIGURE 40-2.** Clinical management of rash related to lamotrigine treatment.



CBC=complete blood count; LFT=liver function test.

*Source.* Reprinted from Calabrese JR, Sullivan JR, Bowden CL, et al.: "Rash in Multicenter Trials of Lamotrigine in Mood Disorders: Clinical Relevance and Management." *Journal of Clinical Psychiatry* 63:1012-1019, 2002. Copyright 2000, Physicians Postgraduate Press. Used with permission.

## Aseptic Meningitis

Rare cases of aseptic meningitis in association with lamotrigine have occurred ([Boot 2009](#); [Kilfoyle et al. 2005](#); [Lam et al. 2010](#)). Clinical manifestations include meningismus, photophobia, headache, vomiting, and fever. Symptoms were reported to appear within 1 day to 1.5 months following initiation of treatment. In several cases, sudden and severe symptoms of meningitis have occurred within minutes of reintroducing lamotrigine. In most cases of drug-induced aseptic meningitis, there is complete recovery once the offending agent has been discontinued ([Moris and Garcia-Monco 1999](#)).

## Weight-Neutral Effects

In comparison with other agents used in the management of bipolar disorder, a distinctive feature of lamotrigine is its weight-neutral tolerability profile ([Sachs et al. 2006](#)). A post hoc analysis found that nonobese patients taking lamotrigine are unlikely to experience a change in weight. However, obese patients are significantly more likely to lose weight with lamotrigine and to gain weight with lithium ([Bowden et al. 2006](#)).

# Safety in Overdose

Among 493 cases of lamotrigine toxicity in overdose, the majority of patients (52.1%) experienced no toxic clinical effects ([Lofton and Klein-Schwartz 2004](#)). Common symptoms included drowsiness, vomiting, nausea, ataxia, dizziness, and tachycardia. Rare cases of coma, seizures, heart conduction delay, and respiratory depression have been reported in overdose. Some ingestions of lamotrigine involving quantities up to 15 grams have been fatal.

# Use During Pregnancy and Lactation

For women who are capable of becoming pregnant or who are already pregnant, lamotrigine may represent a safer option than valproate because of its favorable tolerability profile and lower risk of major congenital malformations ([Campbell et al. 2014](#)). An observational study by [Newport et al. \(2008\)](#) examined risk of illness recurrence in pregnant women with stable bipolar disorder who continued lamotrigine treatment during pregnancy ( $n=10$ ) compared with those who discontinued mood stabilizer therapy during pregnancy ( $n=16$ ). The risk of illness recurrence was 3.3 times lower when lamotrigine was continued (30.0% recurrence [3/10] vs. 100% recurrence [16/16] when patients discontinued mood stabilizers;  $P<0.0001$ ), suggesting that lamotrigine may provide protective effects in pregnancy.

Potential adverse effects on the developing fetus of mothers receiving lamotrigine have been suggested by data collected as part of international pregnancy registries ([Cunnington et al. 2005](#); [Holmes et al. 2008](#)). As with any

mood stabilizer, lamotrigine use during pregnancy represents an inherent dilemma for clinicians and expectant mothers, who must balance the risks associated with untreated bipolar disorder in the mother against the risk of major congenital malformations in the fetus. Neural tube defects are estimated to occur in 1%–5% of neonates exposed to valproate or carbamazepine in the first trimester. The risk of neural tube defects with lamotrigine appears lower than that with valproate. However, studies have yielded mixed findings regarding an increased risk for teratogenesis with lamotrigine. In the North American Antiepileptic Drug Pregnancy Registry, the risk of cleft palate, cleft lip, or both for infants exposed to lamotrigine was 7.3 out of 1,000, approximately 10 times higher than the risk for unexposed infants ([Holmes et al. 2008](#)). An analysis from an Australian pregnancy registry found no statistically significant difference between the risk of fetal malformations among women exposed to lamotrigine monotherapy during pregnancy and the risk among pregnant women with epilepsy taking no antiepileptic drugs ([Vajda et al. 2010](#)).

Although early reports suggested a likely relation between higher dosages of lamotrigine (>400 mg/day) taken by a woman during pregnancy and greater risk of a major congenital malformation in her offspring, a more recent report found minimal differences in risk between high- and low-dosage lamotrigine exposures ([Campbell et al. 2014](#)). Nevertheless, limiting the dosage during the first trimester should be considered ([Harden et al. 2009a](#)). Lamotrigine is listed as Pregnancy Category C in terms of teratogenic effects.

A prospective observational study that followed children born to mothers who took antiepileptic medications as

monotherapy during pregnancy found at the 3-year assessment that children exposed to lamotrigine in utero had higher IQ scores compared with children exposed to valproate, carbamazepine, or phenytoin ([Meador et al. 2009](#)).

In newborns of mothers receiving lamotrigine, extensive placental transfer of drug has been found to occur, with umbilical cord concentrations approaching those of maternal serum ([Ohman et al. 2000](#)). Plasma lamotrigine concentrations in nursing infants are approximately 23%–50% of maternal levels.

---

## Drug-Drug Interactions

---

Lamotrigine is not known to inhibit the activity of the cytochrome P450 2D6 enzyme. However, the addition of adjunctive lamotrigine to enzyme inducers such as carbamazepine, phenytoin, primidone, and phenobarbital decreases lamotrigine plasma concentrations by approximately 40%–50% ([Hahn et al. 2004](#)). The inducing effect of oxcarbazepine is approximately half that of carbamazepine ([Weintraub et al. 2005](#)). Because lamotrigine is nearly exclusively metabolized by glucuronidation, the introduction of adjunctive valproate (an enzyme inhibitor) results in immediate and successful competition for metabolism, with resultant increases in half-life.

Evidence has emerged that oral contraceptives containing estrogen have the potential to decrease serum concentrations of lamotrigine by up to 64% ([Sabers et al. 2001, 2003](#)). Progestins, however, are not associated with a

decrease in lamotrigine levels ([Reimers et al. 2005](#)). During the long-term treatment of bipolar disorder, use of ethinyl estradiol-containing compounds may require an increase in the maintenance dosage of lamotrigine of as much as twice the recommended target maintenance dose. Conversely, stopping estrogen-containing oral contraceptives, including during the “pill-free” week, may increase lamotrigine levels to a clinically significant range.

---

## Conclusion

---

Although initial results from trials of lamotrigine in the treatment of mania were unfavorable, subsequent maintenance studies have provided compelling data to show that lamotrigine prevents the recurrence of mood episodes and possesses antidepressant efficacy, albeit most convincingly for prophylaxis against depression recurrence as opposed to acute resolution of depression. Even with its ability to stabilize mood, lamotrigine appears to have a low propensity to trigger affective switches to mania or hypomania, with a switch risk similar to that of placebo. Lamotrigine’s neutral effects on body weight and favorable side-effect profile make it appealing for use in patients who have comorbid metabolic syndrome or those who are unable to tolerate other treatments. At present, lamotrigine remains the only antiepileptic drug mood stabilizer with more established efficacy in the depressed illness phase than in mania or hypomania.

---

## References

---

- Barbee JG, Thompson TR, Jamhour NJ, et al: A double-blind placebo-controlled trial of lamotrigine as an antidepressant augmentation agent in treatment-refractory unipolar depression. *J Clin Psychiatry* 72(10):1405-1412, 2011 21367355
- Boot B: Recurrent lamotrigine-induced aseptic meningitis. *Epilepsia* 50(4):968-969, 2009 19385984
- Bowden CL, Calabrese JR, Ascher J, et al: Spectrum of efficacy of lamotrigine in bipolar disorder: overview of double-blind, placebo-controlled studies. Presented at the American College of Neuropsychopharmacology (ACNP) Annual Meeting, San Juan, PR, December 2000
- Bowden CL, Calabrese JR, Sachs G, et al; Lamictal 606 Study Group: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 60(4):392-400, 2003 12695317
- Bowden CL, Asnis GM, Ginsberg LD, et al: Safety and tolerability of lamotrigine for bipolar disorder. *Drug Saf* 27(3):173-184, 2004 14756579
- Bowden CL, Calabrese JR, Ketter TA, et al: Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. *Am J Psychiatry* 163(7):1199-1201, 2006 16816224
- Brown EB, McElroy SL, Keck PE Jr, et al: A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry* 67(7):1025-1033, 2006 16889444
- Brown E, Dunner DL, McElroy SL, et al: Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. *Int J Neuropsychopharmacol* 12(6):773-782, 2009 19079815
- Calabrese JR, Bowden CL, McElroy SL, et al: Spectrum of activity of lamotrigine in treatment-refractory bipolar

- disorder. *Am J Psychiatry* 156(7):1019-1023, 1999a 10401445
- Calabrese JR, Bowden CL, Sachs GS, et al: A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 60(2):79-88, 1999b 10084633
- Calabrese JR, Suppes T, Bowden CL, et al: A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry* 61(11):841-850, 2000 11105737
- Calabrese JR, Sullivan JR, Bowden CL, et al: Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry* 63(11): 1012-1019, 2002 12444815
- Calabrese JR, Bowden CL, Sachs G, et al; Lamictal 605 Study Group: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 64(9):1013-1024, 2003 14628976
- Calabrese JR, Goldberg JF, Ketter TA, et al: Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies. *Biol Psychiatry* 59(11):1061-1064, 2006 16769295
- Calabrese JR, Huffman RF, White RL, et al: Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord* 10(2):323-333, 2008 18271912
- Campbell E, Kennedy F, Russell A, et al: Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry* 85(9):1029-1034, 2014 24444855
- Chen H, Yang K, Choi S, et al: Up-regulation of UDP-glucuronosyltransferase (UGT) 1A4 by 17 $\beta$ -estradiol: a

potential mechanism of increased lamotrigine elimination in pregnancy. *Drug Metab Dispos* 37(9):1841-1847, 2009 19546240

Clark CT, Klein AM, Perel JM, et al: Lamotrigine dosing for pregnant patients with bipolar disorder. *Am J Psychiatry* 170(11): 1240-1247, 2013 24185239

Croarkin PE, Thomas MA, Port JD, et al: N-acetylaspartate normalization in bipolar depression after lamotrigine treatment. *Bipolar Disord* 17(4):450-457, 2015 25495884

Cunnington M, Tennis P; International Lamotrigine Pregnancy Registry Scientific Advisory Committee: Lamotrigine and the risk of malformations in pregnancy. *Neurology* 64(6):955-960, 2005 15781807

Deligiannidis KM, Byatt N, Freeman MP: Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. *J Clin Psychopharmacol* 34(2):244-255, 2014 24525634

Fotopoulou C, Kretz R, Bauer S, et al: Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. *Epilepsy Res* 85(1):60-64, 2009 19272754

Gabriel A: Lamotrigine adjunctive treatment in resistant unipolar depression: an open, descriptive study. *Depress Anxiety* 23(8):485-488, 2006 16845646

Geddes JR, Calabrese JR, Goodwin GM: Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 194(1):4-9, 2009 19118318

German Society for Bipolar Disorder (Deutschen Gesellschaft für Bipolare Störungen [DGBS]); German Society of Psychiatry, Psychotherapy and Nervous Diseases (Deutschen Gesellschaft für Psychiatrie,



Psychotherapie und Nervenheilkunde [DGPPN]): S3 Guideline for Diagnosis and Treatment of Bipolar Disorders, Long Version. Berlin, Germany, Springer-Verlag, 2012. Available at: [www.leitlinie-bipolar.de](http://www.leitlinie-bipolar.de). Accessed September 4, 2016.

Ghaemi SN, Pardo TB, Hsu DJ: Strategies for preventing the recurrence of bipolar disorder. J Clin Psychiatry 65 (suppl 10):16-23, 2004 15242328

GlaxoSmithKline: A randomized, multicenter, double-blind, placebo-controlled, fixed-dose, 7-week evaluation of the efficacy and safety of lamotrigine in patients with major depression (result summary for study SCA20022). September 28, 2008a. Available at: [http://www.gsk-clinicalstudyregister.com/study/SCA20022?study\\_ids=SCA20022#rs](http://www.gsk-clinicalstudyregister.com/study/SCA20022?study_ids=SCA20022#rs). Accessed May 16, 2016.

GlaxoSmithKline: A randomized, multicenter, double-blind, placebo-controlled, fixed-dose, 7-week evaluation of the efficacy and safety of lamotrigine in treatment of a major depressive episode in unipolar depressed patients (result summary for study SCA20025). September 28, 2008b. Available at: [http://www.gsk-clinicalstudyregister.com/study/SCA20025?study\\_ids=SCA20025#rs](http://www.gsk-clinicalstudyregister.com/study/SCA20025?study_ids=SCA20025#rs). Accessed May 16, 2016.

GlaxoSmithKline: An eight-week, multicenter, double-blind, randomized, fixed-dose evaluation of the efficacy and safety of lamotrigine (200mg/d), desipramine (200mg/d), and placebo in outpatients with unipolar depression (result summary for study SCAA2011. April 26, 2011. Available at: [http://www.gsk-clinicalstudyregister.com/study/SCAA2011?study\\_ids=SCAA2011#rs](http://www.gsk-clinicalstudyregister.com/study/SCAA2011?study_ids=SCAA2011#rs). Accessed May 16, 2016.

GlaxoSmithKline: Lamictal (lamotrigine) prescribing information. Research Triangle Park, NC, GlaxoSmithKline, May 2015. Available at: [http://us.gsk.com/products/assets/us\\_lamictal.pdf](http://us.gsk.com/products/assets/us_lamictal.pdf). Accessed May 16, 2016.

- Goff DC, Keefe R, Citrome L, et al: Lamotrigine as add-on therapy in schizophrenia: results of 2 placebo-controlled trials. *J Clin Psychopharmacol* 27(6):582-589, 2007 18004124
- Goodwin GM, Bowden CL, Calabrese JR, et al: A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry* 65(3):432-441, 2004 15096085
- Grunze H, von Wegerer J, Greene RW, et al: Modulation of calcium and potassium currents by lamotrigine. *Neuropsychobiology* 38(3):131-138, 1998 9778600
- Grunze H, Vieta E, Goodwin GM, et al; WFSBP Task Force on Treatment Guidelines for Bipolar Disorders: The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* 11(2):81-109, 2010 20148751
- Guberman AH, Besag FM, Brodie MJ, et al: Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia* 40(7):985-991, 1999 10403224
- Hahn CG, Gyulai L, Baldassano CF, Lenox RH: The current understanding of lamotrigine as a mood stabilizer. *J Clin Psychiatry* 65(6):791-804, 2004 15291656
- Harden CL, Meador KJ, Pennell PB, et al; American Academy of Neurology; American Epilepsy Society: Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 73(2):133-141, 2009a 19398681

- Harden CL, Pennell PB, Koppel BS, et al; American Academy of Neurology; American Epilepsy Society: Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 73(2):142–149, 2009b 19398680
- Holmes LB, Baldwin EJ, Smith CR, et al: Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 70(22 pt 2):2152–2158, 2008 18448870
- Jawad S, Richens A, Goodwin G, et al: Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. *Epilepsia* 30(3): 356–363, 1989 2498073
- Kilfoyle DH, Anderson NE, Wallis WE, Nicholls DW: Recurrent severe aseptic meningitis after exposure to lamotrigine in a patient with systemic lupus erythematosus. *Epilepsia* 46(2):327–328, 2005 15679516
- Köhler S, Gaus S, Bschor T: The challenge of treatment in bipolar depression: evidence from clinical guidelines, treatment recommendations and complex treatment situations. *Pharmacopsychiatry* 47(2):53–59, 2014 24549861
- Lam GM, Edelson DP, Whelan CT: Lamotrigine: an unusual etiology for aseptic meningitis. *Neurologist* 16(1):35–36, 2010 20065794
- Leach MJ, Lees G, Riddall DR: Lamotrigine: mechanisms of action, in *Antiepileptic Drugs*, 4th Edition. Edited by Levy RH, Mattson RH, Meldrum BS. New York, Raven, 1995, pp 861–869
- Lee CY, Fu WM, Chen CC, et al: Lamotrigine inhibits postsynaptic AMPA receptor and glutamate release in

- the dentate gyrus. *Epilepsia* 49(5):888-897, 2008 18248444
- Licht RW, Nielsen JN, Gram LF, et al: Lamotrigine versus lithium as maintenance treatment in bipolar I disorder: an open, randomized effectiveness study mimicking clinical practice. The 6th trial of the Danish University Antidepressant Group (DUAG-6). *Bipolar Disord* 12(5):483-493, 2010 20712749
- Lofton AL, Klein-Schwartz W: Evaluation of lamotrigine toxicity reported to poison centers. *Ann Pharmacother* 38(11):1811-1815, 2004 15353576
- Meador KJ, Baker GA, Browning N, et al; NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 360(16):1597-1605, 2009 19369666
- Messenheimer J, Mullens EL, Giorgi L, Young F: Safety review of adult clinical trial experience with lamotrigine. *Drug Saf* 18(4):281-296, 1998 9565739
- Mitchell PB, Hadzi-Pavlovic D, Evoniuk G, et al: A factor analytic study in bipolar depression, and response to lamotrigine. *CNS Spectr* 18(4):214-224, 2013 23702258
- Moris G, Garcia-Monco JC: The challenge of drug-induced aseptic meningitis. *Arch Intern Med* 159(11):1185-1194, 1999 10371226
- Newport DJ, Stowe ZN, Viguera AC, et al: Lamotrigine in bipolar disorder: efficacy during pregnancy. *Bipolar Disord* 10(3): 432-436, 2008 18402631
- Normann C, Hummel B, Schäfer LO, et al: Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. *J Clin Psychiatry* 63(4):337-344, 2002 12000208
- Ohman I, Vitols S, Tomson T: Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 41(6):709-713, 2000 10840403

- Pennell PB, Newport DJ, Stowe ZN, et al: The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 62(2):292-295, 2004 14745072
- Reich DB, Zanarini MC, Bieri KA: A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. *Int Clin Psychopharmacol* 24(5):270-275, 2009 19636254
- Reimers A, Helde G, Brodtkorb E: Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* 46(9):1414-1417, 2005 16146436
- Robakis TK, Holtzman J, Stemmle PG, et al: Lamotrigine and GABAA receptor modulators interact with menstrual cycle phase and oral contraceptives to regulate mood in women with bipolar disorder. *J Affect Disord* 175:108-115, 2015 25601310
- Sabers A, Buchholt JM, Uldall P, Hansen EL: Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res* 47(1-2):151-154, 2001 11673029
- Sabers A, Ohman I, Christensen J, Tomson T: Oral contraceptives reduce lamotrigine plasma levels. *Neurology* 61(4):570-571, 2003 12939444
- Sachs G, Bowden C, Calabrese JR, et al: Effects of lamotrigine and lithium on body weight during maintenance treatment of bipolar I disorder. *Bipolar Disord* 8(2):175-181, 2006 16542188
- Santos MA, Rocha FL, Hara C: Efficacy and safety of antidepressant augmentation with lamotrigine in patients with treatment-resistant depression: a randomized, placebo-controlled, double-blind study. *Prim Care Companion J Clin Psychiatry* 10(3):187-190, 2008 18615166
- Schulze TG, Detera-Wadleigh SD, Akula N, et al; NIMH Genetics Initiative Bipolar Disorder Consortium: Two variants in Ankyrin 3 (ANK3) are independent genetic

- risk factors for bipolar disorder. *Mol Psychiatry* 14(5):487-491, 2009 19088739
- Smith D, Chadwick D, Baker G, et al: Seizure severity and the quality of life. *Epilepsia* 34 (suppl 5):S31-S35, 1993 8339714
- Spearing MK, Post RM, Leverich GS, et al: Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res* 73(3):159-171, 1997 9481807
- Stefani A, Spadoni F, Siniscalchi A, et al: Lamotrigine inhibits Ca<sup>2+</sup> currents in cortical neurons: functional implications. *Eur J Pharmacol* 307(1):113-116, 1996 8831112
- Tritt K, Nickel C, Lahmann C, et al: Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. *J Psychopharmacol* 19(3):287-291, 2005 15888514
- Vajda FJ, Graham JE, Hitchcock AA, et al: Is lamotrigine a significant human teratogen? Observations from the Australian Pregnancy Register. *Seizure* 19(9):558-561, 2010 20739196
- van der Loos ML, Mulder PG, Hartong EG, et al; LamLit Study Group: Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 70(2):223-231, 2009 19200421
- van der Loos ML, Mulder P, Hartong EG, et al; LamLit Study Group: Efficacy and safety of two treatment algorithms in bipolar depression consisting of a combination of lithium, lamotrigine or placebo and paroxetine. *Acta Psychiatr Scand* 122(3):246-254, 2010 20136801
- van der Loos ML, Mulder P, Hartong EG, et al; LamLit Study Group: Long-term outcome of bipolar depressed patients receiving lamotrigine as add-on to lithium with the possibility of the addition of paroxetine in nonresponders: a randomized, placebo-controlled trial

- with a novel design. *Bipolar Disord* 13(1):111–117, 2011 21320258
- von Wegerer J, Hesslinger B, Berger M, et al: A calcium antagonistic effect of the new antiepileptic drug lamotrigine. *Eur Neuropsychopharmacol* 7(2):77–81, 1997 9169293
- Weintraub D, Buchsbaum R, Resor SR Jr, Hirsch LJ: Effect of antiepileptic drug comedication on lamotrigine clearance. *Arch Neurol* 62(9):1432–1436, 2005 16157751
- Xie X, Hagan RM: Cellular and molecular actions of lamotrigine: possible mechanisms of efficacy in bipolar disorder. *Neuropsychobiology* 38(3):119–130, 1998 9778599
- Yatham LN, Kennedy SH, Parikh SV, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord* 15(1):1–44, 2013 23237061
- Zhou X, Ravindran AV, Qin B, et al: Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *J Clin Psychiatry* 76(4):e487–e498, 2015 25919841

# CHAPTER 41

## Topiramate

Susan L. McElroy, M.D.

Paul E. Keck Jr., M.D.

---

### History and Discovery

---

Topiramate was approved by the U.S. Food and Drug Administration (FDA) for the treatment of epilepsy in 1996, for migraine prevention in 2004, and in combination with phentermine for chronic weight management in 2012. Reports appearing in the late 1990s of the drug having potential beneficial effects in bipolar disorder led Johnson & Johnson Pharmaceutical Research and Development, the discoverer and manufacturer of topiramate, to conduct a large clinical study program of topiramate in the treatment of acute bipolar mania ([McElroy and Keck 2004](#)). Controlled trials of the drug in adults with manic or mixed symptoms of bipolar disorder failed to demonstrate significant separation between the topiramate and placebo groups ([Kushner et al. 2006](#); [Roy Chengappa et al. 2006](#)). However,



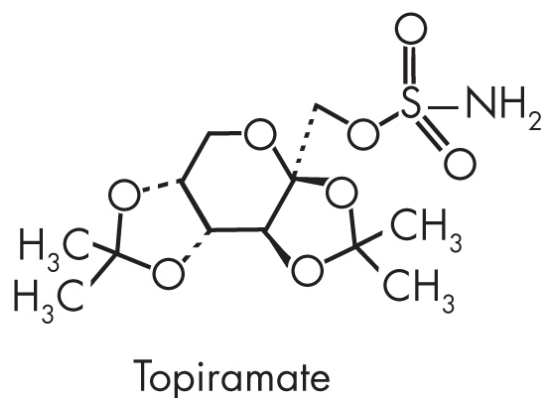
topiramate has been shown in placebo-controlled trials to be efficacious in several neuropsychiatric conditions often comorbid with bipolar disorder, including binge-eating disorder, bulimia nervosa, alcohol use disorder, borderline personality disorder, psychotropic-associated weight gain, and obesity, in addition to migraine headache. Additionally, mounting evidence suggests that topiramate augmentation of antipsychotic therapy may reduce psychological symptoms in schizophrenia spectrum disorders.

---

## Pharmacological Profile

---

Topiramate ([Figure 41-1](#)) has multiple pharmacological properties that may contribute to its anticonvulsant and neuropsychiatric effects ([Langtry et al. 1997](#); [Rho and Sankar 1999](#); [Rosenfeld 1997](#); [Shank et al. 2000](#); [White 2002, 2005](#); [White et al. 2007](#)). First, topiramate inhibits voltage-gated sodium channels in a voltage-sensitive, use-dependent manner and thus suppresses action potentials associated with sustained repetitive cell firing ([Kawasaki et al. 1998](#); [Shank et al. 2000](#)). Second, topiramate increases brain  $\gamma$ -aminobutyric acid (GABA) levels, possibly by activating a site on the GABA<sub>A</sub> receptor, thereby enhancing the inhibitory chloride ion influx mediated by the GABA<sub>A</sub> receptor and potentiating GABA-evoked currents ([Kuzniecky et al. 1998](#); [Petroff et al. 2001](#); [Simeone et al. 2006](#)). Because this action is not blocked by the benzodiazepine antagonist flumazenil, it is thought that topiramate exerts this effect via an interaction with the GABA<sub>A</sub> receptor that is not modulated by benzodiazepines ([White et al. 2000](#)).




---

**FIGURE 41-1.** Chemical structure of topiramate.

Third, topiramate antagonizes glutamate receptors of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate subtype and may selectively inhibit glutamate receptor 5 (GluR<sub>5</sub>) kainate receptors ([Kaminski et al. 2004](#)). It has essentially no effect on glutamate *N*-methyl-D-aspartate (NMDA) receptors. AMPA/kainate receptors mediate fast excitatory postsynaptic potentials responsible for excitatory neurotransmission; blockade of kainate-evoked currents decreases neuronal excitability.

Fourth, topiramate negatively modulates high-voltage-activated calcium channels ([Zhang et al. 2000](#)). Of note, [Shank et al. \(2000\)](#) proposed that topiramate's combined effects on voltage-activated sodium channels, GABA<sub>A</sub> receptors, AMPA/kainate receptors, and high-voltage-activated calcium channels are unique as compared with those of other antiepileptic drugs. Indeed, [Schiffer et al. \(2001\)](#) found that pretreatment with topiramate inhibited nicotine-induced increases in mesolimbic extracellular dopamine and norepinephrine, but not serotonin. They hypothesized that this property was a result of the drug's ability to affect both GABAergic and glutamatergic function.

Fifth, topiramate weakly inhibits some carbonic anhydrase isoenzymes, including subtypes II and VI. Carbonic anhydrase is essential for the generation of GABA<sub>A</sub>-mediated depolarizing responses. By inhibiting carbonic anhydrase, topiramate has been shown to reversibly reduce the GABA<sub>A</sub>-mediated depolarizing responses evoked by either synaptic stimulation or pressure application of GABA (but not to modify GABA<sub>A</sub>-mediated hyperpolarizing postsynaptic potentials) ([Herrero et al. 2002](#)).

Finally, topiramate has a number of other properties. These include an interaction with glycine receptor channels ([Mohammadi et al. 2005](#)), effects on mitochondrial permeability ([Kudin et al. 2004](#)), and antikindling properties in some animal models ([Wauquier and Zhou 1996](#)).

---

## Pharmacokinetics and Disposition

---

Topiramate has a favorable pharmacokinetic profile ([Bialer et al. 2004](#); [Doose and Streeter 2002](#); [Langtry et al. 1997](#); [Rosenfeld 1997](#); [Shank et al. 2000](#)). It is rapidly and almost completely absorbed after oral administration, with bioavailability estimated to be about 80%. Peak plasma concentrations are reached within 2–4 hours. Plasma concentration increases in proportion to dose over the pharmacologically relevant dose range. Topiramate is minimally protein bound (9%–17%).

Topiramate is minimally metabolized by the liver in the absence of hepatic enzyme-inducing drugs. It inhibits cytochrome P450 (CYP) enzyme 2C19 but not other hepatic CYP enzymes. Topiramate is excreted mostly unchanged (approximately 70%) in the urine. The nonrenal (hepatic) clearance of topiramate increases two- to threefold when the drug is administered with hepatic enzyme-inducing drugs such as carbamazepine and phenytoin. Six minor metabolites have been identified ([Shank et al. 2000](#)).

Topiramate's elimination half-life is 19-25 hours, with linear pharmacokinetics in the dose range of 100-1,200 mg. The pharmacokinetics of topiramate in children are similar to those in adults, except that clearance is 50% higher, resulting in 33% lower plasma concentrations. Moderate or severe renal failure is associated with reduced renal clearance and increased elimination half-life of topiramate. Moderate or severe liver impairment is associated with clinically insignificant increased plasma concentrations of the drug.

---

## Mechanism of Action

---

Although the mechanism of topiramate's anticonvulsant action is unknown, it has been hypothesized to be due to some combination of the drug's multiple pharmacological properties ([Rho and Sankar 1999](#); [Shank et al. 2000](#); [White 2002, 2005](#); [White et al. 2007](#)). For example, the drug's anticonvulsant profile, as well as its benefits in substance use and eating disorders, has been hypothesized to be due to its dual actions on the GABAergic and glutamatergic

systems ([Johnson et al. 2003, 2005](#); [McElroy et al. 2003, 2007](#); [Rho and Sankar 1999](#); [Schiffer et al. 2001](#)).

---

## Indications and Efficacy

---

### FDA-Approved Indications

Topiramate is indicated by the FDA as initial monotherapy in patients ages 10 years and older with partial-onset or primary generalized tonic-clonic seizures; as adjunctive therapy for adults and for pediatric patients ages 2–16 years with partial-onset seizures or primary generalized tonic-clonic seizures; and in patients ages 2 years and older with seizures associated with Lennox-Gastaut syndrome ([van Passel et al. 2006](#)). Topiramate is also approved for the prophylaxis of migraine headache in adults ([Brandes 2005](#); [Bussone et al. 2006](#)). In 2012, the FDA approved topiramate extended release in combination with phentermine (marketed under the trade name Qsymia [[Vivus 2014](#)]) for chronic weight management as an adjunct to lifestyle modification in people who are obese (body mass index [BMI]  $\geq 30$  mg/kg) or who are overweight (BMI  $\geq 27$  mg/kg) and also have at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus) ([Alfaris et al. 2015](#)).

### Other Indications

Topiramate is not approved by the FDA for use in the treatment of any psychiatric disorder. Because the drug

was widely used off-label in the treatment of bipolar disorder after it came to market (see subsection “Bipolar Disorder” below), Johnson & Johnson Pharmaceutical Research and Development, the discoverer of topiramate, conducted a large study program of topiramate in adults with acute bipolar mania. These placebo-controlled studies failed to demonstrate significant benefit from topiramate versus placebo on Young Mania Rating Scale (YMRS) scores ([Kushner et al. 2006](#); [McElroy and Keck 2004](#)). By contrast, findings from randomized, placebo-controlled trials suggest that topiramate may be efficacious in major depressive disorder, schizophrenia, binge-eating disorder (BED), bulimia nervosa, alcohol use disorder, psychotropic-induced weight gain, and obesity.

## **Bipolar Disorder**

Five randomized, placebo-controlled studies have shown that topiramate monotherapy is not efficacious in the short-term treatment of acute manic or mixed episodes in adults with bipolar I disorder ([Kushner et al. 2006](#); [McElroy and Keck 2004](#)). All five studies used week 3 as the primary endpoint; in addition, three of the studies had a week 12 secondary endpoint, two studies had lithium comparator groups, and all trials measured weight as a secondary outcome. In each trial, the primary efficacy outcome—the change from baseline to week 3 in the YMRS score—failed to show a statistically significant separation between topiramate and placebo. There was also no drug-versus-placebo separation in the three trials with week 12 data. By contrast, in the two trials in which lithium was used, lithium did show statistical superiority to placebo.

Similarly, in the only placebo-controlled study of adjunctive topiramate in bipolar disorder, 287 outpatients

experiencing a manic or mixed episode (by DSM-IV [[American Psychiatric Association 1994](#)] criteria) and a YMRS score of 18 or higher while taking therapeutic levels of valproate or lithium showed similar reductions (40%) in baseline YMRS scores for both topiramate and placebo after 12 weeks ([Roy Chengappa et al. 2006](#)). In the only placebo-controlled study of topiramate in pediatric bipolar I disorder, 56 children and adolescents (ages 6–17 years) experiencing a manic or mixed episode were randomly assigned to topiramate or placebo for 4 weeks ([DelBello et al. 2005](#)). Initially designed to enroll approximately 230 subjects, the study was prematurely discontinued when results from the adult mania trials were negative. Decrease in mean YMRS score from baseline to final visit using last observation carried forward (LOCF) analysis was not statistically different between treatment groups. However, a post hoc repeated-measures linear regression model of the primary efficacy analysis showed a statistically significant difference in the slopes of the linear mean profiles ( $P=0.003$ ).

No placebo-controlled study of topiramate has yet been done in acute bipolar depression. Results from an 8-week single-blind comparison trial in which 36 outpatient adults with bipolar depression were randomly assigned to receive either topiramate (mean dosage=176 mg/day; range=50–300 mg/day) or bupropion sustained release (mean dosage=250 mg/day; range=100–400 mg/day) suggested that the drug might have antidepressant properties in some bipolar patients ([McIntyre et al. 2002](#)). The percentage of patients meeting a priori response criteria ( $\geq 50\%$  decrease from baseline in mean total score on the 17-item Hamilton Rating Scale for Depression [Ham-D]) was significant for

both topiramate (56%) and bupropion sustained release (59%).

## Depressive Disorders

Two randomized, placebo-controlled studies of topiramate in patients with major depressive disorder have been conducted. In the first, 64 females with DSM-IV recurrent major depressive disorder were randomly assigned to receive topiramate or placebo for 10 weeks ([C. Nickel et al. 2005a](#)). Topiramate was superior to placebo in reducing depressive and anger symptoms. All subjects tolerated topiramate well, and there were no suicidal events. In the second study, 53 patients with DSM-IV major depressive disorder that had been inadequately responsive to an 8-week trial of a selective serotonin reuptake inhibitor (SSRI) were randomly assigned to receive adjunctive topiramate (100–200 mg/day) or placebo for 8 weeks ([Mowla and Kardeh 2011](#)). Topiramate recipients had a 32% mean decrease in Ham-D score, whereas placebo recipients had a mean decrease of 5.5%. Topiramate augmentation also produced significantly greater global improvement in depressive symptoms compared with placebo augmentation. Six patients discontinued topiramate because of side effects, which included loss of appetite, gastric disturbance, memory problems, and akathisia. No suicidal events were reported.

## Psychotic Disorders

**Studies.** Seven randomized, placebo-controlled studies of topiramate targeting psychopathology in patients with psychotic disorders have been conducted, with mixed results. Six of these studies involved patients with



schizophrenia, and one involved patients with schizoaffective disorder, bipolar type.

*Schizophrenia.* In the first schizophrenia study, 26 patients with treatment-resistant illness had topiramate (gradually increased to 300 mg/day) or placebo added to their ongoing antipsychotic regimens over two 12-week crossover treatment periods ([Tiihonen et al. 2005](#)). In the intent-to-treat analysis, topiramate was superior to placebo in reducing general psychopathological symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS), but no significant improvement was observed in positive or negative symptoms.

In the second study, 66 inpatients with schizophrenia who were being treated with risperidone were randomly assigned to receive augmentation with topiramate 100 mg/day, topiramate 200 mg/day, or placebo for 12 weeks ([Ko et al. 2005](#)). Both dosages of topiramate were superior to placebo in reducing psychopathology, as assessed with the Clinical Global Impressions (CGI) Severity of Illness subscale (CGI-S) and the Brief Psychiatric Rating Scale (BPRS).

In the third study, either topiramate (up to 300 mg/day) or placebo was added to the clozapine regimens of 32 patients with schizophrenia for 56 days ([Afshar et al. 2009](#)). At day 56, total PANSS values, as well as scores for all three subscales (negative symptoms, positive symptoms, and general psychopathology), were significantly improved in the topiramate-augmentation group compared with the placebo-augmentation group.

In the fourth study, 72 drug-naïve patients with schizophrenia were randomly assigned to receive olanzapine plus topiramate 100 mg/day or olanzapine plus

placebo for 12 weeks ([Narula et al. 2010](#)). Compared with the placebo-treated group, the topiramate-treated group showed significantly greater improvement on PANSS total scores ( $P=0.001$ ) and general psychopathology measures ( $P<0.001$ ).

In the fifth study, 43 patients with treatment-resistant schizophrenia who were receiving clozapine were given adjunctive topiramate (up to 200 mg/day) or placebo for 24 weeks ([Muscatello et al. 2011](#)). The addition of topiramate was associated with a significant reduction in bizarre behavior as assessed on the Scale for the Assessment of Positive Symptoms (SAPS) ( $P<0.002$ ); however, no significant improvement in positive, negative, affective, or overall clinical symptomatology was otherwise seen with topiramate.

In the sixth study, either topiramate (200–300 mg/day) or placebo was added to clozapine in 80 hospitalized patients with schizophrenia for 17 weeks ([Behdani et al. 2011](#)). At endpoint, add-on topiramate was not superior to add-on placebo in reducing positive, negative, or general psychopathological symptoms as assessed by the PANSS.

*Schizoaffective disorder.* In the schizoaffective disorder study, 48 patients with a diagnosis of DSM-IV schizoaffective disorder, bipolar type, were randomly assigned in a 2:1 ratio (favoring topiramate) to 8 weeks of double-blind treatment with topiramate (100–400 mg/day) or placebo ([Roy Chengappa et al. 2007](#)). Patients who had achieved at least a 20% decrease from baseline in their PANSS total scores were given the opportunity to continue for an additional 8 weeks of double-blind treatment. Adjunctive topiramate (nearly 275 mg/day) did not show increased efficacy relative to placebo on the PANSS (the

primary outcome measure) or on any of the secondary outcome measures.

**Case reports.** There are several case reports of the successful use of topiramate to treat catatonia in patients with chronic psychotic disorders ([McDaniel et al. 2006](#)). By contrast, there are also reports of the emergence of psychotic symptoms with topiramate treatment ([Duggal and Singh 2004](#); [Miller et al. 2010](#)).

## Eating Disorders

Five positive randomized, placebo-controlled studies involving subjects with bulimia nervosa (two studies) or BED (three studies) have demonstrated that topiramate reduces binge eating.

**Bulimia nervosa.** In the first bulimia nervosa study, a 10-week trial with 69 subjects, topiramate (median dosage=100 mg/day; range=25–400 mg/day) was superior to placebo in reducing the frequency of binge and purge days (days during which at least one binge-eating or purging episode occurred;  $P=0.004$ ) ([Hedges et al. 2003](#); [Hoopes et al. 2003](#)). Binge-eating/purging remission rates were 32% for topiramate and 6% for placebo ( $P=NS$ ). Dropout rates were 34% for topiramate and 47% for placebo. In the second study, subjects with DSM-IV bulimia nervosa received 10 weeks of topiramate (titrated to 250 mg/day in the sixth week) ( $n=30$ ) or placebo ( $n=30$ ) ([C. Nickel et al. 2005b](#)). Topiramate was associated with significant decreases in binge/purge frequency (defined as a >50% reduction; 37% for topiramate and 3% for placebo), body weight (difference in weight loss between

the two groups=3.8 kg), and all of the Short Form 36-Item Health Survey (SF-36) scales (all  $P$ s < 0.001).

**Binge-eating disorder.** In the first controlled study in BED, 61 subjects with DSM-IV BED and obesity received topiramate or placebo for 14 weeks ([McElroy et al. 2003](#)). Topiramate was significantly superior to placebo in reducing binge frequency, as well as global severity of illness, obsessive-compulsive features of binge-eating symptoms, body weight, and BMI. The dropout rate, however, was high: 14 (47%) subjects receiving topiramate and 12 (39%) subjects receiving placebo did not complete the trial.

The second controlled study of topiramate in BED was a multicenter trial in which subjects with DSM-IV BED and at least three binge-eating days per week, a BMI ranging from 30 kg/m<sup>2</sup> to 50 kg/m<sup>2</sup>, and no current psychiatric disorders or substance abuse were randomly assigned to receive topiramate or placebo for 16 weeks ([McElroy et al. 2007](#)). Of 407 subjects enrolled, 13 did not meet inclusion criteria; 195 topiramate and 199 placebo subjects were therefore evaluated for efficacy. Topiramate significantly reduced binge-eating days per week, binge episodes per week, weight, and BMI compared with placebo (all  $P$ s < 0.001). The drug also significantly decreased measures of obsessive-compulsive symptoms, impulsivity, hunger, and disability. Fifty-eight percent of topiramate-treated subjects achieved remission compared with 29% of placebo-treated subjects ( $P$  < 0.001). Discontinuation rates were 30% in each group; adverse events were the most common reason for topiramate discontinuation (16%; placebo, 8%).

The third controlled study of topiramate in BED was another multicenter trial in which 73 patients with BED and

obesity were randomly assigned to 19 sessions of cognitive-behavioral therapy (CBT) in conjunction with topiramate or placebo for 21 weeks ([Claudino et al. 2007](#)). Compared with patients given placebo, patients given topiramate showed a significantly greater rate of reduction in weight, the primary outcome measure, over the course of treatment ( $P<0.001$ ). Topiramate recipients also showed a significant weight loss ( $-6.8$  kg) relative to placebo recipients ( $-0.9$  kg). A greater percentage of topiramate-treated patients (31 of 37) than of placebo-treated patients (22 of 36) attained remission of binge eating ( $P=0.03$ ). There was no difference between groups in completion rates, although one topiramate recipient withdrew because of an adverse effect.

**Other eating disorders.** There are no randomized controlled studies of topiramate in anorexia nervosa. However, there are reports of topiramate triggering or worsening anorexia nervosa as well as reports of eating disorder patients misusing the drug to lose weight ([McElroy et al. 2008](#)). In contrast, there are case reports of the successful treatment of night eating syndrome with topiramate ([Kucukgoncu et al. 2015](#)).

## **Substance-Related and Addictive Disorders**

Growing evidence suggests that topiramate may have therapeutic effects in some substance-related and addictive disorders, especially alcohol use disorder.

**Alcohol use disorder.** At least eight studies examined topiramate in alcohol use disorder. In the first, 150 subjects with DSM-IV alcohol dependence were randomly assigned to receive topiramate (up to 300 mg/day) or placebo for 12

weeks ([Johnson et al. 2003](#)). All subjects also received compliance enhancement therapy. At study end, subjects receiving topiramate, compared with those receiving placebo, had significantly fewer drinks per day ( $P=0.0006$ ), fewer drinks per drinking day ( $P=0.0009$ ), fewer heavy drinking days ( $P=0.0003$ ), more days abstinent ( $P=0.0003$ ), and a log plasma  $\gamma$ -glutamyl transferase (GGT) ratio of 0.07 less ( $-0.11$  to  $-0.02$ ) ( $P=0.0046$ ). Craving was also significantly more improved with topiramate than with placebo.

In the second study, 371 subjects with DSM-IV alcohol dependence were randomly assigned to receive topiramate (up to 300 mg/day) or placebo, along with a weekly compliance enhancement intervention, at 16 sites for 14 weeks ([Johnson et al. 2007](#)). Topiramate was significantly superior to placebo in reducing the percentage of heavy drinking days and other drinking outcomes such as drinks per drinking day, increasing the percentage of days abstinent, and improving the log plasma GGT ratio (all  $P_s \leq 0.002$ ).

In the third study, 155 subjects with DSM-IV alcohol dependence who had been detoxified for 1 week were randomized to receive topiramate (up to 300 mg/day), naltrexone, or placebo in addition to relapse prevention counseling and encouragement to participate in Alcoholics Anonymous for 12 weeks ([Baltieri et al. 2008](#)). Topiramate was superior to placebo on a number of measures, including time to first relapse, cumulative abstinence duration, weeks of heavy drinking, and percentage of subjects abstinent, at 4 weeks and 8 weeks, but not at 12 weeks. There were no significant differences between naltrexone versus placebo or between topiramate versus naltrexone.

In the fourth study, 63 patients with DSM-IV alcohol dependence were randomly assigned to receive topiramate or placebo for 12 weeks ([Rubio et al. 2009](#)). Compared with placebo recipients, topiramate recipients had significantly lower numbers of drinks per drinking day ( $P<0.05$ ) and of heavy drinking days ( $P<0.001$ ).

In the fifth study, 170 subjects with comorbid DSM-IV alcohol and cocaine dependence who had attained baseline abstinence were randomly assigned to receive topiramate (300 mg/day) or placebo in addition to weekly psychotherapy for 13 weeks ([Kampman et al. 2013](#)). Topiramate was not superior to placebo in reducing cocaine or alcohol use.

In the sixth study, 106 patients with DSM-IV alcohol dependence receiving residential treatment were randomly assigned to topiramate (100–300 mg/day) or placebo for 12 weeks ([Likhitsathian et al. 2013](#)). No significant differences between the two groups were found in mean percentages of heavy drinking days or time to first day of heavy drinking.

In the seventh study, 138 individuals with heavy drinking (most of whom met criteria for DSM-IV alcohol dependence) were randomly assigned to receive topiramate (titrated to 100 mg twice daily) or placebo for 12 weeks ([Kranzler et al. 2014](#)). Compared with placebo, topiramate significantly reduced heavy drinking days and increased abstinent days ( $P=0.001$  and  $0.03$ , respectively). Moreover, a single-nucleotide polymorphism (rs2832407) in *GRIK1*, which encodes for the kainite GluK1 receptor subunit, may have moderated topiramate's effect on heavy drinking. Specifically, topiramate's effect on heavy drinking days was significantly greater than that of placebo only in participants who were rs2832407 C-allele homozygotes.



In the eighth study, 85 participants with DSM-IV alcohol dependence were randomly assigned to receive topiramate, zonisamide, levetiracetam, or placebo for 14 weeks (including a 2-week taper period) ([Knapp et al. 2015](#)). Both topiramate and zonisamide produced significant reductions in drinking behavior. However, whereas topiramate and zonisamide both were associated with modest reductions in verbal fluency and working memory, only topiramate produced a significant increase in mental slowing,

**Cocaine use disorder.** Five randomized, placebo-controlled trials have evaluated topiramate in DSM-IV cocaine dependence, with mixed results. In the first study, 40 cocaine-dependent individuals were randomly assigned to topiramate (titrated gradually over 8 weeks to 200 mg/day) or placebo for 13 weeks ([Kampman et al. 2004](#)). Topiramate-treated subjects were more likely than placebo-treated subjects to be abstinent from cocaine after week 8 ( $P=0.01$ ). They were also more likely to achieve 3 weeks of continuous abstinence from cocaine ( $P=0.05$ ).

In the second study, 81 cocaine-dependent subjects were randomly assigned to receive topiramate (titrated to 150 mg twice daily) plus mixed amphetamine salts or placebo for 12 weeks ([Mariani et al. 2012](#)). The proportion of patients achieving 3 weeks of abstinence was larger for active drug treatment (33.3%) than for placebo (16.7%). Combination treatment may have been more effective in subjects with a high baseline frequency of cocaine use.

In the third study, 142 patients with DSM-IV cocaine dependence were randomly assigned to receive topiramate (target maintenance dosage=300 mg/day) or placebo in combination with CBT for 12 weeks ([Johnson et al. 2013](#)). Topiramate was more efficacious than placebo at increasing



the weekly proportion of nonuse days, and also was associated with significantly more urinary cocaine-free weeks, decreased craving, and improved global functioning.

In the fourth trial, 170 subjects with comorbid DSM-IV cocaine and alcohol dependence were randomly assigned to receive topiramate 300 mg/day or placebo for 13 weeks ([Kampman et al. 2013](#)). Topiramate was not superior to placebo for reducing cocaine or alcohol use.

In the fifth study, 171 cocaine-dependent patients undergoing methadone maintenance treatment were randomly assigned to receive topiramate or placebo in addition to monetary voucher incentives that were either contingent or noncontingent on drug abstinence for 15 weeks (including 8 weeks at a maintenance dosage of 300 mg/day) ([Umbricht et al. 2014](#)). There were no significant differences between the topiramate and placebo conditions, or between the contingent and noncontingent incentive conditions. Additionally, there were no topiramate-contingency interactions, and topiramate was associated with cognitive impairment.

**Methamphetamine use disorder.** Two randomized controlled trials have assessed topiramate in DSM-IV methamphetamine addiction. In the first study, 140 methamphetamine-addicted subjects were randomly assigned to receive topiramate (target maintenance dosage=200 mg/day) or placebo for 13 weeks ([Elkashef et al. 2012](#)). Topiramate did not increase abstinence from methamphetamine over weeks 6-12 of treatment (the primary outcome measure). On secondary outcomes, however, topiramate reduced weekly median urine methamphetamine levels and overall severity of dependence scores ( $P=0.03$  for both).

In the second study, 62 adults with DSM-IV methamphetamine dependence were randomly assigned to receive topiramate (up to 200 mg/day) or placebo for 10 weeks ([Rezaei et al. 2016](#)). At week 6, compared with the placebo group, the topiramate group had a significantly lower proportion of methamphetamine-positive urine tests ( $P=0.01$ ). The topiramate-treated subjects also had lower scores on the drug use severity and drug need items of the Addiction Severity Index (ASI) (both  $P$ s<0.001).

**Smoking cessation.** Three randomized controlled trials have assessed topiramate in smoking cessation. In the first study, topiramate was superior to placebo in 94 subjects with comorbid DSM-IV alcohol dependence ([Johnson et al. 2003](#)). This study was a subgroup analysis of the first controlled study of topiramate in alcohol dependence ([Johnson et al. 2003](#)). In the second study, topiramate was superior to placebo for smoking cessation in male ( $n=38$ ) but not female ( $n=49$ ) subjects who had no associated psychopathology ([Anthenelli et al. 2008](#)). In the third study, which followed a placebo-controlled trial in 155 male outpatients with ICD-10 ([World Health Organization 1993](#)) alcohol dependence ([Baltieri et al. 2008](#)), a subset of the alcoholic participants who were smokers ( $n=103$ ) were randomly assigned to receive topiramate, naltrexone, or placebo for 12 weeks ([Baltieri et al. 2009](#)). Whereas naltrexone did not separate from placebo, topiramate was found to be more effective than placebo in reducing the number of cigarettes smoked.

**Gambling disorder.** One 14-week placebo-controlled trial assessed topiramate in 42 patients with DSM-IV pathological gambling ([Berlin et al. 2013](#)). There were no

significant treatment effects of topiramate on the primary (Y-BOCS Modified for Pathological Gambling) or any secondary outcome measures.

## **Posttraumatic Stress Disorder**

Topiramate has been evaluated in three placebo-controlled studies of posttraumatic stress disorder (PTSD). In the first study, 38 civilian patients with PTSD were randomly assigned to flexible dosages of topiramate alone (median dosage=150 mg/day) or placebo for 12 weeks ([Tucker et al. 2007](#)). No significant difference between topiramate and placebo was found on the primary efficacy measure, change in total Clinician-Administered PTSD Scale (CAPS) score. However, significant or near-significant effects in favor of topiramate were observed on the eight-item Treatment Outcome PTSD scale (TOP-8) score (decrease in overall severity of 68% for topiramate vs. 42% for placebo;  $P=0.025$ ) and the endpoint CGI Improvement subscale (CGI-I) score ( $1.9\pm1.2$  vs.  $2.6\pm1.1$ ;  $P=0.055$ ).

In the second study, 40 male veterans with chronic PTSD, most of whom were receiving antidepressants, were given topiramate (up to 200 mg/day) or placebo for 7 weeks ([Lindley et al. 2007](#)). No significant drug-versus-placebo difference was found for the primary outcome measures (CAPS, CGI-S, or Patient Global Impression of Improvement Scale [PGI-I] scores).

In the third study, 30 veterans with PTSD and a co-occurring alcohol use disorder were randomly assigned to receive topiramate (up to 300 mg/day) or placebo for 12 weeks ([Batki et al. 2014](#)). Compared with placebo, topiramate tended to reduce the primary outcome measure—frequency of drinking days ( $P=0.063$ )—but not measures of PTSD symptoms.

## Obsessive-Compulsive Disorder

Four placebo-controlled trials have evaluated adjunctive topiramate in subjects with obsessive-compulsive disorder (OCD), with mixed results. In the first study, 41 subjects with OCD that had not improved after at least 12 weeks of treatment with an SSRI were randomly assigned to receive topiramate or placebo plus their current OCD regimen for 12 weeks. Topiramate recipients had a mean decrease of 32% in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores, whereas placebo recipients had a decrease of 2.4% ([Mowla et al. 2010](#)). In the second study, adjunctive topiramate (mean endpoint dosage 179 mg/day) significantly reduced the Y-BOCS Compulsions subscale score ( $P=0.014$ ), but not the Obsessions subscale score or the total score, in 36 adult subjects with OCD receiving SSRIs ([Berlin et al. 2011](#)). In the third study, 39 inpatients with OCD and bipolar mania were randomly assigned to receive the addition of topiramate or placebo to their current regimen of lithium, olanzapine, and clonazepam was associated with significantly for 4 months ([Sahraian et al. 2014](#)). Y-BOCS scores showed a greater numeric decline for patients receiving placebo than for those receiving topiramate. By contrast, among the 32 completers, there were significantly more responders (defined as >34% reduction in Y-BOCS scores) among topiramate recipients than among placebo recipients (53% and 12.5%, respectively;  $P<0.01$ ). However, in the fourth study, involving 38 patients with refractory OCD, topiramate (mean dosage=137.5 mg/day) was not superior to placebo in reducing Y-BOCS scores after 12 weeks of treatment ([Afshar et al. 2014](#)).

## Borderline Personality Disorder

Three placebo-controlled studies, all conducted by the same group, have evaluated topiramate in DSM-IV-defined borderline personality disorder. In the first study, 29 female subjects were randomly assigned in a 2:1 ratio to topiramate or placebo for 8 weeks ([Nickel et al. 2004](#)). Topiramate dosage was increased to 250 mg/day over 6 weeks. At study end, significant improvement on four subscales of the State-Trait Anger Expression Inventory (STAXI)—state-anger, trait-anger, anger-out, and anger-control—was observed for topiramate compared with placebo.

In the second study, 42 male subjects with borderline personality disorder received topiramate or placebo for 8 weeks (M.K. [Nickel et al. 2005a](#)). Similar to the study in females, significant improvement on the same four STAXI subscales was found for topiramate compared with placebo.

In the third study, 56 women with borderline personality disorder received topiramate or placebo for 10 weeks ([Loew et al. 2006](#)). Topiramate was titrated to 200 mg/day over 6 weeks and then held constant. Topiramate was superior to placebo on the somatization, interpersonal sensitivity, anxiety, hostility, phobic anxiety, and Global Severity Index subscales of the Symptom Checklist-90—Revised (SCL-90-R) (all  $P$ s<0.001), all eight scales of the SF-36 (all  $P$ s<0.01), and four of eight scales of the Inventory of Interpersonal Problems (all  $P$ s<0.001). In all three studies, topiramate was well tolerated, and there were no psychotic or suicidal adverse events.

## Psychotropic Medication-Associated Weight Gain

At least four placebo-controlled studies have suggested that topiramate reduces antipsychotic-related weight gain in patients with psychotic or mood disorders. In one study, 66 inpatients with schizophrenia receiving antipsychotic medication and “carrying excess weight” were randomly assigned to receive topiramate 100 mg/day, topiramate 200 mg/day, or placebo for 12 weeks ([Ko et al. 2005](#)). Body weight, BMI, and waist and hip circumferences decreased significantly in the topiramate 200 mg/day group compared with the topiramate 100 mg/day and placebo groups.

In another study, 43 women with mood or psychotic disorders who had gained weight while receiving olanzapine were given topiramate or placebo for 10 weeks ([M.K. Nickel et al. 2005b](#)). Weight loss was significantly greater (by 5.6 kg) in the topiramate group. Topiramate-treated subjects also experienced significantly greater improvement in measures of health-related quality of life and psychological impairment.

In a third study, topiramate as an adjunct to lithium or valproate treatment was ineffective for manic symptoms in patients with bipolar I disorder experiencing a manic or mixed episode but was associated with significantly greater reductions in body weight compared with placebo (−2.5 and 0.2 kg, respectively;  $P<0.001$ ) and in BMI (−0.84 and 0.07 kg/m<sup>2</sup>, respectively;  $P<0.001$ ) ([Roy Chengappa et al. 2006](#)).

In a fourth study, adjunctive topiramate was evaluated for utility in prevention of olanzapine-related weight gain ([Narula et al. 2010](#)). In this 12-week trial, 72 patients with schizophrenia were randomly assigned to receive olanzapine plus topiramate 100 mg or olanzapine plus placebo. Whereas topiramate augmentation was associated with statistically significant weight loss, placebo-augmented

olanzapine was associated with significant weight gain ( $P=0.05$  between-group difference). Topiramate augmentation was also associated with significantly greater improvement in several metabolic variables, systolic and diastolic blood pressure, and PANSS General Psychopathology Scale and total scores.

## Obesity

At least nine randomized, placebo-controlled trials have evaluated topiramate ([Astrup et al. 2004](#); [Bray et al. 2003](#); [Eliasson et al. 2007](#); [Stenlöf et al. 2007](#); [Tonstad et al. 2005](#); [Toplak et al. 2007](#); [Tremblay et al. 2007](#); [Wilding et al. 2004](#)) or a controlled-release formulation of topiramate ([Rosenstock et al. 2007](#)) for weight loss in subjects with obesity. In all nine studies, topiramate was superior to placebo for weight loss at all dosages (range=64–400 mg/day) and at all endpoints (ranging from 28 weeks to 1 year) evaluated. The four long-term studies (duration ranging from 40 weeks to 1 year) found that topiramate was associated with weight loss that continued for up to 1 year without plateauing ([Astrup et al. 2004](#); [Eliasson et al. 2007](#); [Stenlöf et al. 2007](#); [Wilding et al. 2004](#)). In a study of subjects with comorbid obesity and hypertension, there were significant decreases in diastolic but not systolic blood pressure in the two groups receiving topiramate (either 96 mg/day or 192 mg/day) compared with the placebo group ([Tonstad et al. 2005](#)). In four studies of topiramate in subjects with comorbid obesity and type 2 diabetes, topiramate-treated subjects showed significant decreases in glycosylated hemoglobin ( $Hb_{A1c}$ ) compared with placebo-treated subjects ([Eliasson et al. 2007](#); [Rosenstock et al. 2007](#); [Stenlöf et al. 2007](#); [Toplak et al. 2007](#)). In the pivotal

studies leading to the FDA approval of topiramate extended release plus phentermine for chronic weight management, topiramate monotherapy was superior to placebo for weight loss, and the drug combination was superior to either topiramate or phentermine monotherapy ([Alfaris et al. 2015](#)).

---

## Side Effects and Toxicology

---

The side-effect profile of topiramate may vary with the patient's illness, mood state, and concomitant medications.

### Common Side Effects

The most common side effects of topiramate in the initial dose-ranging studies in patients with epilepsy when used in combination with other antiepileptic drugs at dosages of 200–1,000 mg/day were related to the central nervous system and included dizziness, somnolence, psychomotor slowing, nervousness, paresthesias, ataxia, difficulty with memory, difficulty with concentration or attention, confusion, and speech disorders or related speech problems ([Langtry et al. 1997](#); [Shorvon 1996](#)). Other side effects were nystagmus, depression, nausea, diplopia, abnormal vision, anorexia, language problems, and tremor. When topiramate was used as monotherapy in patients with epilepsy, the most common side effects were dizziness, anxiety, paresthesias, insomnia, somnolence, myalgia, anorexia, nausea, dyspepsia, and diarrhea. The most common side effects of topiramate in the large registration trials for migraine headache (which used total daily dosages



of 50, 100, and 200 mg) were paresthesias, fatigue, memory difficulties, concentration/attention problems, and mood problems ([Bussone et al. 2006](#)). In the monotherapy trials in adult mania, paresthesias, decreased appetite, dry mouth, and weight loss were more common with topiramate than placebo ([Kushner et al. 2006](#)). In the obesity trials, events related to the central or peripheral nervous system or to psychiatric disorders were most commonly reported ([Rosenstock et al. 2007](#)). These included paresthesias; fatigue; difficulty with attention, concentration, and/or memory; taste perversion; and anorexia. Overall, paresthesias and cognitive complaints were the most troublesome adverse events ([van Passel et al. 2006](#)). A meta-analysis suggested that a dose-response relationship exists for dizziness, cognitive impairment, and fatigue ([Zaccara et al. 2008](#)).

The central nervous system and gastrointestinal effects of topiramate are usually mild to moderate in severity and often decrease or resolve with time or dosage reduction ([Meador et al. 2003](#); [Shorvon 1996](#)). Also, they may be minimized through slow titration of topiramate dosage ([Biton et al. 2001](#)). However, topiramate may be associated with more cognitive impairment than some of the other new antiepileptic drugs ([Martin et al. 1999](#); [Meador et al. 2003](#)).

## Infrequent Adverse Effects

Infrequent but serious side effects of topiramate include nephrolithiasis, an ocular syndrome of acute myopia with secondary angle-closure glaucoma, oligohydrosis and hyperthermia, and metabolic acidosis ([van Passel et al. 2006](#)). Mild hypokalemia, which usually is not clinically

significant, may also occur in about 10% of topiramate recipients ([Dell'Orto et al. 2014](#)).

The incidence of topiramate-associated nephrolithiasis has been estimated to be 1.5% ([Shorvon 1996](#)). In the epilepsy trials, more than 75% of the patients who developed renal stones elected to continue treatment with topiramate ([Reife et al. 2000](#)). Nephrolithiasis is thought to be related to topiramate's inhibition of carbonic anhydrase in the kidney ([Welch et al. 2006](#)).

The secondary angle-closure glaucoma associated with topiramate is characterized by acute onset of bilateral blurred vision and ocular pain ([Fraunfelder and Fraunfelder 2004](#); [Fraunfelder et al. 2004](#)). Ophthalmological findings include bilateral myopia, conjunctival hyperemia, anterior chamber shallowing, and increased intraocular pressure. Most cases have occurred within 1 month of topiramate initiation and fully resolve with drug discontinuation. Peripheral iridectomy and laser iridotomy are not effective. The syndrome has been attributed to sulfamate-induced ciliary body edema.

Oligohydrosis and hyperthermia occurring with topiramate can present as heat stroke or fever, may be related to exercise or high environmental temperature, can be fatal, is probably more common in children than in adults, and is reversible upon drug discontinuation ([Karachristianou et al. 2013](#)). Topiramate-induced metabolic acidosis is usually asymptomatic and associated with low bicarbonate, and to a lesser degree, increased chloride levels ([Dell'Orto et al. 2014](#); [Sciegienka et al. 2015](#)). Rarely, it presents with Kussmaul breathing or even altered mental status. It may be due to the carbonic anhydrase-inhibiting properties of topiramate, and it is also reversible upon drug discontinuation.

Because there were no clinically relevant changes in hepatic, renal, or hematological parameters in the registration trials of topiramate, laboratory monitoring was initially thought to be unnecessary ([Reife et al. 2000](#); [Sachdeo and Karia 2002](#)). In addition, no treatment-related changes were noted in physical or neurological examinations (except body weight loss), electrocardiograms, or ophthalmological or audiometric test results. However, because topiramate may cause metabolic acidosis and hypokalemia in some patients, it is now recommended that baseline and periodic serum bicarbonate and potassium levels be measured in patients receiving topiramate ([Dell'Orto et al. 2014](#); [Sachdeo and Karia 2002](#); [van Passel et al. 2006](#); [Welch et al. 2006](#)).

## Psychiatric Adverse Events

A growing concern is the psychiatric adverse-event profile of antiepileptic drugs in patients with epilepsy, including whether such drugs cause depression, suicidality, or psychosis. Thus, topiramate may be associated with depression in epilepsy patients, especially during rapid titration ([Mula and Sander 2007](#)). There are also isolated reports of topiramate's induction of mood and anxiety symptoms in psychiatric patients ([Damsa et al. 2006](#); [Klufas and Thompson 2001](#)). Moreover, one obesity study reported eight (6.2%) suicide-related events occurring in topiramate-treated subjects versus none in placebo-treated subjects ([Rosenstock et al. 2007](#)).

## Use in Pregnancy

Topiramate can cause fetal harm when given to pregnant women. Prenatal exposure to topiramate is associated with an increased risk of oral clefts ([Hunt et al. 2008](#)).

---

## Drug-Drug Interactions

---

The clearance of topiramate can be increased by the coadministration of hepatic enzyme-inducing drugs ([Bialer et al. 2004](#); [Gidal 2002](#); [Langtry et al. 1997](#); [Rosenfeld et al. 1997](#); [van Passel et al. 2006](#)). Thus, carbamazepine and phenytoin may substantially decrease topiramate levels.

Conversely, topiramate has mild enzyme-inducing properties and may enhance the metabolism of ethinyl estradiol. Available data suggest that at topiramate dosages of 200 mg/day or lower, this induction is insignificant, but at dosages greater than 200 mg/day, induction becomes dose dependent and occurs to a great extent ([Bialer et al. 2004](#)). Therefore, women taking combination oral contraceptive agents need to be counseled about this potential interaction.

Although there have been reports of topiramate causing increased lithium levels ([Abraham and Owen 2004](#)), this effect appears to be rarely clinically significant ([Bialer et al. 2004](#)).

---

## Conclusion

---

In sum, although topiramate does not have regulatory approval for a psychiatric disorder, considerable data suggest that the drug may be helpful in a wide range of

psychiatric conditions. In particular, topiramate appears efficacious in BED, bulimia nervosa, alcohol use disorder, and psychotropic-associated weight gain. It might also be efficacious for major depressive disorder, schizophrenia, and borderline personality disorder. Data on topiramate's efficacy in cocaine or methamphetamine use disorders, smoking cessation, and OCD have been mixed. Of note, there is no evidence to suggest that topiramate has acute anti-manic or long-term mood-stabilizing effects in bipolar disorder. The use of topiramate in psychiatric disorders, however, is limited by its adverse event profile.

---

## References

---

- Abraham G, Owen J: Topiramate can cause lithium toxicity. *J Clin Psychopharmacol* 24(5):565–567, 2004 15349023
- Afshar H, Roohafza H, Mousavi G, et al: Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol* 23(2):157–162, 2009 18515465
- Afshar H, Akuchekian S, Mahaky B, Zarean E: Topiramate augmentation in refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial. *J Res Med Sci* 19(10):976–981, 2014 25538783
- Alfaris N, Minnick AM, Hopkins CM, et al: Combination phentermine and topiramate extended release in the management of obesity. *Expert Opin Pharmacother* 16(8):1263–1274, 2015 25958964
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Anthenelli RM, Blom TJ, McElroy SL, et al: Preliminary evidence for gender-specific effects of topiramate as a

- potential aid to smoking cessation. *Addiction* 103(4):687-694, 2008 18339115
- Astrup A, Caterson I, Zelissen P, et al: Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res* 12(10):1658-1669, 2004 15536230
- Baltieri DA, Daró FR, Ribeiro PL, et al: Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction* 103(12):2035-2044, 2008 18855810
- Baltieri DA, Daró FR, Ribeiro PL, et al: Effects of topiramate or naltrexone on tobacco use among male alcohol-dependent outpatients. *Drug Alcohol Depend* 105(1-2):33-41, 2009 19595518
- Batki SL, Pennington DL, Lasher B, et al: Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: a randomized controlled pilot trial. *Alcohol Clin Exp Res* 38(8):2169-2177, 2014 25092377
- Behdani F, Hebrani P, Rezaei Ardani A, et al: Effect of topiramate augmentation in chronic schizophrenia: a placebo-controlled trial. *Arch Iran Med* 14(4):270-275, 2011 21726104
- Berlin HA, Koran LM, Jenike MA, et al: Double-blind, placebo-controlled trial of topiramate augmentation in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry* 72(5):716-721, 2011 20816027
- Berlin HA, Braun A, Simeon D, et al: A double-blind, placebo-controlled trial of topiramate for pathological gambling. *World J Biol Psychiatry* 14(2):121-128, 2013 21486110
- Bialer M, Doose DR, Murthy B, et al: Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* 43(12):763-780, 2004 15355124
- Biton V, Edwards KR, Montouris GD, et al; Topiramate TPS-TR Study Group: Topiramate titration and tolerability.

- Ann Pharmacother 35(2):173-179, 2001 11215835
- Brandes JL: Practical use of topiramate for migraine prevention. Headache 45 (suppl 1): S66-S73, 2005 15833092
- Bray GA, Hollander P, Klein S, et al: A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. Obes Res 11(6): 722-733, 2003 12805393
- Bussone G, Usai S, D'Amico D: Topiramate in migraine prophylaxis: data from a pooled analysis and open-label extension study. Neurol Sci 27 (suppl 2):S159-S163, 2006 16688622
- Claudino AM, de Oliveira IR, Appolinario JC, et al: Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. J Clin Psychiatry 68(9):1324-1332, 2007 17915969
- Damsa C, Warczyk S, Cailhol L, et al: Panic attacks associated with topiramate. J Clin Psychiatry 67(2):326-327, 2006 16566634
- DelBello MP, Findling RL, Kushner S, et al: A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 44(6):539-547, 2005 15908836
- Dell'Orto VG, Belotti EA, Goeggel-Simonetti B, et al: Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. Br J Clin Pharmacol 77(6):958-964, 2014 24219102
- Doose DR, Streeter AJ: Topiramate: chemistry, biotransformation, and pharmacokinetics, in Antiepileptic Drugs, 5th Edition. Edited by Levy RH, Mattson RH, Meldrum BS, et al. Philadelphia, PA, Lippincott Williams & Wilkins, 2002, pp 727-734
- Duggal HS, Singh I: Worsening of psychosis or topiramate-induced adverse event? Gen Hosp Psychiatry 26(3):245-247, 2004 15121357

- Eliasson B, Gudbjörnsdottir S, Cederholm J, et al: Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial. *Int J Obes* 31(7):1140-1147, 2007 17264849
- Elkashef A, Kahn R, Yu E, et al: Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. *Addiction* 107(7):1297-1306, 2012 22221594
- Fraunfelder FW, Fraunfelder FT: Adverse ocular drug reactions recently identified by the National Registry of Drug-Induced Ocular Side Effects. *Ophthalmology* 111(7):1275-1279, 2004 15234126
- Fraunfelder FW, Fraunfelder FT, Keates EU: Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 111(1):109-111, 2004 14711721
- Gidal BE: Topiramate: drug interactions, in *Antiepileptic Drugs*, 5th Edition. Edited by Levy RH, Mattson RH, Meldrum BS, et al. Philadelphia, PA, Lippincott Williams & Wilkins, 2002, pp 735-739
- Hedges DW, Reimherr FW, Hoopes SP, et al: Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 2: improvement in psychiatric measures. *J Clin Psychiatry* 64(12):1449-1454, 2003 14728106
- Herrero AI, Del Olmo N, González-Escalada JR, et al: Two new actions of topiramate: inhibition of depolarizing GABA(A)-mediated responses and activation of a potassium conductance. *Neuropharmacology* 42(2):210-220, 2002 11804617
- Hoopes SP, Reimherr FW, Hedges DW, et al: Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 1: improvement in binge and purge measures. *J Clin Psychiatry* 64(11):1335-1341, 2003 14658948



- Hunt S, Russell A, Smithson WH, et al; UK Epilepsy and Pregnancy Register: Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 71(4):272-276, 2008 18645165
- Johnson BA, Ait-Daoud N, Bowden CL, et al: Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 361(9370):1677-1685, 2003 12767733
- Johnson BA, Ait-Daoud N, Akhtar FZ, et al: Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: a randomized controlled trial. *Arch Intern Med* 165(14):1600-1605, 2005 16043677
- Johnson BA, Rosenthal N, Capece JA, et al; Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group: Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 298(14):1641-1651, 2007 17925516
- Johnson BA, Ait-Daoud N, Wang XQ, et al: Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA Psychiatry* 70(12):1338-1346, 2013 24132249
- Kaminski RM, Banerjee M, Rogawski MA: Topiramate selectively protects against seizures induced by ATPA, a GluR5 kainate receptor agonist. *Neuropharmacology* 46(8):1097-1104, 2004 15111016
- Kampman KM, Pettinati H, Lynch KG, et al: A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend* 75(3):233-240, 2004 15283944
- Kampman KM, Pettinati HM, Lynch KG, et al: A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug Alcohol Depend* 133(1):94-99, 2013 23810644
- Karachristianou S, Papamichalis E, Sarantopoulos A, et al: Hypohidrosis induced by topiramate in an adult patient.

- Epileptic Disord 15(2):203-206, 2013 23773932
- Kawasaki H, Tancredi V, D'Arcangelo G, et al: Multiple actions of the novel anticonvulsant drug topiramate in the rat subiculum in vitro. Brain Res 807(1-2):125-134, 1998 9757016
- Klufas A, Thompson D: Topiramate-induced depression (letter). Am J Psychiatry 158(10):1736, 2001 11579016
- Knapp CM, Ciraulo DA, Sarid-Segal O, et al: Zonisamide, topiramate, and levetiracetam: efficacy and neuropsychological effects in alcohol use disorders. J Clin Psychopharmacol 35(1):34-42, 2015 25427171
- Ko YH, Joe SH, Jung IK, et al: Topiramate as an adjuvant treatment with atypical antipsychotics in schizophrenic patients experiencing weight gain. Clin Neuropharmacol 28(4):169-175, 2005 16062095
- Kranzler HR, Covault J, Feinn R, et al: Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry 171(4):445-452, 2014 24525690
- Kucukgoncu S, Midura M, Tek C: Optimal management of night eating syndrome: challenges and solutions. Neuropsychiatr Dis Treat 11:751-760, 2015 25834450
- Kudin AP, Debska-Vielhaber G, Vielhaber S, et al: The mechanism of neuroprotection by topiramate in an animal model of epilepsy. Epilepsia 45(12):1478-1487, 2004 15571505
- Kushner SF, Khan A, Lane R, et al: Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. Bipolar Disord 8(1):15-27, 2006 16411977
- Kuzniecky R, Hetherington H, Ho S, et al: Topiramate increases cerebral GABA in healthy humans. Neurology 51(2):627-629, 1998 9710056
- Langtry HD, Gillis JC, Davis R: Topiramate: a review of its pharmacodynamic and pharmacokinetic properties and

- clinical efficacy in the management of epilepsy. *Drugs* 54(5):752-773, 1997 9360061
- Likhitsathian S, Uttawichai K, Booncharoen H, et al: Topiramate treatment for alcoholic outpatients recently receiving residential treatment programs: a 12-week, randomized, placebo-controlled trial. *Drug Alcohol Depend* 133(2):440-446, 2013 23906999
- Lindley SE, Carlson EB, Hill K: A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. *J Clin Psychopharmacol* 27(6):677-681, 2007 18004136
- Loew TH, Nickel MK, Muehlbacher M, et al: Topiramate treatment for women with borderline personality disorder: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 26(1):61-66, 2006 16415708
- Mariani JJ, Pavlicova M, Bisaga A, et al: Extended-release mixed amphetamine salts and topiramate for cocaine dependence: a randomized controlled trial. *Biol Psychiatry* 72(11):950-956, 2012 22795453
- Martin R, Kuzniecky R, Ho S, et al: Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 52(2):321-327, 1999 9932951
- McDaniel WW, Spiegel DR, Sahota AK: Topiramate effect in catatonia: a case series. *J Neuropsychiatry Clin Neurosci* 18(2): 234-238, 2006 16720802
- McElroy SL, Keck PE Jr: Topiramate, in *American Psychiatric Publishing Textbook of Psychopharmacology*, 3rd Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, American Psychiatric Publishing, 2004, pp 627-636
- McElroy SL, Arnold LM, Shapira NA, et al: Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am J Psychiatry* 160(2):255-261, 2003 12562571
- McElroy SL, Hudson JI, Capece JA, et al; Topiramate Binge Eating Disorder Research Group: Topiramate for the

treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol Psychiatry* 61(9):1039–1048, 2007 17258690

McElroy SL, Guerdjikova A, Keck PE Jr, et al: Antiepileptic drugs in obesity, psychotropic-associated weight gain, and eating disorders, in *Antiepileptic Drugs to Treat Psychiatric Disorders*. Edited by McElroy SL, Keck PE Jr, Post RM. New York, Informa Healthcare, 2008, pp 283–309

McIntyre RS, Mancini DA, McCann S, et al: Topiramate versus bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. *Bipolar Disord* 4(3):207–213, 2002 12180276

Meador KJ, Loring DW, Hulihan JF, et al; CAPSS-027 Study Group: Differential cognitive and behavioral effects of topiramate and valproate. *Neurology* 60(9): 1483–1488, 2003 12743236

Miller AD, Prost VM, Bookstaver PB, et al: Topiramate-induced myoclonus and psychosis during migraine prophylaxis. *Am J Health Syst Pharm* 67(14):1178–1180, 2010 20592323

Mohammadi B, Krampfl K, Cetinkaya C, et al: Interaction of topiramate with glycine receptor channels. *Pharmacol Res* 51(6):587–592, 2005 15829441

Mowla A, Kardeh E: Topiramate augmentation in patients with resistant major depressive disorder: a double-blind placebo-controlled clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry* 35(4):970–973, 2011 21291943

Mowla A, Khajeian AM, Sahraian A, et al: Topiramate augmentation in resistant OCD: a double-blind placebo-controlled clinical trial. *CNS Spectr* 15(11):613–617, 2010 24726048

Mula M, Sander JW: Negative effects of antiepileptic drugs on mood in patients with epilepsy. *Drug Saf* 30(7):555–

567, 2007 17604407

- Muscatello MR, Bruno A, Pandolfo G, et al: Topiramate augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. *J Psychopharmacol* 25(5):667-674, 2011 20615930
- Narula PK, Rehan HS, Unni KE, et al: Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophr Res* 118(1-3):218-223, 2010 20207521
- Nickel C, Lahmann C, Tritt K, et al: Topiramate in treatment of depressive and anger symptoms in female depressive patients: a randomized, double-blind, placebo-controlled study. *J Affect Disord* 87(2-3):243-252, 2005a 15985295
- Nickel C, Tritt K, Muehlbacher M, et al: Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord* 38(4):295-300, 2005b 16231337
- Nickel MK, Nickel C, Mitterlehner FO, et al: Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin Psychiatry* 65(11):1515-1519, 2004 15554765
- Nickel MK, Nickel C, Kaplan P, et al: Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. *Biol Psychiatry* 57(5):495-499, 2005a 15737664
- Nickel MK, Nickel C, Muehlbacher M, et al: Influence of topiramate on olanzapine-related adiposity in women: a random, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 25(3):211-217, 2005b 15876898
- Petroff OA, Hyder F, Rothman DL, et al: Topiramate rapidly raises brain GABA in epilepsy patients. *Epilepsia* 42(4):543-548, 2001 11440351
- Reife R, Pledger G, Wu S-C: Topiramate as add-on therapy: pooled analysis of randomized controlled trials in adults.

- Epilepsia 41 (suppl 1):S66-S71, 2000 10768304
- Rezaei F, Ghaderi E, Mardani R, et al: Topiramate for the management of methamphetamine dependence: a pilot randomized, double-blind, placebo-controlled trial. *Fundam Clin Pharmacol* 30(3):282-289, 2016 26751259
- Rho JM, Sankar R: The pharmacologic basis of antiepileptic drug action. *Epilepsia* 40(11):1471-1483, 1999 10565572
- Rosenfeld WE: Topiramate: a review of preclinical, pharmacokinetic, and clinical data. *Clin Ther* 19(6):1294-1308, 1997 9444441
- Rosenfeld WE, Doose DR, Walker SA, et al: Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* 38(3):317-323, 1997 9070594
- Rosenstock J, Hollander P, Gadde KM, et al; OBD-202 Study Group: A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. *Diabetes Care* 30(6):1480-1486, 2007 17363756
- Roy Chengappa KN, Schwarzman LK, Hulihan JF, et al: Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry* 67(11):1698-1706, 2006 17196048
- Roy Chengappa KN, Kupfer DJ, Parepally H, et al: A placebo-controlled, random-assignment, parallel-group pilot study of adjunctive topiramate for patients with schizoaffective disorder, bipolar type. *Bipolar Disord* 9(6):609-617, 2007 17845276
- Rubio G, Martínez-Gras I, Manzanares J: Modulation of impulsivity by topiramate: implications for the treatment of alcohol dependence. *J Clin Psychopharmacol* 29(6):584-589, 2009 19910725

- Sachdeo RC, Karia RM: Topiramate: adverse effects, in Antiepileptic Drugs, 5th Edition. Edited by Levy RH, Mattson RH, Meldrum BS, et al. Philadelphia, PA, Lippincott Williams & Wilkins, 2002, pp 760-764
- Sahraian A, Bigdeli M, Ghanizadeh A, et al: Topiramate as an adjuvant treatment for obsessive compulsive symptoms in patients with bipolar disorder: a randomized double blind placebo controlled clinical trial. J Affect Disord 166:201-205, 2014 25012432
- Schiffer WK, Gerasimov MR, Marsteller DA, et al: Topiramate selectively attenuates nicotine-induced increases in monoamine release. Synapse 42(3):196-198, 2001 11746717
- Sciegienka A, Argo T, Cantrell M, Alexander B: Association between topiramate use and serum bicarbonate levels in a veteran population. Ann Pharmacother 49(6):670-673, 2015 25829486
- Shank RP, Gardocki JF, Streeter AJ, et al: An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 41 (suppl 1):S3-S9, 2000 10768292
- Shorvon SD: Safety of topiramate: adverse events and relationships to dosing. Epilepsia 37 (suppl 2):S18-S22, 1996 8641242
- Simeone TA, Wilcox KS, White HS: Subunit selectivity of topiramate modulation of heteromeric GABA(A) receptors. Neuropharmacology 50(7):845-857, 2006 16490221
- Stenlöf K, Rössner S, Vercruysse F, et al; OBDM-003 Study Group: Topiramate in the treatment of obese subjects with drug-naïve type 2 diabetes. Diabetes Obes Metab 9(3):360-368, 2007 17391164
- Tiihonen J, Halonen P, Wahlbeck K, et al: Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. J Clin Psychiatry 66(8):1012-1015, 2005 16086616

- Tonstad S, Tykarski A, Weissgarten J, et al: Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension. *Am J Cardiol* 96(2):243-251, 2005 16018851
- Toplak H, Hamann A, Moore R, et al: Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Int J Obes* 31(1):138-146, 2007 16703004
- Tremblay A, Chaput J-P, Bérubé-Parent S, et al: The effect of topiramate on energy balance in obese men: a 6-month double-blind randomized placebo-controlled study with a 6-month open-label extension. *Eur J Clin Pharmacol* 63(2):123-134, 2007 17200837
- Tucker P, Trautman RP, Wyatt DB, et al: Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 68(2):201-206, 2007 17335317
- Umbricht A, DeFulio A, Winstanley EL, et al: Topiramate for cocaine dependence during methadone maintenance treatment: a randomized controlled trial. *Drug Alcohol Depend* 140:92-100, 2014 24814607
- van Passel L, Arif H, Hirsch LJ: Topiramate for the treatment of epilepsy and other nervous system disorders. *Expert Rev Neurother* 6(1):19-31, 2006 16466308
- Vivus: Qsymia: Prescribing information. Mountain View, CA, Vivus, Inc., October 2014. Available at: <https://qsymia.com/patient/include/media/pdf/prescribing-information.pdf>. Accessed July 3, 2016.
- Wauquier A, Zhou S: Topiramate: a potent anticonvulsant in the amygdala-kindled rat. *Epilepsy Res* 24(2):73-77, 1996 8796355
- Welch BJ, Graybeal D, Moe OW, et al: Biochemical and stone-risk profiles with topiramate treatment. *Am J*



- Kidney Dis 48(4):555-563, 2006 16997051
- White HS: Topiramate: mechanisms of action, in Antiepileptic Drugs, 5th Edition. Edited by Levy RH, Mattson RH, Meldrum BS, et al. Philadelphia, PA, Lippincott Williams & Wilkins, 2002, pp 719-726
- White HS: Molecular pharmacology of topiramate: managing seizures and preventing migraine. Headache 45 (suppl 1):S48-S56, 2005 15833090
- White HS, Brown SD, Woodhead JH, et al: Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. Epilepsia 41 (suppl 1):S17-S20, 2000 10768294
- White HS, Smith MD, Wilcox KS: Mechanisms of action of antiepileptic drugs. Int Rev Neurobiol 81:85-110, 2007 17433919
- Wilding J, Van Gaal L, Rissanen A, et al; OBES-002 Study Group: A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. Int J Obes Relat Metab Disord 28(11):1399-1410, 2004 15486569
- World Health Organization: International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Geneva, Switzerland, World Health Organization, 1993
- Zaccara G, Gangemi PF, Cincotta M: Central nervous system adverse effects of new antiepileptic drugs. A meta-analysis of placebo-controlled studies. Seizure 17(5): 405-421, 2008 18262442
- Zhang X, Velumian AA, Jones OT, et al: Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia 41 (suppl 1):S52-S60, 2000 10768302

# **Other Agents**

# CHAPTER 42

## Agents for Cognitive Disorders

Frank W. Brown, M.D.

Disruption of cholinergic neurotransmission and excitatory amino acids is correlated with the development of cognitive impairment and, specifically, Alzheimer's disease ([Mesulam 2004](#)). Multiple mechanisms exist that may account for the progression of cognitive impairment, including those related to cholinesterase, *N*-methyl-D-aspartate (NMDA), vascular disease, defective neurogenesis, and oxidative damage ([Aisen and Davis 1994](#); [Bartus et al. 1982](#); [Behl 1999](#); [Behl et al. 1992](#); [Crews and Masliah 2010](#); [Jick et al. 2000](#); [Kalaria et al. 1996](#); [Liu et al. 2015](#); [Selkoe 2000](#); [Terry and Buccafusco 2003](#); [Wolozin et al. 2000](#)). An outcome of the disruption of many neurotransmitter systems, cognitive impairment may occur at any time during the disease process as synaptic plasticity becomes impaired, degrading the efficiency of neuronal transmission ([Malik et al. 2007](#)). It is intuitive that the

earliest intervention prior to irreversible disease progression is optimal. Currently, it is unknown when the irreversible disease processes begin. The identification of specific markers that can guide clinicians in the initiation of prophylactic or abortive treatment prior to the development of cognitive or behavioral manifestations is highly desired. Continuing studies of circulating microRNAs in the cerebrospinal fluid and blood serum show promise as reliable biomarkers for early diagnosis of Alzheimer's disease (Kim et al. 2014). For early-onset autosomal dominant Alzheimer's disease, mutations in presenilin 1, presenilin 2, and amyloid precursor protein are known (Kim et al. 2014).

*Cognitive enhancer* is a general term that denotes a pharmacological or nutraceutical intervention that improves cognitive functioning in an impaired or normal brain by reversing or delaying underlying neuropathological changes within the brain or by modulating the existing neurochemistry to facilitate a desired performance differential. The molecular pathogenesis of cognitive impairment is not fully understood; thus, an ideal pharmacological agent has been difficult to develop. No single agent developed to date is ideally suited for this task; however, several agents have shown beneficial results. In this chapter, I review the established and the most promising potential cognitive enhancers.

---

## **Cholinesterase-Related Therapies**

---

Impairment of cholinergic neurotransmission, especially in the hippocampus and cerebral cortex (temporoparietal), has been clearly established over the past 40 years as a significant factor in the clinical signs of cognitive impairment, including those of Alzheimer's disease ([Davies and Maloney 1976](#); [Mesulam 2004](#); [Whitehouse et al. 1982](#)). Butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) are the two main types of cholinesterase present in the brain. The development of AChE inhibitors (AChEIs) to increase acetylcholine levels in the brain for enhanced synaptic transmission has been successful, with marginal positive clinical outcomes to date ([Birks 2006](#); [Tan et al. 2014](#); [Thompson et al. 2004](#)). Four AChEIs have been marketed in the United States for cognitive therapy: tacrine, donepezil, rivastigmine, and galantamine. These pharmaceuticals are primarily for symptomatic relief and have limited current value in stopping or reversing the disease process. A significant number of AChEI nonresponders exist ([Jones 2003](#)). Improvements in cognitive functioning have been shown with AChEIs without major differences in their efficacy ([Birks 2006](#); [Colović et al. 2013](#); [Seltzer 2006](#); [Thompson et al. 2004](#)). There are limited data to support the use of these agents in mild neurocognitive disorder ([Cooper et al. 2013](#)). The major side effects of AChEIs are gastrointestinal.

## Recommendations

Tacrine is no longer recommended for routine clinical use. Donepezil, rivastigmine, and galantamine are recommended with or without other cognitive enhancers (e.g., memantine). Tolerability is improved by slow dosage

titration. All cholinesterase inhibitors have significant potential for side effects; it is difficult to determine whether one AChEI has a significantly better side-effect profile than another AChEI, given individual patients' variability. Switching AChEIs can be a reasonable treatment strategy if lack of efficacy or tolerability is an issue.

## Donepezil

Donepezil, a piperidine-based, reversible, noncompetitive AChEI with a plasma half-life of about 70 hours, was approved for the treatment of mild to moderate Alzheimer's disease in the United States in 1996 and for severe Alzheimer's disease in 2006. Donepezil is given once daily in 5-mg, 10-mg, or 23-mg doses; 5-mg therapy is only slightly less effective than 10-mg therapy and is an appropriate regimen for mild to moderate Alzheimer's disease, especially when tolerability is an issue ([Birks and Harvey 2006](#)). For moderate to severe Alzheimer's disease, 10-mg or 23-mg therapy is indicated; the 23-mg dose is generally initiated after a patient has been stable for at least 3 months on the 10-mg dose. Donepezil is also available as an orally disintegrating tablet in 5-mg and 10-mg doses. A formulation combining memantine extended-release and donepezil is now available.

Donepezil has shown benefit in treating mild, moderate, and severe Alzheimer's disease ([Birks and Harvey 2006](#); [Wallin et al. 2007](#)) and has been studied for efficacy in patients with mild neurocognitive disorder ([Chen et al. 2006](#); [Pa et al. 2013](#); [Seltzer 2007](#)). A meta-analysis of pooled data on the use of donepezil indicated that caution is warranted in its use to treat mild neurocognitive disorder due to modest treatment effects with significant side effects ([Birks and Flicker 2006](#)). In another review of 41 studies,

donepezil and other AChEIs were not recommended for use in mild neurocognitive disorder ([Cooper et al. 2013](#)).

## Rivastigmine

Rivastigmine, a carbamyl derivative, is a slowly reversible AChEI and BChE inhibitor (BChEI) with an elimination half-life of about 2 hours. It was approved in 2000 for use in the United States and is indicated for the treatment of mild to moderate dementia of Alzheimer's disease and Parkinson's disease. Rivastigmine inhibits the G1 isoenzyme of AChE selectively up to four times more potently than it does the G4 isoenzyme ([Enz et al. 1993](#)). This unique compound with its BChEI properties has been postulated to be of greater benefit than other AChEIs in the treatment of Alzheimer's disease because BChE activity increases in the hippocampus and cortex while AChE activity diminishes ([Tasker et al. 2005](#)); to date, this has not been conclusively shown to be of clinical significance ([Noetzli and Eap 2013](#)). However, as a therapy involving multiple target receptor sites, this agent does have a theoretical advantage over single-target approaches. A recent Cochrane review noted that rivastigmine appears to be beneficial for the treatment of mild to moderate Alzheimer's disease ([Birks and Grimley Evans 2015](#)). Rivastigmine capsules are available in 1.5-mg, 3-mg, 4.5-mg, and 6-mg doses. A rivastigmine skin patch received U.S. Food and Drug Administration approval in 2007; gastrointestinal side effects are reduced in frequency with this drug delivery system. An oral solution is also available.

For Alzheimer's disease, rivastigmine is initiated at 1.5 mg taken orally twice daily. If tolerated, the dosage is increased every 2 weeks, first to 3 mg twice daily and then to 4.5 mg twice daily, up to a maximum dosage of 6 mg

twice daily. Transdermal therapy is initiated at one 4.6-mg skin patch applied daily for at least 4 weeks, at which time the dosage may be increased to the 9.5-mg daily patch. For Parkinson's disease, the oral rivastigmine dosage is increased as done in Alzheimer's disease, except that the minimum interval is extended to every 4 weeks (rather than every 2 weeks), up to a maximum dosage of 6 mg twice daily.

## **Galantamine**

Galantamine hydrobromide, a tertiary alkaloid, is a specific, competitive, and reversible AChEI with a plasma half-life of 6–8 hours that was first marketed in the United States in 2001 as a treatment for mild to moderate dementia of Alzheimer's disease. Galantamine is unique in that it modulates neuronal nicotinic receptors ([Coyle and Kershaw 2001](#)). Whether this nicotinic receptor modulation imparts any significant clinical benefit in disease modification remains unknown. Oral dosing is initiated at 4 mg twice daily, with an increase after a minimum of 4 weeks to 8 mg twice daily as tolerated. The optimal dosage range is 16–24 mg/day. The extended-release galantamine formulation for once-daily dosing has efficacy and side effects similar to those of the twice-daily dosing formulation; it is generally initiated at a dosage of 8 mg/day (taken in the morning), increased to 16 mg/day after a minimum interval of 4 weeks, and (if tolerated after a minimum of 4 additional weeks) increased to 24 mg/day. An oral suspension is available as well. Pooled data from early trials in patients with mild cognitive impairment showed significantly higher rates of death due to bronchial carcinoma, cerebrovascular disorder/syncope, myocardial infarction, and suicide in the galantamine treatment groups ([Cusi et al. 2007](#); [Loy and](#)



[Schneider 2006](#)), although the use of cholinesterase inhibitors, including galantamine, was found to reduce the risk of myocardial infarction and death in a different study ([Nordström et al. 2013](#)). One double-blind, placebo-controlled trial of galantamine with antipsychotic medication in the treatment of subjects with schizophrenia did not show significant benefit, although there was a trend toward improvement in several cognitive domains ([Lee et al. 2007](#)). Galantamine combined with memantine is being actively studied for its potential to improve cognition in schizophrenia ([Koola 2016](#); [Koola et al. 2014](#)).

## Other Agents

Physostigmine, a reversible inhibitor of BChE and AChE, is poorly tolerated due to multiple gastrointestinal side effects, especially nausea and vomiting, and has a very short half-life.

Huperzine alpha (more commonly known as huperzine A) is sold in the United States as a dietary supplement for cognitive enhancement and is a slow, reversible inhibitor of AChE. Huperzine A is believed to have neuroprotective effects by reducing neuronal cell death caused by glutamate ([Ved et al. 1997](#)). The combination of other AChEIs with huperzine A may exacerbate gastrointestinal side effects; patients' usage of this over-the-counter supplement should be monitored, especially if other AChEIs are considered for treatment. ZT-1, a novel huperzine A analogue, is being investigated as an alternative to huperzine A ([Jia et al. 2013](#)).

Metrifonate, a long-acting irreversible cholinesterase inhibitor, was tested in clinical trials, but further development was discontinued after a higher-than-expected

incidence of neuromuscular dysfunction and respiratory paralysis was found.

Selective and nonselective neuronal nicotinic receptor agonists have shown statistically significant cognitive enhancement in young, healthy subjects and mixed results in subjects with Alzheimer's disease ([Dunbar et al. 2007](#); [Frölich et al. 2011](#); [Lombardo and Maskos 2015](#); [Newhouse et al. 1997](#); [Potter et al. 1999](#); [Sunderland et al. 1988](#)). More recent studies have found potential neuroprotective effects from analogues of nicotine and cotinine, a nicotine metabolite with fewer side effects than nicotine ([Gao et al. 2014](#)).

---

## **N-Methyl-D-Aspartate-Related Therapies**

---

Glutamate is an agonist of kainate, NMDA, and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Neuronal plasticity of memory and learning is influenced by glutamate's direct modulation of the NMDA postsynaptic receptor; glutamate acts as an excitatory neurotransmitter activating the NMDA receptor. Glutamate excess results in neurotoxicity, affecting cognitive functioning ([Koch et al. 2005](#)).

## **Recommendations**

Memantine appears to reduce the level of cognitive impairment in patients with moderate to severe Alzheimer's disease. Memantine in combination with an AChEI is an

appropriate consideration for improvement in cognition and behavior.

## **Memantine**

Memantine is a noncompetitive NMDA receptor antagonist approved in the United States for treating moderate to severe Alzheimer's disease. The NMDA receptor modulates memory function. Memantine's low-affinity antagonism of glutamate (which has been linked to neurodegeneration and excitotoxicity) may protect against neurotoxicity ([Lipton and Rosenberg 1994](#)). Memantine has been shown to be effective in reducing the level of cognitive impairment in patients with moderate to severe Alzheimer's disease ([Bullock 2006](#); [Nakamura et al. 2014](#); [Reisberg et al. 2003](#)).

Memantine is available in tablets, in extended-release capsules, and as an oral solution; dosing should be adjusted for patients with moderate or severe renal impairment (target of 14 mg/day). It is recommended that memantine tablets be initiated at a dosage of 5 mg/day for 1 week, and increased weekly by 5 mg/day up to a target dosage of 20 mg/day. Memantine tablets are generally given in twice-daily doses, although the elimination half-life ranges from 60 to 80 hours. Memantine is available as an extended-release capsule (7 mg, 14 mg, 21 mg, and 28 mg); it is recommended that memantine capsules be initiated at a dosage of 7 mg/day for 1 week, increasing by 7 mg after a minimum of 1 week to 14 mg/day up to a target dosage of 28 mg/day. Memantine extended-release capsules are given in once-daily dosing. Memantine capsules may be opened and the contents sprinkled on applesauce.

## **Memantine Combination Therapy**

Memantine in combination with an AChEI has been shown to improve cognitive domains significantly and to ameliorate symptoms of behavioral dyscontrol (agitation/aggression, eating/appetite, irritability/lability) ([Cummings et al. 2006](#); [Schmidt et al. 2015](#); [Tariot et al. 2004](#)). Given the disruption of multiple neurotransmitter systems and pathways in Alzheimer's disease and other cognitive disorders, the use of adjunctive cognition-enhancing medications is understandable ([Grossberg et al. 2006](#); [Koola et al. 2014](#)). The specific neurobiological deficits that may be affected by a pharmacological or nutraceutical intervention should be considered. In 2014, fixed-dose combinations of extended-release memantine (14 mg or 28 mg) and donepezil (10 mg) became available. Patients without severe renal impairment who are currently taking donepezil 10 mg once daily and memantine 10 mg twice daily or 28 mg extended-release once daily may be started on the memantine 28 mg/donepezil 10 mg combination tablet (taken once daily in the evening).

---

## **Vascular and Inflammation-Related Therapies**

---

Major known modifiable risk factors for vascular cognitive impairment (with or without dementia) include diabetes mellitus, hypertension, cardiac ischemia, atrial fibrillation, smoking, hyperlipidemia, and peripheral vascular disease ([Desmond et al. 1993](#); [Rockwood et al. 1997](#)). Controversial risk factors include hyperhomocysteinemia. Established vascular therapeutic interventions have included low-dose aspirin and other antiplatelet agents, anti-coagulation

agents, antihypertensives, aggressive management of diabetes mellitus, carotid endarterectomy for selected patients, and treatment of hyperlipidemia. There is a significant overlap of patients with vascular cognitive impairment and those with Alzheimer's disease ([Gearing et al. 1995](#); [O'Brien 1994](#)). Cholinergic receptors (muscarinic and nicotinic) are known modulators of cerebral blood flow ([Schwarz et al. 1999](#); [Zhang et al. 1998](#)). Ischemia-induced NMDA stimulation may cause further cognitive impairment.

A meta-analysis of four randomized, placebo-controlled studies of AChEIs to treat vascular dementia—two with donepezil and two with galantamine—showed statistically significant cognitive enhancement even though the treatment effect was less than what has been observed in Alzheimer's disease patients ([Birks and Flicker 2007](#)). In addition, the authors analyzed pooled results from memantine studies and found statistically significant improvement of cognitive functioning with memantine treatment in patients with vascular impairment similar to that seen with the AChEIs ([Birks and Flicker 2007](#)). A Cochrane review indicated that donepezil in doses of either 5 mg or 10 mg improves both functional ability and cognitive symptoms in patients with mild to moderate vascular cognitive impairment; donepezil was well tolerated in this analysis ([Malouf and Birks 2004](#)). A Cochrane review of the use of galantamine to treat vascular cognitive impairment showed statistically significant results in terms of cognition and executive function with galantamine versus placebo in one study but not in a second study that had fewer subjects; gastrointestinal side effects were noted to be higher in galantamine recipients ([Craig and Birks 2006](#)). Small but clinically detectable treatment effects have been found for donepezil therapy in vascular dementia

([Rockwood et al. 2013](#)). A Cochrane review indicated that rivastigmine had some evidence of benefit in vascular cognitive impairment ([Birks et al. 2013](#)).

## Recommendations

AChEIs appear to have a valid role in the treatment of vascular cognitive impairment. Combination therapy is an important consideration, especially with other known vascular risk modifiers, including aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and cytidine 5'-diphosphocholine (CDP-choline). Randomized controlled trials do not currently support the use of aspirin or other NSAIDs for the treatment of vascular cognitive impairment ([Jaturapatporn et al. 2012](#)). The active use of statins for the prevention and treatment of vascular cognitive impairment is currently not well supported by the literature; however, research with statins remains very active in this pursuit ([McGuinness et al. 2016](#)). Aspirin remains a cornerstone first-line intervention for decreasing potential cardiovascular comorbidity; aspirin may have a future role as a combination therapy with cognitive enhancers.

---

## Other Therapies

---

Antioxidant-related treatment for cognitive impairment remains poorly supported by placebo-controlled, double-blind studies. *Ginkgo biloba* could be classified within several potential treatment categories, including antioxidants, nutraceuticals, cholinergic agents, and

vasodilators; most studies have shown no to only marginal benefit for this agent ([Laws et al. 2012](#)). Vitamin E (including tocopherols and tocotrienols), vitamin C, and carotenoids have antioxidant properties; however, reports of benefit in treating patients with cognitive impairment are mixed. Although antioxidants may have potential as a combination therapy modality, further research is required before endorsing specific treatment recommendations with current antioxidants.

Various other agents have been tested and studied for their potential to improve cognitive impairment; these include secretase inhibitors, tramiprosate, modafinil, hormone replacement therapy, nutraceuticals (*Rubia cordifolia*, *Salvia lavandulaefolia*, *Rosmarinus officinalis*, and *Melissa officinalis*), dehydro-3-epiandrosterone (DHEA), aniracetam, piracetam, latrepirdine, and unifiram. Currently, no recommendations can be made for use of any of these agents as monotherapy or combination therapy.

Antiamyloid immunization may provide one of the greatest opportunities to prevent amyloid- $\beta$  deposition. Immunization strategies generally focus on active or passive immunization and direct central nervous system delivery of anti-amyloid- $\beta$  antibodies. Active immunization with  $\beta$ -amyloid antibodies can reduce plaque formation ([Lemere et al. 2006](#); [Singh et al. 2012](#); [Solomon 2006](#)). Passive immunization with monoclonal antibodies, preparations of immunoconjugates, or entire Alzheimer's disease-associated immunogenes shows promise for treating cognitive impairment due to Alzheimer's disease and may be safer than active immunization ([Geylis and Steinitz 2006](#); [Marciani 2015](#); [Solomon 2007](#)). Active and passive immunization may cause microhemorrhages, and further research continues to seek safer vaccines.

---

# Conclusion

---

The molecular pathogenesis of nerve cell death remains elusive, especially as it relates to the onset and progression of cognitive impairment. Alzheimer's disease and other types of cognitive impairment represent a wide spectrum of neurosystem dysfunction, and no single treatment modality yet found is sufficient to address the global apoptosis and degeneration that occur. Due to the multiple types of neurochemical and substructure dysfunction occurring in cognitive impairment, multiple-drug interventions will likely be required ([Campos et al. 2016](#); [Siskou et al. 2007](#); [Sunderland et al. 1992](#)).

Future studies will explore second-messenger modulation, inhibition of the synthesis of amyloid- $\beta$  using a mimic of the prion protein to inhibit  $\beta$ -secretase cleavage of the amyloid precursor protein, amyloid plaque sheet breakers, AMPA receptor modulators, hyperactive signaling pathway blockers, epigenetic drug candidates, and the role of  $\sigma_1$ -receptor agonists and selective neuronal nicotinic receptor agonists ([Crews and Masliah 2010](#); [Parkin et al. 2007](#); [Rose et al. 2005](#); [Sarter 2006](#)). Currently, the AChEIs and memantine are appropriate choices for slowing the progression of cognitive impairment. Several other promising agents are likely to become available within the next decade.

---

# References

---

Aisen PS, Davis KL: Inflammatory mechanisms in Alzheimer's disease: implications for therapy. *Am J*



- Psychiatry 151(8): 1105-1113, 1994 7518651
- Bartus RT, Dean RL 3rd, Beer B, et al: The cholinergic hypothesis of geriatric memory dysfunction. Science 217(4558):408-414, 1982 7046051
- Behl C: Vitamin E and other antioxidants in neuroprotection. Int J Vitam Nutr Res 69(3):213-219, 1999 10389030
- Behl C, Davis J, Cole GM, et al: Vitamin E protects nerve cells from amyloid beta protein toxicity. Biochem Biophys Res Commun 186(2):944-950, 1992 1497677
- Birks J: Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev (1):CD005593, 2006 16437532
- Birks J, Flicker L: Donepezil for mild cognitive impairment. Cochrane Database Syst Rev (3):CD006104, 2006 16856114
- Birks J, Flicker L: Investigational treatment for vascular cognitive impairment. Expert Opin Investig Drugs 16(5):647-658, 2007 17461738
- Birks JS, Grimley Evans J: Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev (4):CD001191, 2015 25858345
- Birks J, Harvey RJ: Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev (1):CD001190, 2006 16437430
- Birks J, McGuinness B, Craig D: Rivastigmine for vascular cognitive impairment. Cochrane Database Syst Rev (5):CD004744, 2013 23728651
- Bullock R: Efficacy and safety of memantine in moderate-to-severe Alzheimer disease: the evidence to date. Alzheimer Dis Assoc Disord 20(1):23-29, 2006 16493232
- Campos C, Rocha NB, Vieira RT, et al: Treatment of cognitive deficits in Alzheimer's disease: a psychopharmacological review. Psychiatr Danub 28(1):2-12, 2016 26938815

- Chen X, Magnotta VA, Duff K, et al: Donepezil effects on cerebral blood flow in older adults with mild cognitive deficits. *J Neuropsychiatry Clin Neurosci* 18(2):178-185, 2006 16720794
- Colović MB, Krstić DZ, Lazarević-Pašti TD, et al: Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr Neuropharmacol* 11(3):315-335, 2013 24179466
- Cooper C, Li R, Lyketsos C, et al: Treatment for mild cognitive impairment: systematic review. *Br J Psychiatry* 203(3):255-264, 2013 24085737
- Coyle J, Kershaw P: Galantamine, a cholinesterase inhibitor that allosterically modulates nicotinic receptors: effects on the course of Alzheimer's disease. *Biol Psychiatry* 49(3):289-299, 2001 11230880
- Craig D, Birks J: Galantamine for vascular cognitive impairment. *Cochrane Database Syst Rev* (1):CD004746, 2006 16437493
- Crews L, Masliah E: Molecular mechanisms of neurodegeneration in Alzheimer's disease. *Hum Mol Genet* 19(R1):R12-R20, 2010 20413653
- Cummings JL, Schneider E, Tariot PN, et al; Memantine MEM-MD-02 Study Group: Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology* 67(1):57-63, 2006 16832078
- Cusi C, Cantisani TA, Celani MG, et al; Cochrane Neurological Network: Galantamine for Alzheimer's disease and mild cognitive impairment. *Neuroepidemiology* 28(2):116-117, 2007 17409773
- Davies P, Maloney AJ: Selective loss of central cholinergic neurons in Alzheimer's disease (letter). *Lancet* 2(8000):1403, 1976 63862
- Desmond DW, Tatemichi TK, Paik M, et al: Risk factors for cerebrovascular disease as correlates of cognitive

- function in a stroke-free cohort. *Arch Neurol* 50(2):162-166, 1993 8431135
- Dunbar G, Boeijinga PH, Demazières A, et al: Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. *Psychopharmacology (Berl)* 191(4):919-929, 2007 17225162
- Enz A, Amstutz R, Boddeke H, et al: Brain selective inhibition of acetylcholinesterase: a novel approach to therapy for Alzheimer's disease. *Prog Brain Res* 98:431-438, 1993 8248533
- Frölich L, Ashwood T, Nilsson J, et al; Sirocco Investigators: Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. *J Alzheimers Dis* 24(2):363-374, 2011 21258153
- Gao J, Adam BL, Terry AV Jr: Evaluation of nicotine and cotinine analogs as potential neuroprotective agents for Alzheimer's disease. *Bioorg Med Chem Lett* 24(6):1472-1478, 2014 24581918
- Gearing M, Mirra SS, Hedreen JC, et al: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. *Neurology* 45(3 Pt 1):461-466, 1995 7898697
- Geylis V, Steinitz M: Immunotherapy of Alzheimer's disease (AD): from murine models to anti-amyloid beta (Abeta) human monoclonal antibodies. *Autoimmun Rev* 5(1):33-39, 2006 16338209
- Grossberg GT, Edwards KR, Zhao Q: Rationale for combination therapy with galantamine and memantine in Alzheimer's disease. *J Clin Pharmacol* 46 (7 suppl 1):17S-26S, 2006 16809811
- Jaturapatporn D, Isaac MG, McCleery J, Tabet N: Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease. *Cochrane Database Syst Rev* (2):CD006378, 2012 22336816

- Jia JY, Zhao QH, Liu Y, et al: Phase I study on the pharmacokinetics and tolerance of ZT-1, a prodrug of huperzine A, for the treatment of Alzheimer's disease. *Acta Pharmacol Sin* 34(7):976-982, 2013 23624756
- Jick H, Zornberg GL, Jick SS, et al: Statins and the risk of dementia. *Lancet* 356(9242): 1627-1631, 2000 11089820
- Jones RW: Have cholinergic therapies reached their clinical boundary in Alzheimer's disease? *Int J Geriatr Psychiatry* 18 (suppl 1):S7-S13, 2003 12973745
- Kalaria RN, Cohen DL, Premkumar DR: Cellular aspects of the inflammatory response in Alzheimer's disease. *Neurodegeneration* 5(4):497-503, 1996 9117569
- Kim DH, Yeo SH, Park JM, et al: Genetic markers for diagnosis and pathogenesis of Alzheimer's disease. *Gene* 545(2):185-193, 2014 24838203
- Koch HJ, Uyanik G, Fischer-Barnicol D: Memantine: a therapeutic approach in treating Alzheimer's and vascular dementia. *Curr Drug Targets CNS Neurol Disord* 4(5):499-506, 2005 16266284
- Koola MM: Kynurenine pathway and cognitive impairments in schizophrenia: pharmacogenetics of galantamine and memantine. *Schizophr Res Cogn* 4:4-9, 2016 27069875
- Koola MM, Buchanan RW, Pillai A, et al: Potential role of the combination of galantamine and memantine to improve cognition in schizophrenia. *Schizophr Res* 157(1-3):84-89, 2014 24878431
- Laws KR, Sweetnam H, Kondel TK: Is Ginkgo biloba a cognitive enhancer in healthy individuals? A meta-analysis. *Hum Psychopharmacol* 27(6):527-533, 2012 23001963
- Lee SW, Lee JG, Lee BJ, et al: A 12-week, double-blind, placebo-controlled trial of galantamine adjunctive treatment to conventional antipsychotics for the cognitive impairments in chronic schizophrenia. *Int Clin Psychopharmacol* 22(2):63-68, 2007 17293705

- Lemere CA, Maier M, Jiang L, et al: Amyloid-beta immunotherapy for the prevention and treatment of Alzheimer disease: lessons from mice, monkeys, and humans. *Rejuvenation Res* 9(1):77-84, 2006 16608400
- Lipton SA, Rosenberg PA: Excitatory amino acids as a final common pathway for neurologic disorders. *N Engl J Med* 330(9):613-622, 1994 7905600
- Liu W, Wong A, Law AC, et al: Cerebrovascular disease, amyloid plaques, and dementia. *Stroke* 46(5):1402-1407, 2015 25765727
- Lombardo S, Maskos U: Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment. *Neuropharmacology* 96(Pt B):255-262, 2015 25514383
- Loy C, Schneider L: Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev* (1):CD001747, 2006 16437436
- Malik R, Sangwan A, Saihgal R, et al: Towards better brain management: nootropics. *Curr Med Chem* 14(2):123-131, 2007 17266573
- Malouf R, Birks J: Donepezil for vascular cognitive impairment. *Cochrane Database Syst Rev* (1):CD004395, 2004 14974068
- Marciani DJ: Alzheimer's disease vaccine development: a new strategy focusing on immune modulation. *J Neuroimmunol* 287:54-63, 2015 26439962
- McGuinness B, Craig D, Bullock R, Passmore P: Statins for the treatment of dementia. *Cochrane Database Syst Rev* (1):CD003160, 2016 26727124
- Mesulam M: The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learn Mem* 11(1):43-49, 2004 14747516
- Nakamura Y, Kitamura S, Homma A, et al: Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in

- Japan. *Expert Opin Pharmacother* 15(7):913-925, 2014 24673497
- Newhouse PA, Potter A, Levin ED: Nicotinic system involvement in Alzheimer's and Parkinson's diseases. Implications for therapeutics. *Drugs Aging* 11(3):206-228, 1997 9303280
- Noetzli M, Eap CB: Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. *Clin Pharmacokinet* 52(4):225-241, 2013 23408070
- Nordström P, Religa D, Wimo A, et al: The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease. *Eur Heart J* 34(33):2585-2591, 2013 23735859
- O'Brien MD: How does cerebrovascular disease cause dementia? *Dementia* 5(3-4):133-136, 1994 8087167
- Pa J, Berry AS, Compagnone M, et al: Cholinergic enhancement of functional networks in older adults with mild cognitive impairment. *Ann Neurol* 73(6):762-773, 2013 23447373
- Parkin ET, Watt NT, Hussain I, et al: Cellular prion protein regulates beta-secretase cleavage of the Alzheimer's amyloid precursor protein. *Proc Natl Acad Sci U S A* 104(26):11062-11067, 2007 17573534
- Potter A, Corwin J, Lang J, et al: Acute effects of the selective cholinergic channel activator (nicotinic agonist) ABT-418 in Alzheimer's disease. *Psychopharmacology (Berl)* 142(4):334-342, 1999 10229057
- Reisberg B, Doody R, Stöffler A, et al; Memantine Study Group: Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* 348(14):1333-1341, 2003 12672860
- Rockwood K, Ebly E, Hachinski V, et al: Presence and treatment of vascular risk factors in patients with

- vascular cognitive impairment. Arch Neurol 54(1):33-39, 1997 9006411
- Rockwood K, Mitnitski A, Black SE, et al; VASPECT study investigators: Cognitive change in donepezil treated patients with vascular or mixed dementia. Can J Neurol Sci 40(4):564-571, 2013 23786741
- Rose GM, Hopper A, De Vivo M, et al: Phosphodiesterase inhibitors for cognitive enhancement. Curr Pharm Des 11(26):3329-3334, 2005 16250839
- Sarter M: Preclinical research into cognition enhancers. Trends Pharmacol Sci 27(11): 602-608, 2006 16997388
- Schmidt R, Hofer E, Bouwman FH, et al: EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. Eur J Neurol 22(6):889-898, 2015 25808982
- Schwarz RD, Callahan MJ, Coughenour LL, et al: Milameline (CI-979/RU35926): a muscarinic receptor agonist with cognition-activating properties: biochemical and in vivo characterization. J Pharmacol Exp Ther 291(2):812-822, 1999 10525104
- Selkoe DJ: Toward a comprehensive theory for Alzheimer's disease. Hypothesis: Alzheimer's disease is caused by the cerebral accumulation and cytotoxicity of amyloid beta-protein. Ann N Y Acad Sci 924:17-25, 2000 11193794
- Seltzer B: Cholinesterase inhibitors in the clinical management of Alzheimer's disease: importance of early and persistent treatment. J Int Med Res 34(4):339-347, 2006 16989488
- Seltzer B: Donepezil: an update. Expert Opin Pharmacother 8(7):1011-1023, 2007 17472546
- Singh S, Kushwah AS, Singh R, et al: Current therapeutic strategy in Alzheimer's disease. Eur Rev Med Pharmacol Sci 16(12): 1651-1664, 2012 23161037
- Siskou IC, Rekka EA, Kourounakis AP, et al: Design and study of some novel ibuprofen derivatives with potential

- nootropic and neuroprotective properties. *Bioorg Med Chem* 15(2):951-961, 2007 17126019
- Solomon B: Alzheimer's disease immunotherapy: from in vitro amyloid immunomodulation to in vivo vaccination. *J Alzheimers Dis* 9 (3 suppl):433-438, 2006 16914882
- Solomon B: Clinical immunologic approaches for the treatment of Alzheimer's disease. *Expert Opin Investig Drugs* 16(6):819-828, 2007 17501694
- Sunderland T, Tariot PN, Newhouse PA: Differential responsivity of mood, behavior, and cognition to cholinergic agents in elderly neuropsychiatric populations. *Brain Res* 472(4):371-389, 1988 3066441
- Sunderland T, Molchan S, Lawlor B, et al: A strategy of "combination chemotherapy" in Alzheimer's disease: rationale and preliminary results with physostigmine plus deprenyl. *Int Psychogeriatr* 4 (suppl 2):291-309, 1992 1288668
- Tan CC, Yu JT, Wang HF, et al: Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 41(2):615-631, 2014 24662102
- Tariot PN, Farlow MR, Grossberg GT, et al; Memantine Study Group: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 291(3):317-324, 2004 14734594
- Tasker A, Perry EK, Ballard CG: Butyrylcholinesterase: impact on symptoms and progression of cognitive impairment. *Expert Rev Neurother* 5(1):101-106, 2005 15853480
- Terry AV Jr, Buccafusco JJ: The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. *J Pharmacol Exp Ther* 306(3):821-827, 2003 12805474



- Thompson S, Lanctôt KL, Herrmann N: The benefits and risks associated with cholinesterase inhibitor therapy in Alzheimer's disease. *Expert Opin Drug Saf* 3(5):425-440, 2004 15335298
- Ved HS, Koenig ML, Dave JR, et al: Huperzine A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamate. *Neuroreport* 8(4): 963-968, 1997 9141073
- Wallin AK, Andreasen N, Eriksson S, et al; Swedish Alzheimer Treatment Study Group: Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. *Dement Geriatr Cogn Disord* 23(3):150-160, 2007 17312368
- Whitehouse PJ, Price DL, Struble RG, et al: Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 215(4537):1237-1239, 1982 7058341
- Wolozin B, Kellman W, Ruosseau P, et al: Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 57(10):1439-1443, 2000 11030795
- Zhang W, Edvinsson L, Lee TJ: Mechanism of nicotine-induced relaxation in the porcine basilar artery. *J Pharmacol Exp Ther* 284(2):790-797, 1998 9454828

# CHAPTER 43

## Sedative-Hypnotics

Seiji Nishino, M.D., Ph.D.

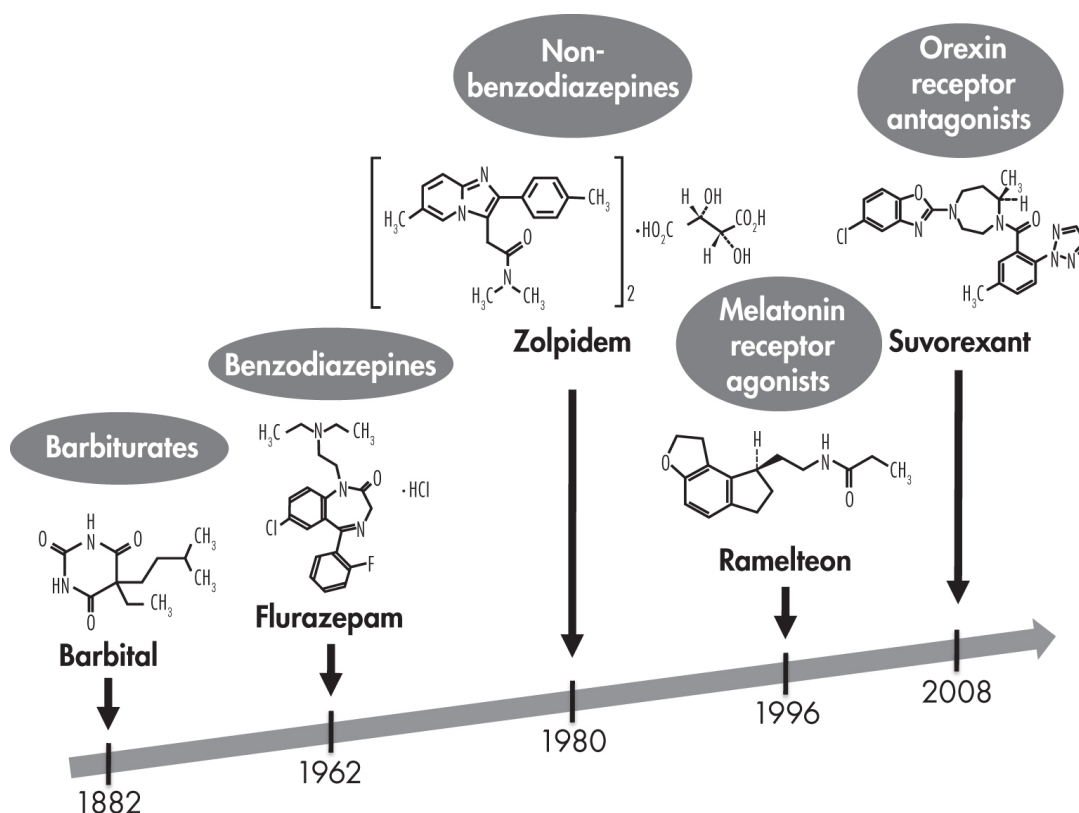
Noriaki Sakai, D.V.M., Ph.D.

Kazuo Mishima, M.D., Ph.D.

Emmanuel Mignot, M.D., Ph.D.

William C. Dement, M.D., Ph.D.

In this chapter, we examine some of the pharmacological properties of benzodiazepines, barbiturates, and other sedative-hypnotic compounds, including orexin (hypocretin) receptor antagonists and melatonin receptor agonists (Figure 43-1). *Sedative* drugs moderate excitement, decrease activity, and induce calmness, whereas *hypnotic* drugs produce drowsiness and facilitate the onset and maintenance of a state that resembles normal sleep in its electroencephalographic characteristics. Although these agents are central nervous system (CNS) depressants, they usually produce therapeutic effects at dosages much lower than those that cause coma and generalized depression of the CNS.



**FIGURE 43-1.** History of sedative-hypnotic development.

Some sedative-hypnotic drugs retain other therapeutic uses as muscle relaxants (especially benzodiazepines), antiepileptics, or preanesthetic medications. Although benzodiazepines are used widely as antianxiety drugs, it is not known whether their effect on anxiety is truly distinct from their effect on sleepiness.

Sedative-hypnotics are also important drugs for neuroscientists. These substances modulate basic behaviors such as arousal and response to stress. As our understanding of the molecular structure of the  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptor has increased, the mechanisms of these drugs' cellular activity have become clearer. In 2000, it was learned that human narcolepsy with cataplexy was associated with deficiency of orexin (or hypocretin), a newly discovered neuropeptide (Nishino et al. 2000). Although replacement therapies for orexin-deficient narcolepsy using synthetic, small-molecule orexin receptor agonists are not yet available, a dual orexin receptor antagonist

has been developed and was approved for the treatment of insomnia in 2014.

Further understanding of the sedative-hypnotics' modes of action could thus help to elucidate the neurochemical and neurophysiological processes that control sleep and sleep-related physiology and behaviors.

---

## **Benzodiazepines and Benzodiazepine-Like Agents**

---

### **History and Discovery**

Benzodiazepines were first synthesized in the 1930s. The introduction of chlorpromazine and meprobamate in the early 1950s led to a decade of development of sophisticated in vivo pharmacological screening methods that were used to identify the sedative properties of benzodiazepines. More than 3,000 benzodiazepines have been synthesized since chlordiazepoxide (synthesized by Sternbach in 1957; see [Baenninger 2004](#)) was introduced into clinical medicine. About 40 of them are in clinical use.

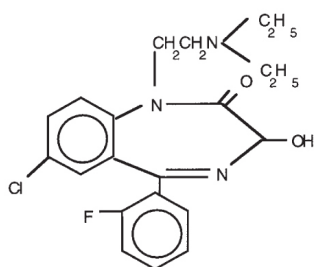
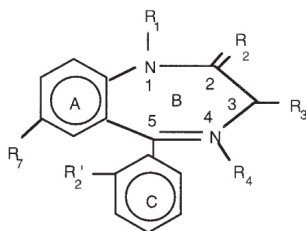
Several drugs chemically unrelated to the benzodiazepines have been shown to exhibit sedative-hypnotic effects with a benzodiazepine-like profile, and these drugs have been found to act via the benzodiazepine binding site on the GABA<sub>A</sub> receptor (see “Molecular Mechanism of GABA<sub>A</sub>-Benzodiazepine Receptor Interaction” section later in this chapter).

Most of the benzodiazepines currently on the market were selected for their high anxiolytic potential rather than their CNS depressive effects. Nevertheless, all benzodiazepines have sedative-hypnotic properties to various degrees, and some compounds that facilitate sleep have been used as hypnotics.

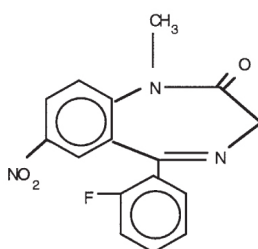
Mainly because of their remarkably low capacity to produce fatal CNS depression, benzodiazepines have displaced barbiturates as the preferred sedative-hypnotic agents.

## Structure-Activity Relations

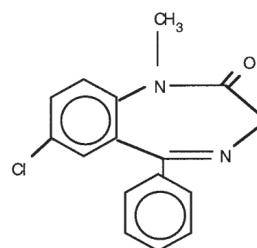
The term *benzodiazepine* refers to the portion of the structure composed of benzene rings (A in top portion of [Figure 43-2](#)) fused to a seven-membered diazepine ring (B). However, most of the older benzodiazepines contain a 5-aryl substituent (C) and a 1,4-diazepine ring, and the term has come to mean the 1,4-benzodiazepines.



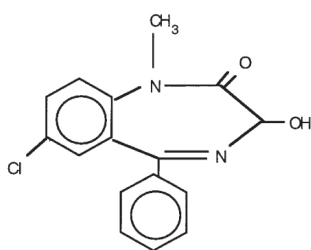
**Flurazepam**



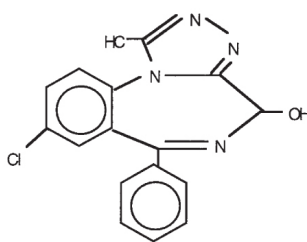
**Flunitrazepam**



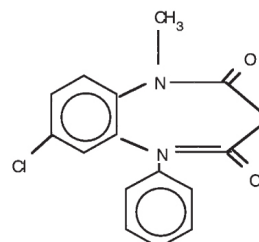
**Diazepam**



**Temazepam**



**Triazolam**



**Clonazepam**

---

**FIGURE 43-2.** Chemical structures of some commonly used benzodiazepines.

A substituent (most often chloride) at position 7 is essential for biological activity. A carbonyl at position 2 enhances activity and is generally present. Most of the newest products also substitute the 2 position, as with flurazepam. These general features are important for the metabolic fate of the compounds. Because the 7 and 2 positions of the molecule are resistant to all major degradative pathways, many of the metabolites retain substantial pharmacological activity.

## Pharmacological Profile

Benzodiazepines share anticonvulsant and sedative-hypnotic effects with the barbiturates. In addition, they have a remarkable ability to reduce anxiety and aggression ([Cook and Sepinwall 1975](#)). In the mammalian CNS, two subtypes of benzodiazepine omega ( $\omega$ ) receptors have been pharmacologically recognized. Benzodiazepine  $\omega_1$  receptors are sensitive to  $\beta$ -carboline, imidazopyridines (e.g., zolpidem), and triazolopyridazines. Benzodiazepine  $\omega_2$  receptors have low affinity for these ligands but relatively high affinity for benzodiazepines. Benzodiazepine  $\omega_1$  sites are enriched in the cerebellum, whereas  $\omega_2$  sites are mostly present in the spinal cord, and both receptor subtypes are found in the cerebral cortex and hippocampus. Benzodiazepine  $\omega_1$  and  $\omega_2$  receptor subtypes are also located peripherally in adrenal chromaffin cells.

Another benzodiazepine subtype,  $\omega_3$ , was identified and is commonly labeled as the *peripheral benzodiazepine receptor subtype* because of its distribution on glial cell membranes in non-nervous tissues such as adrenal, testis, liver, heart, and kidney. This subtype was later detected in the CNS, especially on the mitochondrial membrane, and not in association with GABA<sub>A</sub> receptors ([Gavish et al. 1992](#)). The  $\omega_3$  receptor subtype has high

affinity for benzodiazepines and isoquinoline carboxamides ([Awad and Gavish 1987](#)). The functional role of this receptor subtype is unknown, but it may be involved in the biosynthesis and mediation of the sedative-hypnotic effects of certain neuroactive steroids (e.g., pregnenolone, dehydroepiandrosterone [DHEA], allopregnanolone, tetrahydro-deoxycorticosterone) ([Edgar et al. 1997](#); [Friess et al. 1996](#); [Rupprecht et al. 1996](#)). Neurosteroids modulate GABA<sub>A</sub>-mediated transmission through an allosteric mechanism that is distinct from the modulation mechanism of benzodiazepines and barbiturates. By stimulation of  $\omega_3$  receptors with agonists, cholesterol is transferred from intracellular stores in mitochondria and becomes available to the mitochondrial cytochrome P450 cholesterol side-chain cleavage enzyme (P450scc), and neurosteroid biosynthesis begins ([Papadopoulos et al. 2001](#)). Benzodiazepine  $\omega_3$  receptor subtypes also may serve as mitochondrial membrane stabilizers and protect against pathologically induced mitochondrial and cell toxicity ([Papadopoulos et al. 2001](#)).

The GABA<sub>A</sub> receptor is a ligand-gated ion channel that mediates fast synaptic neurotransmission in the CNS. When the GABA<sub>A</sub> receptor is occupied by GABA or GABA agonists such as muscimol, the chloride channels open and chloride ions diffuse into the cell. Early research established that diazepam (and related benzodiazepines) does not act directly through GABA but instead modulates inhibitory transmission through the GABA<sub>A</sub> receptor in some other way. It was subsequently discovered that benzodiazepines bind specifically to neural elements in the mammalian brain with high affinity and that an excellent correlation exists between drug affinities for these specific binding sites and in vivo pharmacological potencies ([Möhler and Okada 1977](#); [Squires and Brastrup 1977](#)).

The binding of a benzodiazepine to the GABA<sub>A</sub> receptor site is enhanced in the presence of GABA or a GABA agonist, suggesting that a functional (but independent) relationship exists between the GABA<sub>A</sub> receptor and the benzodiazepine receptor binding

sites ([Tallman et al. 1978](#)). Barbiturates (and to some extent alcohol) also seem to produce anxiolytic and sedative effects at least partly by facilitating GABAergic transmission (see “Barbiturates” section later in this chapter). This common action for chemically unrelated compounds can be explained by the shared ability of these compounds to stimulate specific sites on the GABA<sub>A</sub> receptor.

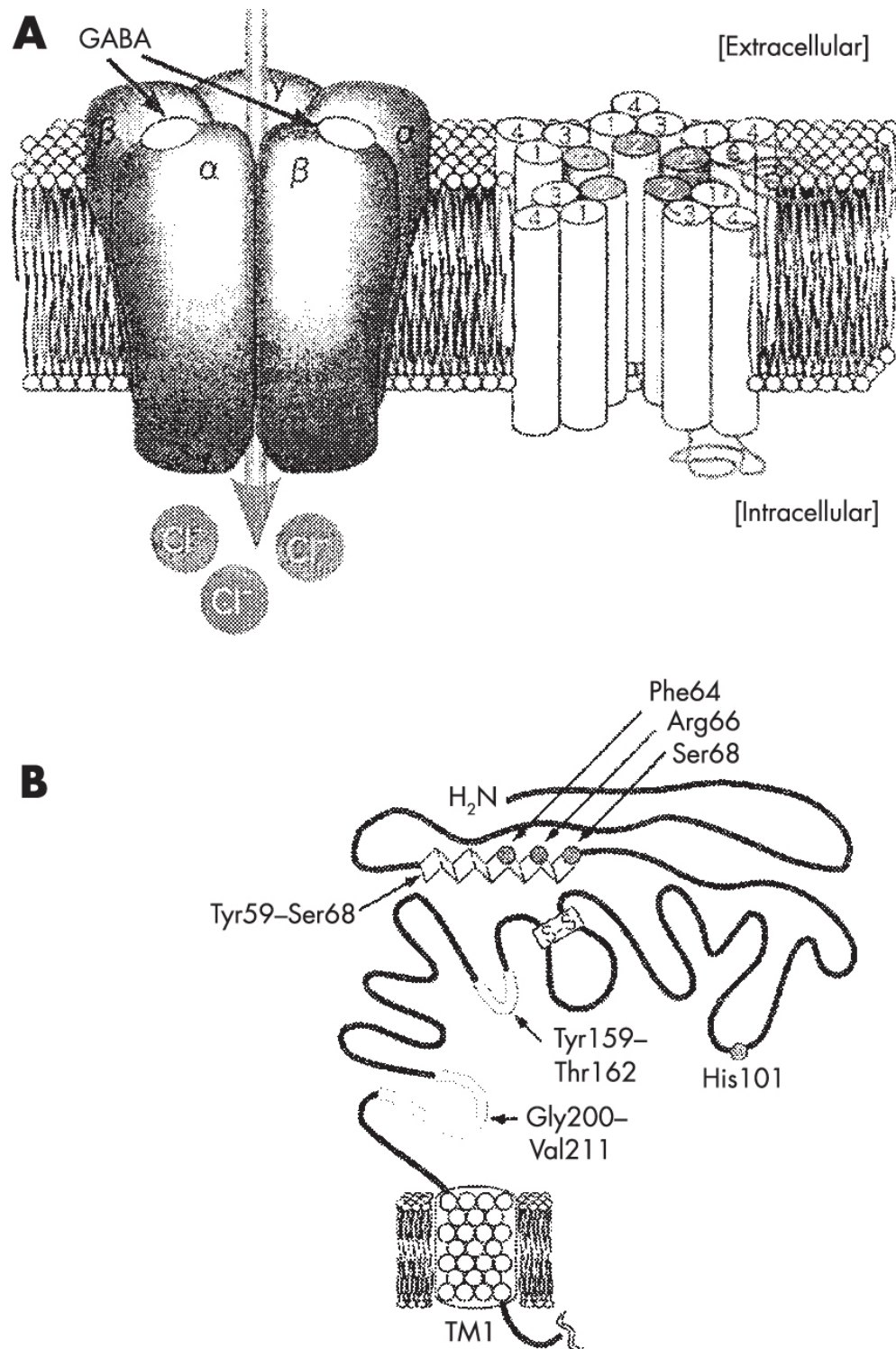
The benzodiazepines bind with high affinity to their binding sites so that the action of GABA at its receptor site is allosterically enhanced. GABA can produce stronger postsynaptic inhibition in the presence of a benzodiazepine. Benzodiazepine agonists are assumed to potentiate only ongoing physiologically initiated actions of GABA (at GABA<sub>A</sub> receptors), whereas barbiturates are thought to cause inhibition at all GABA-ergic synapses regardless of their physiological activity. In addition, barbiturates appear to increase the duration of the open state of the chloride channel, whereas benzodiazepines increase the frequency of channel openings but have little effect on duration ([Twyman et al. 1989](#)). These fundamental differences between the allosteric effects of benzodiazepines within the GABA<sub>A</sub> receptor and the conductive effects of barbiturates on the chloride ion channel may explain why low doses of barbiturates have a pharmacological profile similar to that of benzodiazepines, whereas high doses of barbiturates cause a profound and sometimes fatal suppression of brain synaptic transmission. It is notable that selective GABA<sub>A</sub> receptor agonists, such as muscimol, have no sedative or anxiolytic properties; thus, the entire GABA<sub>A</sub>-benzodiazepine receptor complex must be involved for expression of sedative-hypnotic properties.

## **Molecular Mechanism of GABA<sub>A</sub>-Benzodiazepine Receptor Interaction**

The structure of the GABA<sub>A</sub>-benzodiazepine receptor complex ([Figure 43-3](#)) was elucidated through the cloning of all of the implicated subunit genes and the study of the corresponding



encoded proteins. The GABA<sub>A</sub> receptor is a pentameric protein consisting of five subunits that form a rosette surrounding a transmembrane ion channel pore for Cl<sup>-</sup> (see [Figure 43-3A](#)). The GABA<sub>A</sub> receptor in humans includes the following known subunits:  $\alpha_1$ -  $\alpha_6$ ,  $\beta_1$ -  $\beta_4$ ,  $\gamma_1$ -  $\gamma_4$ ,  $\delta$ ,  $\epsilon$ ,  $\pi$ , and  $\tau$  (seven kinds of subunits, 18 isoforms total) ([Mehta and Ticku 1999](#)). Two alternatively spliced versions of the  $\gamma_2$  subunit,  $\gamma_{2S}$  and  $\gamma_{2L}$ , are also known to exist ([Kofuji et al. 1991](#)).



**FIGURE 43-3.** GABA<sub>A</sub>-benzodiazepine receptor complex.

**(A)** Schematic model of the mammalian  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptor embedded in the cell membrane, containing the  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits (in a ratio of 2:2:1). The binding of two molecules of GABA (*arrows*) to the action site (composed of  $\alpha$  and  $\beta$  subunits) triggers the opening of the chloride channel pore, causing chloride ions (Cl<sup>-</sup>) to diffuse into the cell. Each  $\alpha$  or  $\beta$  subunit is composed of four transmembrane (TM) regions (TM1-TM4). The ion channel central pore is lined by TM2 regions contributed by five subunits, arranged in a rosette formation. **(B)** Structure of the  $\alpha_1$  subunit, with amino acid sequence, indicating amino acid residues implicated in GABA and benzodiazepine binding domains.

*Source.* Modified from [Ueno et al. 2001](#).

Despite many studies, the physiological and neuroanatomical processes mediating benzodiazepine action on the GABA<sub>A</sub> receptor complex remain poorly understood. One reason is that the GABAergic system is the most widespread of all inhibitory neurotransmitter systems and could be involved in many circuits responsive to various effects of benzodiazepine agonists. In addition, the various subtypes of GABA<sub>A</sub> receptor have different ligand affinities and channel functions in response to benzodiazepine agonists. These GABA<sub>A</sub> receptor subtypes are broadly distributed in various brain areas to form a mosaic of receptor subtypes ([Wisden and Stephens 1999](#)), making it difficult to understand the functional mechanisms of interaction of benzodiazepine agonists with the GABA<sub>A</sub>-ergic system from the physiological point of view ([Rudolph et al. 1999](#)). However, site-directed mutagenesis and gene knock-in techniques have identified several important features of the benzodiazepine action sites on GABA<sub>A</sub> receptors and their physiological functions ([Ueno et al. 2001](#)).

It is postulated that the binding of GABA to *N*-terminal extracellular domains of  $\alpha$  and  $\beta$  subunits causes conformational changes within the subunits. Ion channel pores subsequently open, and Cl<sup>-</sup> flows across the neuronal membrane, resulting in neuronal inhibition ([Amin and Weiss 1993](#); [Boileau et al. 1999](#); [Sigel et al. 1992](#); [Smith and Olsen 1994](#)) (see [Figure 43-3A](#)). The

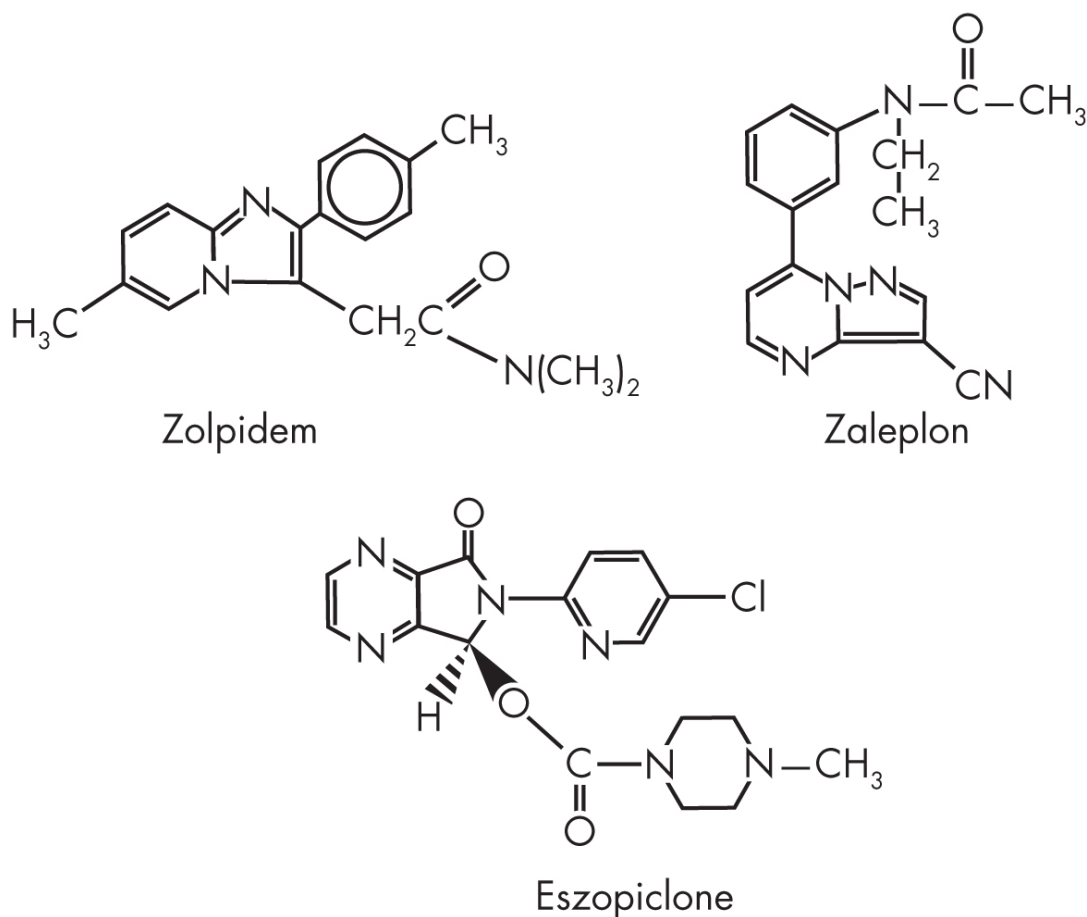
extracellular domains of the  $\alpha$  and  $\gamma$  subunits, which consist of about 220 amino acids in the *N*-terminal region, also have been shown to bind GABA and benzodiazepines. “Pharmacologically classified”  $\omega_1$  and  $\omega_2$  receptors are now thought to correspond to GABA<sub>A</sub> receptors possessing the  $\alpha_1$  and  $\alpha_2$  subunits and the  $\alpha_3$  and  $\alpha_5$  subunits, respectively.

Extracellular benzodiazepine binding sites on these subunits consist of several divided portions (see [Figure 43-3B](#)). His101, Tyr159–Thr162, and Gly200–Val211 on  $\alpha_1$  subunits, as well as Lys41–Trp82 and Arg114–Asp161 on  $\gamma_2$  subunits, are essential to formation of the binding pockets ([Boileau et al. 1998](#)). Most strikingly, His101 is a critical residue for diazepam to exhibit its sedative effect ([Crestani et al. 2001](#); [Löw et al. 2000](#); [McKernan et al. 2000](#); [Rudolph et al. 1999](#)). Knock-in mice with displacement of His101Arg are insensitive to benzodiazepine-induced allosteric modulation of the complex but have preserved physiological regulation by GABA ([Rudolph et al. 1999](#)). These knock-in mice failed to be sedated by diazepam but retained other effects of diazepam, such as anxiolytic-like, myorelaxant, motor-impairing, and ethanol-potentiating effects. This suggests the possibility that the sedative action of the benzodiazepine is mediated through GABA<sub>A</sub> receptors possessing the  $\alpha_1$  subunit. It is also noteworthy that His101Arg knock-in mice responded to diazepam and showed sleep changes similar to those seen in wild-type mice, despite the lack of its sedative response in these animals ([Tobler et al. 2001](#)). Thus, the hypnotic and sedative effects of benzodiazepines may be mediated via different subtypes, with hypnotic effects involving GABA<sub>A</sub> receptors possessing subunits other than  $\alpha_1$  (i.e.,  $\alpha_2$ ,  $\alpha_3$ , or  $\alpha_5$ ) ([Tobler et al. 2001](#)).

## **Nonbenzodiazepine Hypnotics (Acting on the Benzodiazepine Receptor)**

Until about 1980, it was widely accepted that the benzodiazepine structure was a prerequisite for the compound’s anxiolytic profile and for benzodiazepine receptor recognition and binding.

However, more recently, three chemically unrelated drugs—the imidazopyridine zolpidem, the cyclopyrrolone zopiclone (and its S[+]-enantiomer, eszopiclone), and the pyrazolopyrimidine zaleplon—have been shown to be useful sedative-hypnotics with benzodiazepine-like profiles ([Figure 43-4](#)). Other chemical classes of drugs that are structurally dissimilar to the benzodiazepines (e.g., triazolopyridazines) but act through the benzodiazepine receptor also have been developed and have demonstrated anxiolytic activity in humans.



**FIGURE 43-4.** Three nonbenzodiazepine hypnotics—zolpidem (an imidazopyridine), zopiclone (a cyclopyrrolone), and zaleplon (a pyrazolopyrimidine)—shown to be useful sedative-hypnotics with benzodiazepine-like profiles.

Nonbenzodiazepine hypnotics have a pharmacological profile slightly different from that of classic benzodiazepines. For example, zolpidem binds selectively to  $\omega_1$  (the 50% inhibitory concentration [IC<sub>50</sub>] ratio for  $\omega_1/\omega_2$  is nearly 1:10) and has more prominent sedative-hypnotic properties relative to other properties such as anxiolytic activity or muscle relaxation. Zolpidem and zopiclone have short half-lives (3 hours and 6 hours, respectively). These drugs appear not to appreciably affect the rapid eye movement (REM) sleep pattern, whereas the amount of slow-wave sleep (SWS) may be slightly increased (Jovanovic and Dreyfus 1983; Shlarf 1992). Rebound effects (insomnia, anxiety), which are commonly seen following withdrawal of short-acting benzodiazepines, are minimal for zolpidem and zopiclone. These compounds also induce little respiratory depression and have less abuse potential than do the common clinical benzodiazepine hypnotics. However, much longer clinical trials are needed to definitively determine whether the imidazopyridines or cyclopyrrolones have any significant advantages over the short- to medium-half-life benzodiazepines in the treatment of insomnia. Eszopiclone, the active stereoisomer of zopiclone with a longer half-life, was approved by the U.S. Food and Drug Administration (FDA) in 2004 and is claimed to be helpful in sleep maintenance as well as sleep induction. Because eszopiclone induces little tolerance, it is suitable for long-term use.

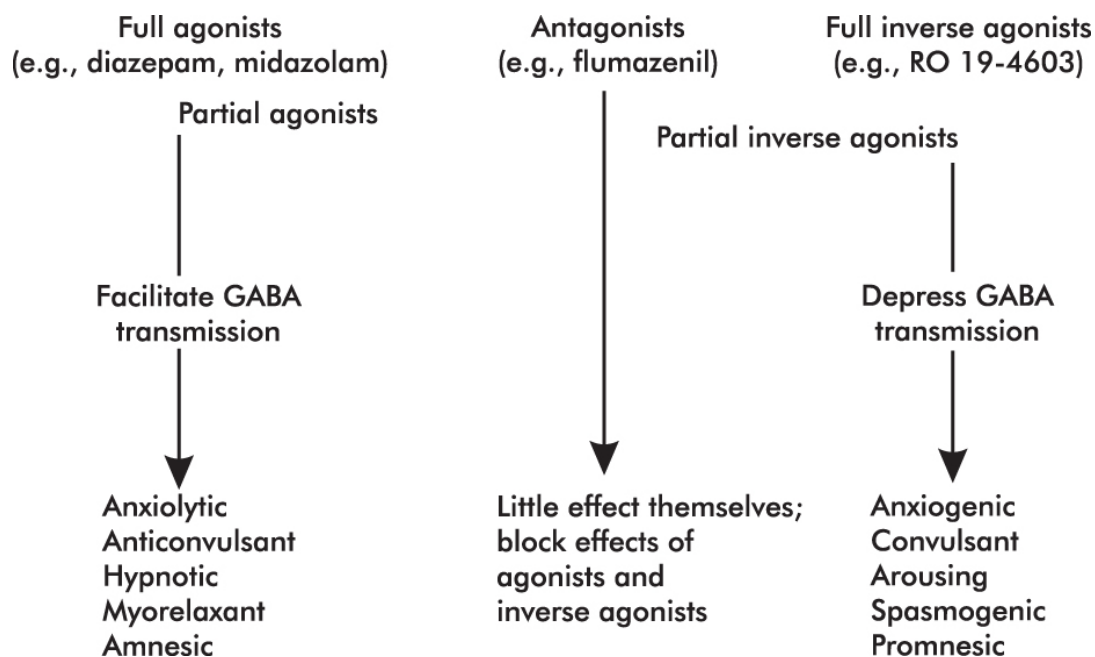
Zaleplon, a pyrazolopyrimidine, also has been developed as a novel nonbenzodiazepine hypnotic (see Figure 43-4). Clinical trials demonstrated that zaleplon is a well-tolerated, safe, rapidly acting, and effective sedative with advantages over lorazepam in regard to unwanted cognitive and psychomotor impairment (Allen et al. 1993; Beer et al. 1994).

## **Benzodiazepine Antagonists, Partial Agonists, and Inverse Agonists**

As knowledge of the relation between the structure of benzodiazepine receptor ligands and their pharmacological properties has increased, potent receptor agonists that stimulate

the receptor and produce pharmacological effects qualitatively similar to those of the classic benzodiazepines have been developed. *Antagonists*, which block the effects of the agonists without having any effects themselves, and *partial agonists*, which have a mixture of agonistic and antagonistic properties, also have been introduced (Haefley 1988). Development of partial agonists may be particularly important in the future because these compounds are free of the ataxic and amnesic side effects commonly associated with the classic benzodiazepine hypnotics.

Braestrup and Nielsen (1986) found that a group of nonbenzodiazepine compounds, the  $\beta$ -carboline, not only antagonized the action of the full agonists but also had intrinsic activity themselves. These compounds are called *benzodiazepine inverse agonists* because they have biological effects exactly opposite those of the pure agonists while also having intrinsic activity like that of agonists. The effects of inverse agonists are blocked by antagonists; thus, the benzodiazepine receptor is unique in that it has a bidirectional function (Figure 43-5).



**FIGURE 43-5.** Properties of the various types of benzodiazepine receptor ligands.



GABA= $\gamma$ -aminobutyric acid.

## Natural Ligands for Benzodiazepine Receptors in the Brain

The presence of benzodiazepine receptors in the brain suggests that natural ligands modulate GABAergic transmission through these sites. Small amounts of endogenous benzodiazepines (e.g., diazepam, desmethyldiazepam) can be detected in human and animal tissues. These benzodiazepines most likely originate from plants, such as wheat, corn, potatoes, or rice, and the levels that are detected are too low to be pharmacologically active (e.g., diazepam,  $<1$  ng/g; desmethyldiazepam, 0.5 ng/g).

Other endogenous benzodiazepine-like substances with neuromodulatory effects probably exist in mammals. Endogenous ligands called *diazepam binding inhibitors*, or *endozepines*, that bind to the benzodiazepine site on the GABA<sub>A</sub>-ergic receptor complex were identified and isolated ([Costa and Guidotti 1991](#); [Marquardt et al. 1986](#); [Rothstein et al. 1992](#)). Like diazepam, these ligands potentiate GABA<sub>A</sub> receptor-mediated neurotransmission by acting as positive allosteric modulators of this receptor. Endozepines are present in the brain at pharmacologically active concentrations and may play a role both physiologically (e.g., regulation of memory, sleep, and learning) and pathologically (e.g., panic attacks, hepatic encephalopathy) ([Mullen et al. 1990](#); [Nutt et al. 1990](#)). Finally, endozepines have been implicated in *idiopathic recurring stupor*, a neurological condition characterized by recurrent episodes of stupor or coma in the absence of any known toxic, metabolic, or structural brain damage ([Cortelli et al. 2005](#)). Endozepine concentrations are greatly increased in the plasma of individuals with this condition, and stupor can be interrupted by injections of flumazenil, a benzodiazepine antagonist. Thus, further knowledge of the roles of endozepines in physiological and pathological processes should be forthcoming once these endogenous ligands have been isolated and characterized ([Farzampour et al. 2015](#); [Rothstein et al. 1992](#)).



[Rye et al. \(2012\)](#) recently reported that the activity of a substance in the cerebrospinal fluid (CSF) that augments inhibitory GABA signaling is enhanced in patients with hypersomnia (including idiopathic hypersomnia with and without long sleep time, long sleepers [ $>10$  hours/day]), and narcolepsy without cataplexy). The authors demonstrated that in the presence of GABA, CSF samples from hypersomnolent patients stimulated GABA<sub>A</sub> receptor function in vitro (measures of GABA<sub>A</sub> receptor-mediated chloride currents in recombinant pentameric human GABA<sub>A</sub> receptor-expressed cultured cells). Interestingly, the stimulation of GABA<sub>A</sub> receptor function induced by the CSF from hypersomnolent patients was significantly greater than that induced by CSF samples from control subjects. The bioactive CSF component had a mass of 500–3,000 daltons and was neutralized by trypsin. The benzodiazepine receptor antagonist flumazenil reversed the enhancement of GABA<sub>A</sub> signaling induced by hypersomnolent CSF in vitro, and flumazenil also normalized vigilance in all seven of the hypersomnolent patients who underwent the drug challenge ([Rye et al. 2012](#)). The authors concluded that a naturally occurring substance in CSF augments inhibitory GABA signaling, revealing a new pathophysiology associated with hypersomnia. These findings also suggest the existence of other endogenous GABA<sub>A</sub> receptor modulators in the CNS.

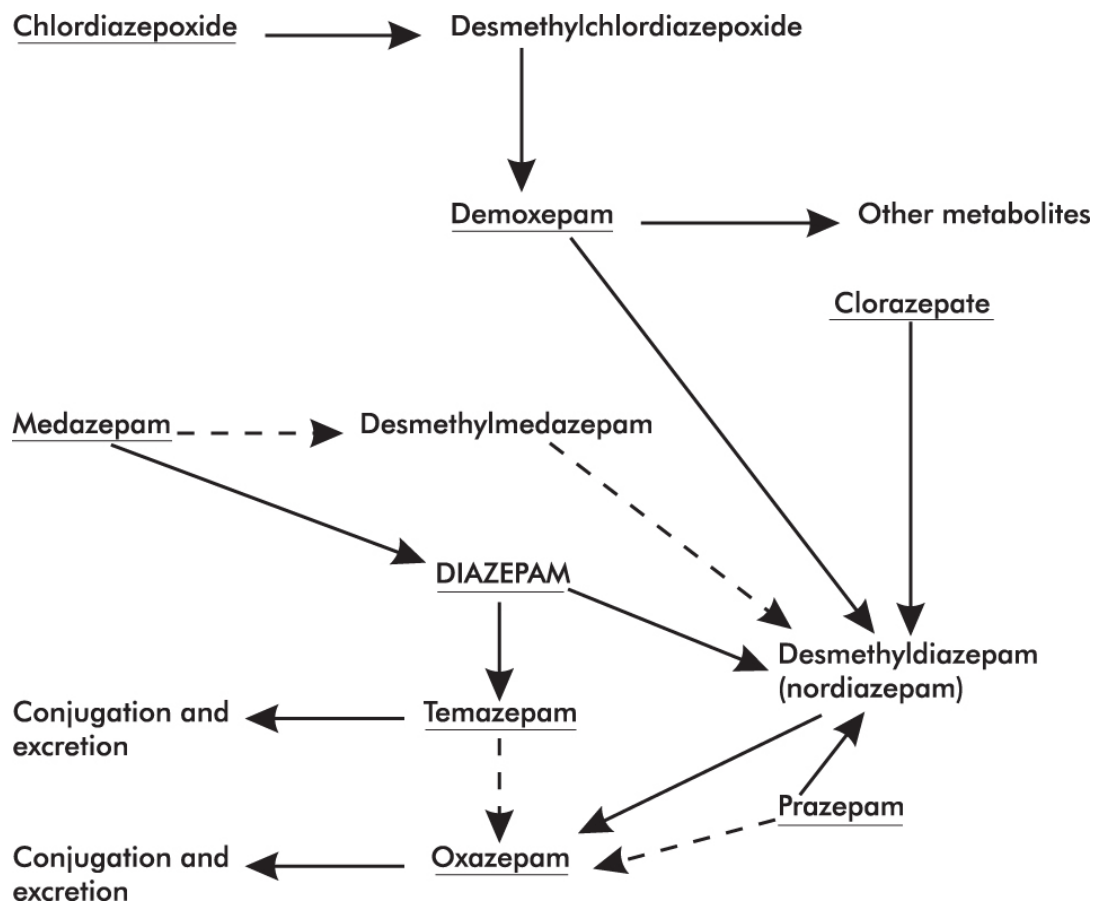
## Pharmacokinetics and Disposition

### **Benzodiazepines**

Benzodiazepines are generally absorbed rapidly and completely. Plasma binding is high (e.g., about 98% for diazepam).

Benzodiazepines are very lipophilic (except for oxazepam), and penetration into the brain is rapid. For swift onset of action, diazepam is available as an emulsion that is administered intravenously for rapid control of epilepsy; midazolam is a water-soluble benzodiazepine suitable for intravenous injection.

The major metabolic pathways for the 1,4-benzodiazepines are shown in [Figure 43-6](#). Medazepam is metabolized to diazepam, which is *N*-desmethylated to desmethyldiazepam. Chlordiazepoxide is also partly converted to desmethyldiazepam. Clorazepate is transformed to desmethyldiazepam. Clorazepate is transformed to desmethyldiazepam.



**FIGURE 43-6.** Metabolic pathways for the principal 1,4-benzodiazepines.

*Solid arrows* and *broken arrows* denote major and minor pathways, respectively; commercially available drugs are underscored. Flurazepam, flunitrazepam, nitrazepam, and triazolam have separate metabolic pathways.

Desmethyldiazepam is a critical metabolite for biological activity because of its long half-life (>72 hours). Because diazepam's half-life is about 36 hours, the concentration of its desmethyl

derivative soon exceeds that of the parent drug during chronic administration. Desmethyldiazepam undergoes oxidation to oxazepam, which (like its 3-hydroxy analog temazepam) is rapidly conjugated with glucuronic acid and excreted.

Among the various benzodiazepines, triazolam has a particularly short half-life (<4 hours), and flurazepam and nitrazepam both have long half-lives. A major active metabolite of flurazepam, *N*-desalkylflurazepam, has a very long half-life (~100 hours).

Because benzodiazepines are often prescribed for long periods, their long-term pharmacokinetics are particularly important. Concentrations of diazepam and desmethyldiazepam reach a plateau after a few weeks. Diazepam concentrations may then decline somewhat without much change in the concentration of the desmethyl metabolite.

Although benzodiazepines can stimulate liver metabolism in some animals, their induction of the hepatic microsomal enzyme system (cytochrome P450 [CYP] enzymes) is of little clinical significance in humans.

## **Nonbenzodiazepine Hypnotics**

Regarding the pharmacokinetics of nonbenzodiazepine hypnotics, no (or only weak) active metabolites exist for the compounds currently available.

## **Effects on Stages of Sleep**

The hypnotic effects of benzodiazepines are thought to derive from the inhibitory effects of the GABAergic system on the raphe and locus coeruleus monoaminergic ascending arousal systems, but this hypothesis may only partially explain their action. Magnocellular regions of the basal forebrain and the preoptic areas have been recognized as important sites for SWS regulation ([Szymusiak 1995](#)). Neurons that are selectively active during SWS have been described in these structures, most typically in the ventrolateral preoptic areas ([Saper et al. 2001](#); [Sherin et al.](#)

1996). These neurons contain GABA and galanin, an inhibitory peptide, and project to the main components of the ascending arousal system, such as the raphe and locus coeruleus and brain-stem cholinergic nuclei (Saper et al. 2001). The ventrolateral preoptic nucleus also sends a dense inhibitory projection to the tuberomammillary histaminergic nucleus, another important wake-promoting system (see Saper et al. 2001; Sherin et al. 1996). Benzodiazepines may thus indirectly modulate these wake-active monoaminergic neurons to promote their hypnotic effects.

Another important site of action for benzodiazepines may be the suprachiasmatic nucleus (SCN). In SCN-lesioned animals, benzodiazepine administration does not induce sleep (Edgar et al. 1993), but the hypnotic effect is restored if the SCN-lesioned animal is sleep deprived before drug administration. Benzodiazepines thus may facilitate the release of a sleep debt accumulated during wakefulness rather than producing de novo sleep (Mignot et al. 1992).

The effects of benzodiazepines on sleep architecture are well known. Most benzodiazepines decrease sleep latency (i.e., the amount of time it takes to fall asleep), especially when first used, and diminish the number of awakenings (Table 43-1). All benzodiazepines increase the time spent in stage 2 sleep. Benzodiazepines also affect the quality of the SWS pattern. Thus, stages 3 and 4 sleep are suppressed and remain so during the period of drug administration. The decrease in stage 4 sleep is accompanied by a reduction in nightmares.

**TABLE 43-1. Comparative effects of benzodiazepines and barbiturates on sleep parameters**

	Benzodiazepines	Barbiturates
Total sleep time	↑ tolerance with short-acting agents	↑ rapid tolerance

*Note.* REM=rapid eye movement sleep; ↑ =increased; ↓ =decreased.

	<b>Benzodiazepines</b>	<b>Barbiturates</b>
Stage 2, %	↑	↑
Slow-wave sleep (stages 3 and 4), %	↓	↓ (slight)
REM latency	↑	↑
REM, %	↓ (slight)	↓
Withdrawal	Rebound insomnia with short-acting agents Carryover effectiveness with long-acting agents REM rebound (slight)	REM rebound Rebound decrease in stage 2 and total sleep time

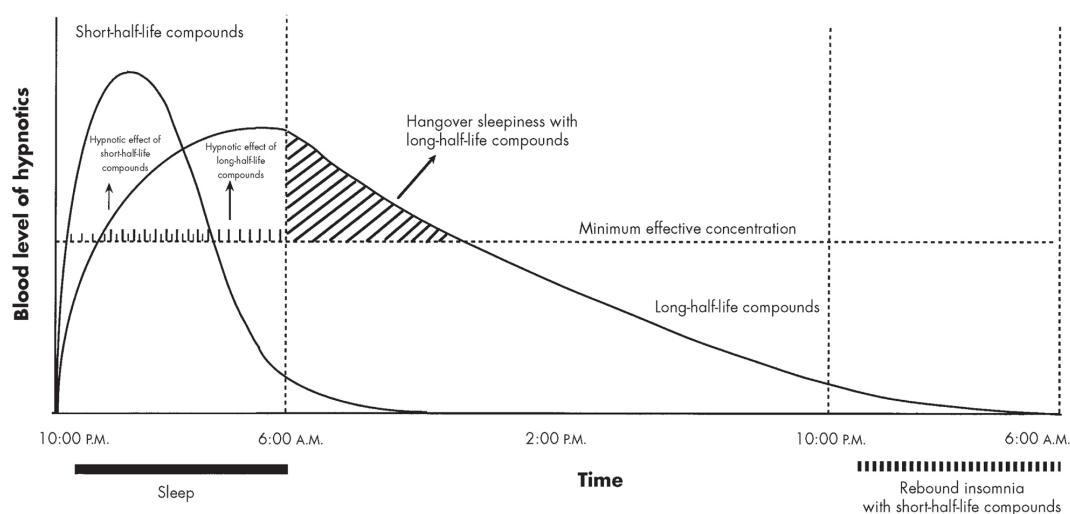
*Note.* REM=rapid eye movement sleep; ↑ =increased; ↓ =decreased.

Most benzodiazepines increase REM latency. The time spent in REM sleep is usually shortened; however, the reduction in percentage of REM sleep is minimal because the number of cycles of REM sleep usually increases late in the sleep time. Despite the shortening of SWS and REM sleep, the net effect of administration of benzodiazepines is usually an increase in total sleep time, so that the individual feels that the quality of sleep has improved. Furthermore, the hypnotic effect is greatest in subjects with the shortest baseline total sleep time.

If the benzodiazepine is discontinued after 3–4 weeks of nightly use, a considerable rebound in the amount and density of REM sleep and SWS may occur. However, this is not a consistent finding.

Because long-acting benzodiazepine hypnotics impair daytime performance and increase the risk of falls in geriatric patients, several shorter-acting benzodiazepines are the preferred choice for elderly individuals (see section “General Considerations in the Pharmacological Treatment of Insomnia” later in this chapter).

However, it has been found that short-acting benzodiazepines can induce rebound insomnia (a worsening of sleep difficulty beyond baseline levels on discontinuation of a hypnotic) (Kales et al. 1979), rebound anxiety, anterograde amnesia, and even paradoxical rage (Figure 43-7). Many other factors, such as the subtype of insomnia being treated and the dosage and duration of treatment, are also important in explaining the occurrence of these specific side effects, which also may occur with longer-acting benzodiazepines. Nevertheless, enthusiasm for shorter-acting compounds has been tempered by the discovery of these adverse effects.



**FIGURE 43-7.** Duration of action of hypnotics and hangover and rebound insomnia effects.

Hypnotics with long half-lives may impair daytime performance the day after drug administration, whereas short-acting compounds may induce rebound insomnia on discontinuation.

## Indications and Efficacy

Benzodiazepines are the drug treatment of choice in the management of anxiety, insomnia, and stress-related conditions.

Although none of the currently available compounds has any significant advantage over the others, some drugs can be selected to match the patient’s symptom patterns to the pharmacokinetics of the various drugs. If a patient has a persistently high level of anxiety, one of the precursors of desmethyldiazepam, such as diazepam or clorazepate, is most appropriate. Patients with fluctuating anxiety may prefer to take a shorter-acting compound, such as oxazepam or lorazepam, when stressful circumstances occur or are expected.

The indications for nonbenzodiazepine hypnotics are equivalent to those of benzodiazepine hypnotics but may be more specific, depending on the pharmacological property of each compound.

An ideal hypnotic should induce sleep rapidly without producing sedation the next day. Both flurazepam and nitrazepam have inappropriately long half-lives as hypnotics unless a persistent anxiolytic effect is desired the next day (see [Figure 43-7](#)). Even in such situations, diazepam given as a single dose at night may be suitable. Oxazepam penetrates too slowly for a dependable hypnotic effect (slow onset of action). Both lorazepam and temazepam are appropriate treatments for insomnia, but the dosage strengths available are quite high ([Table 43-2](#)). Triazolam is the shortest-acting hypnotic available. When very small doses of benzodiazepines (which are assumed to have no significant hypnotic action) are administered to patients with insomnia, sleep quality often improves greatly, and usually it is not necessary to prescribe a benzodiazepine at a hypnotic dose as a first-choice treatment.

**TABLE 43-2.    Pharmacokinetic properties of GABA-enhancing hypnotic compounds most commonly used in the United States**

Hypnotic compounds	Usual dose (mg)	T <sub>max</sub> (hours) <sup>a</sup>	Half-life (hours) <sup>b</sup>	Active metabolites
--------------------	-----------------	---------------------------------------	--------------------------------	--------------------

Hypnotic compounds	Usual dose (mg)	T <sub>max</sub> (hours) <sup>a</sup>	Half-life (hours) <sup>b</sup>	Active metabolites
<b>Benzodiazepines</b>				
Flurazepam (Dalmane)	15-30	0.5-1.0	48-150	<i>N</i> -Desalkylflurazepam
Quazepam (Doral)	7.5-15	2	48-120	2-Oxoquazepam, <i>N</i> -dealkyl-2-oxoquazepam
Estazolam (ProSom)	1-2	4.9	18-30	1-Oxoestazolam
Temazepam (Restoril)	15-30	1.5	8-20	None
Triazolam (Halcion)	0.125-0.25	1.3	2-6	None
<b>Nonbenzodiazepines</b>				
Zolpidem (Ambien)	5-10	0.8	1.5-2.4	None

*Note.* GABA=γ-aminobutyric acid.

<sup>a</sup>T<sub>max</sub> is the time required to reach maximal (peak) plasma concentration.

<sup>b</sup>Half-life is the time required by the body to metabolize or inactivate half the amount of a substrate taken.



<b>Hypnotic compounds</b>	<b>Usual dose (mg)</b>	<b>T<sub>max</sub> (hours)<sup>a</sup></b>	<b>Half-life (hours)<sup>b</sup></b>	<b>Active metabolites</b>
Zopiclone (Imovane in Canada)	3.75–7.5	1.5	5–6	<i>N</i> -Oxide zopiclone (weak agonist)
Eszopiclone (Lunesta)	1–3	1	6–9	<i>S</i> -Desmethylopiclone (weak agonist)
Zaleplon (Sonata)	5–20	1.0	1.0–2.5	None

*Note.* GABA=γ-aminobutyric acid.

<sup>a</sup>T<sub>max</sub> is the time required to reach maximal (peak) plasma concentration.

<sup>b</sup>Half-life is the time required by the body to metabolize or inactivate half the amount of a substrate taken.

Benzodiazepines can increase the frequency of apneic episodes and exacerbate oxygen desaturation both in healthy subjects and in subjects with chronic bronchitis ([Geddes et al. 1976](#)). Although many reports suggest that benzodiazepines are safe in patients with obstructive sleep apnea, some authors disagree, and it seems wise to avoid hypnotics in patients with severe sleep apnea. One of the only other contraindications is myasthenia gravis, a condition in which muscle relaxation with benzodiazepines can exacerbate muscle atonia.

## Side Effects and Toxicology

When a benzodiazepine is taken at high doses, tiredness, drowsiness, and profound feelings of detachment are common but can be minimized by a careful dose adjustment. Headache, dizziness, ataxia, confusion, and disorientation are less common except in the elderly. A marked potentiation of the depressant

effect of alcohol occurs. Other less common side effects include weight gain, skin rash, menstrual irregularities, impairment of sexual function, and (very rarely) agranulocytosis.

Although otherwise asymptomatic individuals clearly show mental impairment with benzodiazepines, the situation with anxious patients is more complex. Because anxiety itself interferes with mental performance, alleviation of anxiety may result in improved functioning, which more than compensates for the direct drug-related decrement. The effects in some patients may be complicated and unpredictable, even at low dosages.

### **Use During Pregnancy and Lactation**

Because the safety of benzodiazepines in early pregnancy is not established, these compounds should be avoided unless absolutely necessary. Diazepam is secreted in breast milk and may make the infant sleepy, unresponsive, and slow to feed.

### **Overdose**

The benzodiazepines are very widely prescribed, so it is not surprising that they are used in many suicide attempts. For adults, overdoses of benzodiazepines reportedly are not fatal unless alcohol or other psychotropic drugs are taken simultaneously. Typically, the patient falls asleep but is arousable and wakes after 24–48 hours. Treatment is supportive. A stomach pump is usually more punitive than therapeutic, and dialysis is usually ineffective because of high plasma binding.

### **Tolerance and Dependence**

The fact that some patients gradually increase the dose suggests tolerance, but increases in dose are sometimes related to particularly stressful crises.

Dependence, both psychological and physical, occurs with benzodiazepines as with other sedative-hypnotics. Abrupt discontinuation results in withdrawal phenomena such as anxiety, agitation, restlessness, and tension, which are usually delayed for several days because of the long half-life of the major metabolite,

desmethyldiazepam. Even with the normal dose, some patients have withdrawal effects. Psychological dependence is also common, based on the high incidence of repeated prescriptions, but it is mild, and the drug-seeking behavior is much less persistent with benzodiazepines than with barbiturates.

---

## Barbiturates

---

### History and Discovery

Barbital, one of the derivatives of barbituric acid, was introduced in 1903 and soon became extremely popular in clinical medicine because of its sleep-inducing and anxiolytic effects ([Maynert 1965](#)). In 1912, phenobarbital was introduced as a sedative-hypnotic. Since then, more than 2,500 barbiturate analogs have been synthesized, about 50 of which have been made commercially available and only 20 of which remain on the market.

The success of the partial separation of anticonvulsant from sedative-hypnotic properties led to the development of nonsedative anticonvulsants such as phenytoin in the late 1930s and trimethadione in the early 1940s. The success of barbiturates as sedative-hypnotics was largely overshadowed by the discovery of the benzodiazepines in the late 1960s. With pharmacological properties very similar to those of barbiturates, the benzodiazepines have a much safer pharmacological profile. Thus, benzodiazepines have replaced barbiturates in many instances, especially for psychiatric conditions in which suicide is a possibility.

### Structure–Activity Relations

Derivatives of barbituric acid, the parent compound of all barbiturates, do not dissolve readily in water but are quite soluble

in nonpolar solvents. In general, structural changes that increase liposolubility also decrease these compounds' duration of action, decrease the latency to onset of activity, accelerate metabolic degradation, and often increase hypnotic potency.

Compared with barbituric acid derivatives with methyl groups at position 5, those with large aliphatic groups at this position have greater activity but shorter duration of action. However, when aliphatic groups have more than seven carbons, they lose their hypnotic activity and tend to exhibit convulsant activity. Methylation of the 1-*N* atom increases liposolubility and shortens duration of action, and desmethylation may increase the duration of action ([Rall 1990](#)).

## Pharmacological Profile and Mechanism of Action

The main effects of barbiturates are sedation, sleep induction, and anesthesia. Some of the barbiturates, such as phenobarbital, also have selective anticonvulsant properties. The mechanisms of action of barbiturates are complex and still not fully understood. Nonanesthetic doses of barbiturates generally suppress polysynaptic responses. Pertinent to their sedative-hypnotic effects is the fact that the mesencephalic reticular activating system is extremely sensitive to these drugs ([Killam 1962](#)). The synaptic site of inhibition is either postsynaptic (e.g., at the level of cortical and cerebellar pyramidal cells and in the cuneate nucleus, substantia nigra, and thalamus relay neurons) or presynaptic (e.g., in the spinal cord). This inhibition occurs only at synapses where physiological inhibition is GABAergic but not glycinergic or monoaminergic. Thus, barbiturates, like benzodiazepines, specifically potentiate GABA-mediated inhibitory processes in the brain. However, it remains unclear whether all of the effects of barbiturates are entirely mediated by GABAergic mechanisms.

Barbiturates do not displace benzodiazepines from their binding sites; instead, barbiturates enhance benzodiazepine binding by

increasing the affinity of the receptor for benzodiazepines ([Leeb-Lundberg et al. 1980](#)). They also enhance the binding of GABA and its agonists to specific binding sites (Asano and Ogasawara [1981](#)). These enhancement effects are almost completely dependent on the presence of chloride or other anions that are known to permeate the chloride channels associated with the GABA receptor complex, and they are competitively antagonized by picrotoxin (a convulsant) ([Olsen et al. 1978](#)).

The molecular correlations of the barbiturate-acting sites on the GABA<sub>A</sub> receptor also have been studied. However, neither the sequences involved in the binding of GABA and other direct receptor agonists nor the sequence involved in the action of benzodiazepines is of vital importance to barbiturate function ([Amin and Weiss 1993](#)). Whereas some earlier reports suggested that the  $\beta$  subunit alone may form a site for barbiturates ([Sanna et al. 1995](#)), recent studies attempting to identify structural characteristics and binding sites have found that barbiturates bind to the GABA<sub>A</sub> receptor at multiple homologous transmembrane pockets at the subunit interfaces ([Chiara et al. 2013](#)). Although there is still much to be learned, new molecular experimental approaches hold great promise for resolving the most important pharmacological questions regarding which molecular species are important for the anticonvulsant, sedative, anesthetic, and toxic actions of the barbiturates.

## Pharmacokinetics and Disposition

For hypnotic use, barbiturates usually are administered orally. Barbiturates are rapidly absorbed in the stomach, and their absorption decreases when the stomach is full.

Barbiturates are metabolized mainly in the liver. Oxidation of the larger of the two side chains at position 5 is a major catabolic pathway. It generally produces inactive polar metabolites that are rapidly excreted in the urine ([Rall 1990](#)). Changes in liver function can markedly alter the metabolic rate. Chronic administration leads to pharmacokinetic tolerance, even when low or infrequent

doses of barbiturates are used (see subsection “Drug-Drug Interactions” later in this section).

In general, liposolubility decreases both latency to onset of action and duration of action. Thiopental, for example, enters the CNS quickly and is used to rapidly induce anesthesia; barbitone crosses into the brain so slowly that it is inappropriate as a hypnotic drug.

## Effects on Stages of Sleep

Barbiturates decrease sleep latency; however, they also slightly increase fast electroencephalogram (EEG) activity during sleep. Barbiturates decrease body movements during sleep. Stage 2 sleep increases, whereas stage 3 and stage 4 SWS generally decreases (except in some patients who have anxiety and in patients who are addicted to barbiturates; see [Table 43-1](#)). REM sleep latency is prolonged, and both the total time spent in REM sleep and the number of REM cycles are diminished. With repeated nighttime administration of barbiturates, drug tolerance to the effects on sleep occurs in a few days. Discontinuation of barbiturates may lead to insomnia and to disrupted sleep patterns (with a decrease in stage 2 sleep and increases in REM sleep) ([Kay et al. 1976](#)).

## Indications and Efficacy

Although clinical trials have shown that the barbiturates have sedative and hypnotic properties, barbiturates generally compare poorly with benzodiazepines. The patient feels “drugged” the next day, and there is always the risk of fatal overdose because of the depressant effect on respiration. The therapeutic dose of barbiturates may cause fatal respiratory depression in patients with sleep apnea; therefore, barbiturate use is contraindicated in such patients. Because of these risks, many clinicians have stopped using barbiturates as hypnotics and sedatives (one

exception is in the treatment of severe psychomotor excitation) and prescribe them only as anticonvulsants.

Barbiturates also have been administered intravenously to facilitate patient interviews (i.e., amobarbital interview).

Because they enhance porphyrin synthesis, barbiturates are contraindicated in patients with porphyria. Liver function should be checked before and during drug administration. Liver dysfunction can significantly prolong the sedative effects of these drugs and may lead to fatal overdose.

## Side Effects and Toxicology

For many patients who are prescribed barbiturates, it is difficult to control symptoms without causing oversedation. Patients typically oscillate between anxiety and torpor. Mental performance is often impaired, and patients should not drive or operate dangerous machinery.

Patients whose conditions have been stabilized for years with barbiturates must be considered drug dependent. Withdrawal leads to anxiety, agitation, trembling, and, frequently, convulsions. Substitution with a benzodiazepine that can be withdrawn more easily later is often successful.

### Overdose

An overdose of barbiturates leads to fatal respiratory and cardiovascular depression. Suicide attempts frequently involve overdoses of barbiturates, taken either alone or in combination with alcohol or other psychotropic drugs, particularly tricyclic antidepressants. These suicide attempts, unfortunately, are often successful. Depending on local factors such as proximity to a hospital and expertise of staff in intensive emergency care, death occurs in 0.5%–10% of these cases. Severe poisoning results at 10 times the hypnotic dose, and twice that amount may be fatal.

### Tolerance and Dependence

Tolerance to barbiturates occurs rapidly and is a result of both pharmacokinetic factors (e.g., liver enzyme induction) and pharmacodynamic factors (e.g., neuronal adaptation to chronic drug administration). Cross-tolerance develops to alcohol, gas anesthetics, and other sedatives, including benzodiazepines.

Psychological dependence (i.e., drug-seeking behavior) is common. Patients typically visit several physicians to obtain more barbiturates. Physical dependence may be induced by dosages of 500 mg/day. Intoxication may occur, as evidenced by impaired mental functioning, emotional instability, and neurological signs. Abrupt discontinuation after high doses is likely to induce convulsions and delirium. After normal doses, withdrawal phenomena include anxiety, insomnia, restlessness, agitation, tremor, muscle twitching, nausea and vomiting, orthostatic hypotension, and weight loss.

## Drug-Drug Interactions

Barbiturates used with other CNS depressants can cause severe depression. Ethanol is the drug most frequently used in combination with barbiturates, and interactions with antihistaminic compounds are also common. Monoamine oxidase inhibitors and methylphenidate also increase the CNS depressant effect of barbiturates.

Barbiturates may increase the activity of hepatic CYP enzymes two- to threefold. Clinically, this change is particularly important for patients who are also receiving metabolic competitors such as warfarin or digitoxin, for which careful control of plasma concentrations is vital ([Rall 1990](#)).

---

## Other Sedative-Hypnotic Compounds

---



## Alcohol-Type Hypnotics

The alcohol-type hypnotics include the chloral derivatives, of which chloral hydrate (0.5–1.0 g), clomethiazole (192 or 384 mg), and ethchlorvynol (0.5–1.0 g) are still used occasionally in the elderly. Chloral hydrate is metabolized to another active sedative-hypnotic—trichloroethanol. These drugs have short half-lives (~4–6 hours) and decrease sleep latency and number of awakenings; SWS is slightly depressed, but overall REM sleep time is largely unaffected. Chloral hydrate and its metabolite have an unpleasant taste and frequently cause epigastric distress and nausea. Undesirable side effects include light-headedness, ataxia, and nightmares. Chronic use of these drugs can lead to tolerance and occasionally to physical dependence. As with barbiturates, overdose can lead to respiratory and cardiovascular depression, and therapeutic use of these drugs has largely been superseded by the use of benzodiazepines.

## Gamma-Hydroxybutyrate/Sodium Oxybate

$\gamma$ -Hydroxybutyrate (GHB) is a hypnotic agent that has been used mostly in the treatment of insomnia in narcoleptic patients ([Scrima et al. 1990](#)). A small amount of GHB also exists naturally in the CNS ([Bessman and Fishbein 1963](#)). The drug is rarely used in other indications and is frequently abused. GHB was classified as a Schedule I controlled substance in March 2000 in the United States, but in July 2002, the drug's sodium salt form, sodium oxybate (Xynem), was approved for the treatment of narcolepsy. Nighttime administration of GHB (20–40 mg/kg) reduces excessive daytime sleepiness associated with narcolepsy. The compound promotes SWS and REM sleep ([Lapierre et al. 1990](#)), but its effects on sleep architecture are short-lasting, and repeated administration usually is necessary during the night. GHB also is used for the treatment of cataplexy in narcolepsy,

although the mechanisms of GHB's effect on cataplexy remain unknown. The physiological significance of a brain GHB signaling pathway and the detailed mechanisms of many actions of exogenous GHB remain unclear. Exogenously administered GHB induces a wide range of neuropharmacological effects, including sedation, memory impairment, an increase in sleep, seizures, dependence/abuse, and coma ([Wong et al. 2004](#)). GHB has long been known to have an effect on dopamine systems in the brain and likely inhibits dopamine release ([Vayer et al. 1987](#)).

Most of the effects of exogenous GHB have been shown to be mediated (either fully or in part) by GABA<sub>B</sub> receptors ([Castelli et al. 2004](#); [Maitre 1997](#); [Wong et al. 2004](#)). In 2003, the cloning of a putative GHB receptor was reported ([Andriamampandry et al. 2003](#)).

Despite this progress, there is an urgent need for a well-validated functional assay for GHB receptors. Moreover, because GHB can also be metabolized to GABA, it remains to be seen whether the many GABA<sub>B</sub> receptor-mediated actions of GHB are caused by GHB itself acting directly on GABA<sub>B</sub> receptors or by a GHB-derived GABA pool (or both) ([Wong et al. 2004](#)).

## Antihistamines

Antihistamines such as promethazine (25–50 mg), diphenhydramine (25–50 mg), and doxylamine (25 mg) are sometimes prescribed as sleep inducers. They decrease sleep latency but do not increase total sleep time (see [Reite et al. 1997](#)). These compounds are especially useful for patients who cannot sleep well because of acute allergic reactions or itching. Because sedative antihistamines lack abuse potential, they also may be a good choice for individuals with substance use disorders. However, rapid tolerance is a problem.

In April 2008, doxepin hydrochloride (marketed under the trade name Silenor), a tricyclic antidepressant with histamine 1 (H<sub>1</sub>) receptor antagonism, received FDA approval for the treatment of

insomnia. Doxepin (as Sinequan) (3 and 6 mg) reduces wake after sleep onset and prolongs total sleep time ([Markov and Doghramji 2010](#)). Several other selective H<sub>1</sub> receptor blockers and H<sub>1</sub> receptor reverse agonists are also under development for use as hypnotics.

## Melatonin and Melatonin Receptor Agonists

### Melatonin

Melatonin is a neurohormone produced by the pineal gland during the dark phase of the day-night cycle. In animals, melatonin has been implicated in the circadian regulation of sleep and in the seasonal control of reproduction. Studies suggest that melatonin administration may have some therapeutic effects in various disturbances of circadian rhythmicity, such as those related to jet lag ([Arendt et al. 1987](#)), shift work ([Folkard et al. 1993](#)), non-24-hour sleep-wake cycle in blind individuals ([Arendt et al. 1988](#)), and delayed-sleep-phase insomnia ([Dahlitz et al. 1991](#)), with few side effects (e.g., headaches or nausea). High doses of melatonin (3–100 mg), which increase serum melatonin levels far beyond the normal nocturnal range, have been suggested to produce hypnotic effects in humans ([Dollins et al. 1994](#)). Lower and more physiological doses of melatonin (e.g., 0.3 mg) might also be active ([Zhdanova et al. 2001](#)).

In humans, the production of melatonin during the dark period declines with age; this effect parallels declines in sleep quantity and quality ([van Coevorden et al. 1991](#)), especially in elderly persons with insomnia ([Haimov et al. 1994](#); [Mishima et al. 2001](#)). These findings appear to suggest that deficiencies in nocturnal melatonin secretion might contribute to disrupted sleep in the elderly; thus, melatonin may be particularly beneficial for insomnia in this population. Indeed, some studies reported favorable effects with supplementary administration of melatonin

in elderly persons with disturbances in sleep maintenance ([Garfinkel et al. 1995](#); [Haimov et al. 1995](#)). However, several studies reported contradictory findings indicating no significant relation between physiological melatonin secretion levels and sleep-maintenance parameters ([Hughes et al. 1998](#); [Lushington et al. 1998](#); [Youngstedt et al. 1998](#); [Zeitzer et al. 1999](#)), as well as no significant therapeutic effect of melatonin replacement on sleep maintenance in elderly persons with insomnia ([Hughes et al. 1998](#)).

One of the difficulties in establishing the therapeutic efficacy of melatonin is its short half-life (20–30 minutes). Bedtime melatonin administration (1–3 mg) reduces sleep latency but has few objective effects on sleep architecture. It is also unclear whether the hypnotic effect from a physiological or pharmacological dose represents a direct effect on sleep, an indirect effect on circadian timing that subsequently gates the release of sleep, or both. Finally, very few double-blind, placebo-controlled studies have been done, and most current reports are confounded by strong placebo effects in the context of a melatonin fad. Melatonin might be an effective hypnotic in some indications, but better-controlled studies are needed to establish its efficacy in specific indications. The purity of the products sold in health food stores is also a problem, and the long-term effects of melatonin administration in humans are unknown.

A prolonged-release formulation of melatonin (marketed under the trade name Circadin) was approved by the European Commission in June 2007 as monotherapy (2 mg) for the short-term treatment of primary insomnia characterized by poor-quality sleep in patients 55 years and older ([Lemoine et al. 2007](#)).

## Melatonin Receptor Agonists

There are at least three subtypes of melatonin receptor with high ( $MT_1$  or  $MT_{1a}$ ) and low ( $MT_2$  or  $MT_{1b}$  and  $MT_3$  or  $MT_{1c}$ ) affinities for this ligand ([Dubocovich 1995](#); [Morgan et al. 1994](#); [Reppert et al. 1994, 1995](#)). The localization of the  $MT_1$  receptor in the SCN, median eminence, and retina in humans and rodents suggests

that this receptor is essential for circadian regulation and reproduction, whereas the MT<sub>2</sub> receptor is localized mainly in the retina. Melatonin receptors in the retina likely play an important role in retinal physiology, including circadian regulation ([Sengupta et al. 2011](#)) and photopigment disc shedding ([Besharse and Dunis 1983](#)).

Ramelteon (8 mg), a melatonin receptor agonist with both high affinity for melatonin MT<sub>1</sub> and MT<sub>2</sub> receptors and low affinity for the MT<sub>3</sub> receptor and with a longer half-life than melatonin, was approved by the FDA in July 2005 for the treatment of insomnia characterized by difficulty with sleep onset (see [Kuriyama et al. 2014](#); [Takeda Pharmaceuticals America, Inc. 2010](#)). Ramelteon does not show any appreciable binding to GABA<sub>A</sub> receptors, which are associated with anxiolytic, myorelaxant, and amnesic effects. Ramelteon has not been demonstrated to produce dependence and has shown no potential for abuse, and the withdrawal and rebound insomnia typically seen with other GABA modulators do not appear to be present.

Animal studies demonstrated that the sleep-enhancing effects of ramelteon are not associated with reductions in REM sleep ([Miyamoto et al. 2004](#)). Ramelteon is currently the only nonscheduled prescription drug for the treatment of insomnia available in the United States. It has no appreciable affinity for receptors that bind neuropeptides, cytokines, serotonin, dopamine, norepinephrine, acetylcholine, and opiates. It also does not interfere with the activity of any known enzymes in standard panels. The activity of ramelteon at the MT<sub>1</sub> and MT<sub>2</sub> receptors, especially those in the SCN, is believed to contribute to its sleep-promoting properties, as these receptors, acted upon by endogenous melatonin, are thought to be involved in maintenance of the circadian rhythm underlying the normal sleep-wake cycle.

The activity of ramelteon is similar to the biological action of melatonin. No published studies have reported comparative data on whether ramelteon is more or less safe or effective than melatonin, a much less expensive drug widely available in the United States without a prescription.

Recent studies have reported findings suggesting that melatonin (0.5 mg) or ramelteon (8 mg) can prevent delirium in elderly patients ([Al-Aama et al. 2011](#); [Hattai et al. 2014](#)). Although significant decline in melatonin levels during aging has been reported by many investigators ([Srinivasan et al. 2006](#)), the mechanisms by which these drugs might reduce or prevent delirium in elderly patients are not known.

Another MT<sub>1</sub>/MT<sub>2</sub> receptor agonist, tasimelteon ([Rajaratnam et al. 2009](#)), was approved by the FDA in January 2014 for the treatment of non-24-hour sleep-wake disorder (N24HSWD) in totally blind people ([Vanda Pharmaceuticals Inc. 2016](#); see also [Sack et al. 1991](#)). Melatonin receptor agonists can produce improvements in sleep timing similar to those produced by melatonin. Synthetic melatonin receptor agonists may also be useful in patients who experience insomnia due to shift work or jet lag, as well as delayed sleep phase syndrome or advanced sleep phase syndrome; beneficial effects of melatonin were reported in these conditions.

## Orexin (Hypocretin) Receptor Antagonists

Orexin A (or hypocretin 1) and orexin B (or hypocretin 2) are newly discovered hypothalamic neuropeptides that play critical roles in the promotion and maintenance of wakefulness and in the pathophysiology of narcolepsy with cataplexy ([Nishino 2011](#); [Sakurai et al. 1998](#)). In humans, chronic loss of orexin neurons is associated with narcolepsy with cataplexy (i.e., *International Classification of Sleep Disorders*, 3rd Edition [ICSD-3; [American Academy of Sleep Medicine 2014](#)]-defined type 1 narcolepsy). Orexin neurons are presumed to be most active during wakefulness and least active during sleep. Two G protein-coupled receptors for orexin peptides (orexin receptor 1 and orexin receptor 2) have been identified ([Nishino 2011](#); [Sakurai et al. 1998](#)).

Although efforts to develop therapies for type 1 narcolepsy using orexin receptor agonists are still in progress, an orally active dual orexin receptor antagonist has been developed, and in August 2014, this agent—suvorexant (marketed under the name Belsomra)—received FDA approval for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance (see [Winrow et al. 2011](#); [Yang 2014](#); also see [Merck & Co 2014](#)). The recommended dosage is 10 mg/day (a maximum of 20 mg once daily), to be taken orally once every night within 30 minutes of bedtime and with at least 7 hours remaining until the planned wake time.

Suvorexant has demonstrated efficacy in both inducing and maintaining sleep ([Jacobson et al. 2014](#)). In Phase II and Phase III studies of suvorexant 15 mg or 20 mg once daily versus placebo, significantly greater improvements on both subjective (total sleep time) and objective (polysomnography-determined wake time after sleep onset) measures were seen at 1 night, 1 month, and 3 months ([Jacobson et al. 2014](#)).

Suvorexant is contraindicated in people diagnosed with narcolepsy, given that the effects of orexin receptor antagonists in narcolepsy—either ICSD-3 type 1 (hypocretin deficient) or type 2 (hypocretin nondeficient)—are not predictable ([Merck & Co 2014](#)). Use of suvorexant is not recommended for individuals with liver impairment or for those who are taking medications that strongly inhibit the CYP3A4 enzyme, such as itraconazole, lopinavir/ritonavir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, or conivaptan ([Merck & Co 2014](#)).

Suvorexant is well tolerated. Adverse effects include next-day sleepiness and fatigue and issues with driving, as well as unusual dreams ([Merck & Co 2014](#)). Sleep paralysis and hypnagogic/hypnopompic hallucinations also have been reported to occur.

Suvorexant's median time to peak plasma concentration ( $T_{\max}$ ) is 2 hours under fasting conditions ([Merck & Co 2014](#)). For a suvorexant 10-mg dose, the mean absolute bioavailability is 82%. Administration of suvorexant with a high-fat meal had no clinically



significant effects on systemic drug exposure but delayed  $T_{\max}$  by 1.5 hours. Steady state is achieved within 3 days. Suvorexant is primarily metabolized by CYP3A4, with a minor contribution from CYP2C19. The main circulating compounds are the unchanged drug and a hydroxyl metabolite, which is not expected to be pharmacologically active. Suvorexant is primarily eliminated in the feces, with about 66% of a radiolabeled dose recovered in the feces (vs. 23% in the urine). The mean elimination half-life of suvorexant is 12 hours.

Concomitant use of suvorexant with other CNS depressant drugs (e.g., benzodiazepines, opioids, tricyclic antidepressants) may produce additive effects; dosage adjustments in either or both drugs may be required ([Merck & Co 2014](#)).

Although it is unlikely that orexin receptor antagonists are themselves addictive, suvorexant has been classified as a Schedule IV controlled substance. There are as yet no published studies comparing suvorexant with other medications used for insomnia. Because insomnia is a very heterogeneous disease condition, it is likely that many patients will benefit from this new agent, and large amounts of clinical data should soon be available.

---

## General Considerations in the Pharmacological Treatment of Insomnia

---

The *International Classification of Sleep Disorders* is the classification system most commonly used by sleep medicine specialists. The first edition of the *International Classification of Sleep Disorders* (ICSD) was published in 1990, and the ICSD was subsequently revised in 2005 (ICSD-2) and 2014 (ICSD-3). The sleep disorder classification in the fifth edition of *The Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; [American](#)



[Psychiatric Association 2013](#)) is similar to that in the ICSD-3 ([American Academy of Sleep Medicine 2014](#)).

Insomnia is a subjective complaint of insufficient, inadequate, or nonrestorative sleep ([Buysse and Reynolds 1990](#)). The ICSD-3 defines insomnia as “a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep and results in some form of daytime impairment” ([American Academy of Sleep Medicine 2014](#)). Inadequate sleep causes disturbances in daytime functioning, such as fatigue, mood problems, and impaired performance.

Insomnia is a common symptom. Estimates of its prevalence depend on the definition criteria used and the population studied. As a result of these differences in case definition, prevalence estimates have varied widely—from 10% to 40% ([Mai and Buysse 2008](#))—but tend to average about 30% for insomnia and 5%–10% for specific insomnia disorders at ([Roth 2007](#)). The current use of hypnotics in the general population is estimated to range between 3.5% and 11.7% ([Mellinger et al. 1985](#); [Ohayon and Caulet 1996](#); [Ohayon et al. 1998](#); [Quera-Salva et al. 1991](#)).

Insomnia is a symptom that must be explored clinically before treatment is initiated. Sleep disturbances often indicate a larger psychiatric problem, such as depression. As mentioned earlier, insomnia is a common complaint in older populations, especially in institutional settings. In some cases, environmental factors (e.g., noise) or other sleep disorders (e.g., periodic leg movements, sleep apneas, parasomnias) may be involved.

## Insomnia Classifications Based on Duration

A useful initial approach to the patient with insomnia is to consider the duration of the complaint. The duration of the insomnia not only suggests its cause but also provides some guidance on how best to use hypnotics in its treatment.

The ICSD-3 identifies three distinct types of insomnia: short-term insomnia, chronic insomnia, and other insomnia (for insomnia symptoms that do not meet criteria for short-term or chronic insomnia). Previous ICSD editions had subclassified chronic insomnia into primary and comorbid types, but these subclasses were eliminated in the ICSD-3 because it was judged that they did not improve diagnostic accuracy.

## **Chronic insomnia Disorder**

ICSD-3 consolidates all chronic insomnia diagnoses under a single disorder, chronic insomnia disorder. Chronic insomnia disorder requires a report of a sleep initiation or sleep maintenance problem, an adequate opportunity and circumstances to sleep, and daytime consequences as the result of the insomnia symptoms.

To meet diagnostic criteria for chronic insomnia disorder, the patient should have symptoms at least three times per week over a duration of 3 or more months. Because insomnia is a component of many psychiatric and medical conditions, a diagnosis of chronic insomnia disorder should be considered only when the insomnia is very prominent and requires further evaluation and treatment.

Chronic insomnia (several months or even years) should first be evaluated with a sleep log of a 2-week period. Most commonly, some degree of sleep-state misperception is present, and patients with chronic insomnia may greatly exaggerate the complaint. In rare cases, insomnia began in childhood and has persisted into adulthood (idiopathic insomnia). In chronic insomnia, improved sleep hygiene and various behavioral techniques that aim to reduce negative conditioning (e.g., stimulus control therapy, sleep restriction, phototherapy) are often helpful on a long-term basis, but these methods are successful only if the patient is motivated and if specialized clinical supervision is available. Pharmacotherapy is most appropriate for patients whose sleep disturbance is clearly causing some daytime dysfunction. If the clinician decides to prescribe medication, it is always helpful to start with the lowest dose of hypnotic possible to reduce the risk

of tolerance and dependence; in addition, it is recommended that daily use be avoided if possible.

## **Short-Term Insomnia Disorder**

To meet diagnostic criteria for ICSD-3 short-term insomnia disorder, the patient must meet the same criteria required for chronic insomnia disorder except that the symptom duration may be less than 3 months. Development of symptoms is often temporarily related to a significant stressor. To qualify for this diagnosis, the insomnia must be an independent focus for the patient and/or require separate clinical attention. Short-term insomnia disorder often resolves when the stressor does, or when the patient develops adequate coping mechanisms or adapts to the stressor ([American Academy of Sleep Medicine 2014](#)).

Transient insomnias (1-2 days) are common and are typically caused by an environmental acute stressor, jet lag, or shift work; these insomnias usually do not require pharmacological treatment. However, if medication is prescribed for transient symptoms, benzodiazepine hypnotics (or other hypnotics with fewer side effects) may be used, because dependency is unlikely to develop when the therapy lasts less than 7-10 days.

It is particularly important that transient and short-term (a few days to a few months) insomnias be recognized and treated so that they do not evolve into longer-term, enduring disorders, such as psychophysiological insomnia. In this subtype, the patient begins to worry excessively about his or her sleep, so that what may have begun as a brief period of insomnia during a stressful time transitions into a behaviorally learned chronic sleep disorder that does not resolve once the stressful period is over. In psychophysiological insomnia, daily use of benzodiazepine hypnotics is also dangerous because it may lead to tolerance and dependence. The clinician should provide reassurance regarding the favorable resolution of the stressful event, and the patient should be instructed to use hypnotic medications intermittently to avoid developing tolerance. Education in proper sleep hygiene is

also important to reduce the possibility of evolution into a chronic problem.

## Insomnia Classifications Based on Clinical Features

Insomnia also can be classified on the basis of individual clinical features—that is, problems with sleep initiation, sleep maintenance, or termination (early-morning awakening). In this context, the most important pharmacological properties to consider when selecting a hypnotic for treatment are how quickly it acts and how long the effects last (see [Table 43-2](#) for this information for commonly used compounds). The rate of absorption is the most critical factor determining onset of action.  $T_{\max}$  is the pharmacological parameter that best predicts onset of action. After absorption, hypnotics are distributed to various organs; distribution and drug elimination influence the duration of action. The elimination half-life (see [Table 43-2](#)) usually provides a good first estimate of the duration of action for drugs that have comparable absorption and distribution profiles.

Hypnotics with a long duration of action are helpful for patients who have difficulty in both initiating and maintaining sleep. One advantage of these long-acting compounds is that rebound insomnia is often delayed and milder if the drugs have to be withdrawn (see [Figure 43-7](#)). Patients who have difficulty initiating sleep might prefer short-acting compounds; however, for these compounds, it may be necessary, paradoxically, to switch to longer-acting hypnotics before withdrawal of all hypnotic treatment.

The importance of determining whether insomnia is the symptom of an underlying neuropsychiatric condition must be emphasized (see [Chapter 53](#) in this volume, “Treatment of Insomnia,” by Krystal). If depression is a contributing factor, a sedating antidepressant such as amitriptyline, doxepin, or trazodone can be used alone or in combination with a hypnotic

(see [Chapter 46, “Treatment of Depression,”](#) by Bobo and Shelton). Individuals with schizophrenia can experience persistent insomnia (affecting both initiation and maintenance of sleep), and antipsychotics with sleep-enhancing effects, such as olanzapine or quetiapine, may be effective therapies (see [Chapter 49, “Treatment of Schizophrenia,”](#) by Woo et al.). For insomnia associated with anxiety disorders, hypnotics supplemented with anxiolytics can be used (see [Chapter 48, “Treatment of Anxiety and Related Disorders,”](#) by David and Davidson).

## Special Considerations for Insomnia Treatment in Elderly Patients

Sleep disturbances are very frequent complaints in old age, and treatment must be initiated carefully in this population. Between 5% and 33% of elderly people in North America and the United Kingdom are prescribed a benzodiazepine or a benzodiazepine receptor agonist (e.g., zolpidem, zopiclone, zaleplon) for sleep problems ([Aparasu et al. 2003](#); [Craig et al. 2003](#); [Gottlieb 1990](#); [Jaussent et al. 2013](#)), and this segment of the population receives 35%–40% of all sedative-hypnotic prescriptions ([Gottlieb 1990](#)).

Before starting pharmacological therapy, all possible causes of insomnia should be examined (e.g., psychophysiological; associated with drugs or alcohol; due to disturbance of the sleep-wake cycle; associated with periodic leg movements, sleep apnea, or other physical or psychiatric conditions). Likewise, before selecting a specific hypnotic, the clinician should consider its pharmacological properties and side-effect profile, the patient’s medical health and medical history, and the patient’s history of sedative-hypnotic use. The special case of melatonin and melatonin receptor agonists was discussed earlier in this chapter (see section “Other Sedative-Hypnotic Compounds”). Data on the efficacy of orexin receptor antagonists in elderly people are still being accumulated.

Hypnotics or their active metabolites often accumulate during chronic use in elderly patients, and this accumulation may cause cognition problems, disorientation, confusion, and (occasionally) falls. Hypnotics with short or intermediate half-lives are thus recommended, and the lowest dose possible should be used. Compounds with a short half-life, such as triazolam or zolpidem, may be effective for problems with sleep initiation and sleep fragmentation. Zolpidem has little muscle-relaxant effect and may be preferable to triazolam. Compounds with an intermediate hypnotic profile, such as estazolam or temazepam, are also reported to be effective in elderly patients. Hypnotics with an intermediate half-life may alter daytime performance and memory to a lesser extent than regular hypnotics, and they are not as likely to induce rebound insomnia after withdrawal.

---

## Conclusion

---

The mechanism of action of most currently available hypnotics (benzodiazepines, barbiturates, alcohol, and nonbenzodiazepine hypnotics) involves a modulatory effect on GABAergic activity. These compounds stimulate GABAergic transmission by acting on the GABA<sub>A</sub>-benzodiazepine-Cl<sup>-</sup> macromolecular complex, which is known to contain multiple modulatory binding sites and many receptor subtypes. This recently discovered molecular diversity within the macromolecular complex suggests that new GABAergic hypnotic compounds, including newly developed nonbenzodiazepine hypnotics with subtype selectivity, may have more favorable side-effect profiles.

Other non-GABAergic hypnotics, including sedative antidepressants, antihistamines, melatonin and melatonin receptor agonists, and (most recently) orexin receptor antagonists, are useful strategies in the treatment of insomnia, especially because these hypnotics may lack some of the hampering side effects often seen with classical GABAergic hypnotics, such as abuse potential and amnesic effects.

Prescription of these non-GABAergic hypnotics, as with the prescription of other regular benzodiazepine-like hypnotic compounds, should be guided by the knowledge that insomnia is a heterogeneous condition that must be explored clinically before any pharmacological treatment is initiated.

---

## References

---

- Al-Aama T, Brymer C, Gutmanis I, et al: Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. *Int J Geriatr Psychiatry* 26(7):687-694, 2011 20845391
- Allen D, Curran HV, Lader M: The effects of single doses of CL284,846, lorazepam, and placebo on psychomotor and memory function in normal male volunteers. *Eur J Clin Pharmacol* 45(4):313-320, 1993 8299662
- American Academy of Sleep Medicine: The International Classification of Sleep Disorders: Diagnostic and Coding Manual, 3rd Edition (ICSD-3). Darien, IL, American Academy of Sleep Medicine, 2014
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Amin J, Weiss DS: GABAA receptor needs two homologous domains of the beta-subunit for activation by GABA but not by pentobarbital. *Nature* 366(6455):565-569, 1993 7504783
- Andriamampandry C, Taleb O, Viry S, et al: Cloning and characterization of a rat brain receptor that binds the endogenous neuromodulator gamma-hydroxybutyrate (GHB). *FASEB J* 17(12):1691-1693, 2003 12958178
- Aparasu RR, Mort JR, Brandt H: Psychotropic prescription use by community-dwelling elderly in the United States. *J Am Geriatr Soc* 51(5):671-677, 2003 12752843
- Arendt J, Aldhous M, Marks V, et al: Some effects of jet-lag and their alleviation by melatonin. *Ergonomics* 30:1379-1393, 1987
- Arendt J, Aldhous M, Wright J: Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment.

- Lancet 1(8588):772-773, 1988 2895305
- Asano T, Ogasawara N: Chloride-dependent stimulation of GABA and benzodiazepine receptor binding by pentobarbital. *Brain Res* 225(1):212-216, 1981 6271340
- Awad M, Gavish M: Binding of [3H]Ro 5-4864 and [3H]PK 11195 to cerebral cortex and peripheral tissues of various species: species differences and heterogeneity in peripheral benzodiazepine binding sites. *J Neurochem* 49(5):1407-1414, 1987 2822854
- Baenninger A: *Good Chemistry: The Life and Legacy of Valium Inventor Leo Sternbach*. New York, McGraw-Hill, 2004
- Beer B, Ieni JR, Wu WH, et al: A placebo-controlled evaluation of single, escalating doses of CL 284,846, a non-benzodiazepine hypnotic. *J Clin Pharmacol* 34(4): 335-344, 1994 8006201
- Besharse JC, Dunis DA: Methoxyindoles and photoreceptor metabolism: activation of rod shedding. *Science* 219(4590):1341-1343, 1983 6828862
- Bessman SP, Fishbein WN: Gamma-Hydroxybutyrate, a Normal Brain Metabolite. *Nature* 200:1207-1208, 1963 14089913
- Boileau AJ, Kucken AM, Evers AR, Czajkowski C: Molecular dissection of benzodiazepine binding and allosteric coupling using chimeric gamma-aminobutyric acidA receptor subunits. *Mol Pharmacol* 53(2):295-303, 1998 9463488
- Boileau AJ, Evers AR, Davis AF, Czajkowski C: Mapping the agonist binding site of the GABAA receptor: evidence for a beta-strand. *J Neurosci* 19(12):4847-4854, 1999 10366619
- Braestrup C, Nielsen M: Benzodiazepine binding in vivo and efficacy, in *Benzodiazepine/GABA Receptors and Chloride Channels: Structural and Functional Properties*. Edited by Olsen RW, Venter JC. New York, Alan R Liss, 1986, pp 167-184
- Buyse DJ, Reynolds CF 3rd: Insomnia, in *Handbook of Sleep Disorders*. Edited by Thorpy MJ. New York, Marcel Dekker, 1990, pp 375-433
- Castelli MP, Pibiri F, Carboni G, Piras AP: A review of pharmacology of NCS-382, a putative antagonist of gamma-hydroxybutyric acid (GHB) receptor. *CNS Drug Rev* 10(3):243-260, 2004 15492774
- Chiara DC, Jayakar SS, Zhou X, et al: Specificity of intersubunit general anesthetic-binding sites in the transmembrane domain



- of the human  $\alpha 1\beta 3\gamma 2$   $\gamma$ -aminobutyric acid type A (GABAA) receptor. *J Biol Chem* 288(27):19343-19357, 2013 23677991
- Cook L, Sepinwall J: Behavioral analysis of the effects and mechanisms of action of benzodiazepines. *Adv Biochem Psychopharmacol* 14(14):1-28, 1975 242196
- Cortelli P, Avallone R, Baraldi M, et al: Endozepines in recurrent stupor. *Sleep Med Rev* 9(6):477-487, 2005 16233983
- Costa E, Guidotti A: Diazepam binding inhibitor (DBI): a peptide with multiple biological actions. *Life Sci* 49(5):325-344, 1991 1649940
- Craig D, Passmore AP, Fullerton KJ, et al: Factors influencing prescription of CNS medications in different elderly populations. *Pharmacoepidemiol Drug Saf* 12(5):383-387, 2003 12899112
- Crestani F, Löw K, Keist R, et al: Molecular targets for the myorelaxant action of diazepam. *Mol Pharmacol* 59(3):442-445, 2001 11179437
- Dahlitz M, Alvarez B, Vignau J, et al: Delayed sleep phase syndrome response to melatonin. *Lancet* 337(8750):1121-1124, 1991 1674014
- Dollins AB, Zhdanova IV, Wurtman RJ, et al: Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci U S A* 91(5):1824-1828, 1994 8127888
- Dubocovich ML: Melatonin receptors: are there multiple subtypes? *Trends Pharmacol Sci* 16(2):50-56, 1995 7762083
- Edgar DM, Dement WC, Fuller CA: Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci* 13(3):1065-1079, 1993 8441003
- Edgar DM, Seidel WF, Gee KW, et al: CCD-3693: an orally bioavailable analog of the endogenous neuroactive steroid, pregnanolone, demonstrates potent sedative hypnotic actions in the rat. *J Pharmacol Exp Ther* 282(1):420-429, 1997 9223583
- Farzampour Z, Reimer RJ, Huguenard J: Endozepines. *Chronobiol Int* 72:147-164, 2015 25600369
- Folkard S, Arendt J, Clark M: Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. *Chronobiol Int* 10(5):315-320, 1993 8261530

- Friess E, Lance M, Holster F: The effects of “neuroactive” steroids upon sleep in human and rats (abstract). *J Sleep Res* 5:S69, 1996
- Garfinkel D, Laudon M, Nof D, Zisapel N: Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 346(8974):541-544, 1995 7658780
- Gavish M, Katz Y, Bar-Ami S, Weizman R: Biochemical, physiological, and pathological aspects of the peripheral benzodiazepine receptor. *J Neurochem* 58(5):1589-1601, 1992 1313848
- Geddes DM, Rudolf M, Saunders KB: Effect of nitrazepam and flurazepam on the ventilatory response to carbon dioxide. *Thorax* 31(5):548-551, 1976 11571
- Gottlieb GL: Sleep disorders and their management. Special considerations in the elderly. *Am J Med* 88(3A):29S-33S, 1990 1968717
- Haefley W: Partial agonists of the benzodiazepine receptor: from animal data to results in patients, in *Chloride Channels and Their Modulation by Neurotransmission and Drugs*. Edited by Biggio G, Costa E. New York, Raven, 1988, pp 275-292
- Haimov I, Laudon M, Zisapel N, et al: Sleep disorders and melatonin rhythms in elderly people. *BMJ* 309(6948):167, 1994 8044096
- Haimov I, Lavie P, Laudon M, et al: Melatonin treatment of sleep onset insomnia in the elderly. *Sleep* 18:598-603, 1995 8552931
- Hatta K, Kishi Y, Wada K, et al: Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry* 71(4):397-403, 2014 24554232
- Hughes RJ, Sack RL, Lewy AJ: The role of melatonin and circadian phase in age-related sleep-maintenance insomnia: assessment in a clinical trial of melatonin replacement. *Sleep* 21(1):52-68, 1998 9485533
- Jacobson LH, Callander GE, Hoyer D: Suvorexant for the treatment of insomnia. *Expert Rev Clin Pharmacol* 7(6):711-730, 2014 25318834
- Jaussent I, Ancelin ML, Berr C, et al: Hypnotics and mortality in an elderly general population: a 12-year prospective study. *BMC Med* 11:212, 2013 24070457

- Jovanovic UJ, Dreyfus JF: Polygraphical sleep recordings in insomniac patients under zopiclone or nitrazepam. *Pharmacology* 27 (suppl 2):136-145, 1983 6669629
- Kales A, Scharf MB, Kales JD, Soldatos CR: Rebound insomnia. A potential hazard following withdrawal of certain benzodiazepines. *JAMA* 241(16):1692-1695, 1979 430730
- Kay DC, Blackburn AB, Buckingham JA, et al: Human pharmacology of sleep, in *Pharmacology of Sleep*. Edited by Williams RL, Karakan I. New York, Wiley, 1976, pp 83-210
- Killam EK: Drug action on the brain-stem reticular formation. *Pharmacol Rev* 14:175-223, 1962 14455916
- Kofuji P, Wang JB, Moss SJ, et al: Generation of two forms of the gamma-aminobutyric acidA receptor gamma 2-subunit in mice by alternative splicing. *J Neurochem* 56(2):713-715, 1991 1846404
- Kuriyama A, Honda M, Hayashino Y: Ramelteon for the treatment of insomnia in adults: a systematic review and meta-analysis. *Sleep Med* 15(4):385-392, 2014 24656909
- Lapierre O, Montplaisir J, Lamarre M, Bedard MA: The effect of gamma-hydroxybutyrate on nocturnal and diurnal sleep of normal subjects: further considerations on REM sleep-triggering mechanisms. *Sleep* 13(1):24-30, 1990 2406848
- Leeb-Lundberg F, Snowman A, Olsen RW: Barbiturate receptor sites are coupled to benzodiazepine receptors. *Proc Natl Acad Sci U S A* 77(12):7468-7472, 1980 6261261
- Lemoine P, Nir T, Laudon M, Zisapel N: Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. *J Sleep Res* 16(4):372-380, 2007 18036082
- Löw K, Crestani F, Keist R, et al: Molecular and neuronal substrate for the selective attenuation of anxiety. *Science* 290(5489):131-134, 2000 11021797
- Lushington K, Lack L, Kennaway DJ, et al: 6-Sulfatoxymelatonin excretion and self-reported sleep in good sleeping controls and 55-80-year-old insomniacs. *J Sleep Res* 7(2):75-83, 1998 9682178
- Mai E, Buysse D: Insomnia: prevalence, impact, pathogenesis, differential diagnosis, and evaluation. *Sleep Med Clin* 3(2):167-174, 2008 19122760

- Maitre M: The gamma-hydroxybutyrate signalling system in brain: organization and functional implications. *Prog Neurobiol* 51(3):337-361, 1997 9089792
- Markov D, Doghramji K: Doxepin for insomnia. *Current Psychiatry* 9(10):67-77, 2010
- Marquardt H, Todaro GJ, Shoyab M: Complete amino acid sequences of bovine and human endozepines. Homology with rat diazepam binding inhibitor. *J Biol Chem* 261(21):9727-9731, 1986 3525533
- Maynert EW: Sedative and hypnotics, II: barbiturates, in *Drill's Pharmacology in Medicine*. Edited by DiPalma IR. New York, McGraw-Hill, 1965, pp 188-209
- McKernan RM, Rosahl TW, Reynolds DS, et al: Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype. *Nat Neurosci* 3(6):587-592, 2000 10816315
- Mehta AK, Ticku MK: An update on GABAA receptors. *Brain Res Brain Res Rev* 29(2-3): 196-217, 1999 10209232
- Mellinger GD, Balter MB, Uhlenhuth EH: Insomnia and its treatment. Prevalence and correlates. *Arch Gen Psychiatry* 42(3):225-232, 1985 2858188
- Merck & Co: BELSOMRA (suvorexant) tablets, full prescribing information. Whitehouse Station, NJ, Merck & Co., Inc., 2014. Available at: [https://www.merck.com/product/usa/pi\\_circulars/b/belsomra/belsomra\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf). Accessed September 5, 2016.
- Mignot E, Edgar DM, Miller JD, et al: Strategies for the development of new treatments in sleep disorders medicine, in *Target Receptors for Anxiolytics and Hypnotics: From Molecular Pharmacology to Therapeutics*. Edited by Mendelwicz J, Racagni G, Karger AG. Basel, Switzerland, Karger, 1992, pp 129-150
- Mishima K, Okawa M, Shimizu T, Hishikawa Y: Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. *J Clin Endocrinol Metab* 86(1):129-134, 2001 11231989
- Miyamoto M, Nishikawa H, Doken Y, et al: The sleep-promoting action of ramelteon (TAK-375) in freely moving cats. *Sleep* 27(7):1319-1325, 2004 15586784

- Möhler H, Okada T: Benzodiazepine receptor: demonstration in the central nervous system. *Science* 198(4319):849-851, 1977 918669
- Morgan PJ, Barrett P, Howell HE, Helliwell R: Melatonin receptors: localization, molecular pharmacology and physiological significance. *Neurochem Int* 24(2):101-146, 1994 8161940
- Mullen KD, Szauter KM, Kaminsky-Russ K: "Endogenous" benzodiazepine activity in body fluids of patients with hepatic encephalopathy. *Lancet* 336(8707):81-83, 1990 1975325
- Nishino S: Hypothalamus, hypocretins/orexin, and vigilance control. *Handb Clin Neurol* 99:765-782, 2011 21056227
- Nishino S, Ripley B, Overeem S, et al: Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 355(9197):39-40, 2000 10615891
- Nutt DJ, Glue P, Lawson C, Wilson S: Flumazenil provocation of panic attacks. Evidence for altered benzodiazepine receptor sensitivity in panic disorder. *Arch Gen Psychiatry* 47(10):917-925, 1990 2171449
- Ohayon MM, Caulet M: Psychotropic medication and insomnia complaints in two epidemiological studies. *Can J Psychiatry* 41(7):457-464, 1996 8884035
- Ohayon MM, Caulet M, Priest RG, Guilleminault C: Psychotropic medication consumption patterns in the UK general population. *J Clin Epidemiol* 51(3):273-283, 1998 9495693
- Olsen RW, Ticku MK, Miller T: Dihydropicrotoxinin binding to crayfish muscle sites possibly related to gamma-aminobutyric acid receptor-ionophores. *Mol Pharmacol* 14(3):381-390, 1978 207967
- Papadopoulos V, Amri H, Li H, et al: Structure, function and regulation of the mitochondrial peripheral-type benzodiazepine receptor. *Therapie* 56(5):549-556, 2001 11806292
- Quera-Salva MA, Orluc A, Goldenberg F, Guilleminault C: Insomnia and use of hypnotics: study of a French population. *Sleep* 14(5):386-391, 1991 1759090
- Rajaratnam SM, Polymeropoulos MH, Fisher DM, et al: Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* 373(9662):482-491, 2009 19054552

- Rall TR: Hypnotics and sedatives: ethanol, in *The Pharmacological Basis of Therapeutics*, 8th Edition. Edited by Gilman AG, Rall TW, Niles AS, et al. New York, Pergamon, 1990, pp 345-382
- Reite M, Ruddy J, Nagel K: *Concise Guide to Evaluation and Management of Sleep Disorders*, 2nd Edition. Washington, DC, American Psychiatric Press, 1997
- Reppert SM, Weaver DR, Ebisawa T: Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. *Neuron* 13(5):1177-1185, 1994 7946354
- Reppert SM, Godson C, Mahle CD, et al: Molecular characterization of a second melatonin receptor expressed in human retina and brain: the Mel1b melatonin receptor. *Proc Natl Acad Sci U S A* 92(19):8734-8738, 1995 7568007
- Roth T: Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med* 3 (5 suppl):S7-S10, 2007 17824495
- Rothstein JD, Guidotti A, Tinuper P, et al: Endogenous benzodiazepine receptor ligands in idiopathic recurring stupor. *Lancet* 340(8826):1002-1004, 1992 1357403
- Rudolph U, Crestani F, Benke D, et al: Benzodiazepine actions mediated by specific gamma-aminobutyric acid(A) receptor subtypes. *Nature* 401(6755):796-800, 1999 10548105
- Rupprecht R, Hauser CAE, Trapp T, Holsboer F: Neurosteroids: molecular mechanisms of action and psychopharmacological significance. *J Steroid Biochem Mol Biol* 56(1-6 Spec No):163-168, 1996 8603037
- Rye DB, Bliwise DL, Parker K, et al: Modulation of vigilance in the primary hypersomnias by endogenous enhancement of GABAA receptors. *Sci Transl Med* 4(161):161ra151, 2012 23175709
- Sack RL, Lewy AJ, Blood ML, et al: Melatonin administration to blind people: phase advances and entrainment. *J Biol Rhythms* 6(3):249-261, 1991 1773095
- Sakurai T, Amemiya A, Ishii M, et al: Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92(4):573-585, 1998 9491897
- Sanna E, Garau F, Harris RA: Novel properties of homomeric beta 1 gamma-aminobutyric acid type A receptors: actions of the

- anesthetics propofol and pentobarbital. *Mol Pharmacol* 47(2):213-217, 1995 7870027
- Saper CB, Chou TC, Scammell TE: The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci* 24(12):726-731, 2001 11718878
- Scrima L, Hartman PG, Johnson FH Jr, et al: The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. *Sleep* 13(6):479-490, 1990 2281247
- Sengupta A, Baba K, Mazzoni F, et al: Localization of melatonin receptor 1 in mouse retina and its role in the circadian regulation of the electroretinogram and dopamine levels. *PLoS One* 6(9):e24483, 2011 21915336
- Sherin JE, Shiromani PJ, McCarley RW, Saper CB: Activation of ventrolateral preoptic neurons during sleep. *Science* 271(5246): 216-219, 1996 8539624
- Shlarf MB: Pharmacology of classic and novel hypnotic drugs, in *Target Receptors for Anxiolytics and Hypnotics: From Molecular Pharmacology to Therapeutics*. Edited by Mendelwicz J, Racagni G. Basel, Switzerland, Karger, 1992, pp 109-116
- Sigel E, Baur R, Kellenberger S, Malherbe P: Point mutations affecting antagonist affinity and agonist dependent gating of GABAA receptor channels. *EMBO J* 11(6): 2017-2023, 1992 1376242
- Smith GB, Olsen RW: Identification of a [3H] muscimol photoaffinity substrate in the bovine gamma-aminobutyric acid A receptor alpha subunit. *J Biol Chem* 269(32): 20380-20387, 1994 8051133
- Squires RF, Brastrup C: Benzodiazepine receptors in rat brain. *Nature* 266(5604):732-734, 1977 876354
- Srinivasan V, Pandi-Perumal SR, Cardinali DP, et al: Melatonin in Alzheimer's disease and other neurodegenerative disorders. *Behav Brain Funct* 2:15, 2006 16674804
- Stahl SM: Selective histamine H1 antagonism: novel hypnotic and pharmacologic actions challenge classical notions of antihistamines. *CNS Spectr* 13(12):1027-1038, 2008 19179941
- Szymusiak R: Magnocellular nuclei of the basal forebrain: substrates of sleep and arousal regulation. *Sleep* 18(6):478-

500, 1995 7481420

- Takeda Pharmaceuticals America, Inc.: ROZEREM (ramelteon) tablets, full prescribing information. Deerfield, IL, Takeda Pharmaceuticals America, Inc., 2010. Available at: <http://general.takedapharm.com/content/file.aspx?filetypecode=rozerempi&cacheRandomizer=2c57f64a-3dc1-4f95-b2c9-08cc584f1a07>. Accessed October 30, 2016.
- Tallman JF, Thomas JW, Gallager DW: GABAergic modulation of benzodiazepine binding site sensitivity. *Nature* 274(5669):383-385, 1978 27722
- Tobler I, Kopp C, Deboer T, Rudolph U: Diazepam-induced changes in sleep: role of the alpha 1 GABA(A) receptor subtype. *Proc Natl Acad Sci U S A* 98(11): 6464-6469, 2001 11353839
- Twyman RE, Rogers CJ, Macdonald RL: Differential regulation of gamma-aminobutyric acid receptor channels by diazepam and phenobarbital. *Ann Neurol* 25(3):213-220, 1989 2471436
- Ueno S, Minami K, Yanagihara N: [Structure and function of GABAA receptors: recent studies by site-directed mutagenesis] (in Japanese). *Protein, Nucleic Acid, and Enzyme* 46(14):2042-2051, 2001 11712333
- van Coevorden A, Mockel J, Laurent E, et al: Neuroendocrine rhythms and sleep in aging men. *Am J Physiol* 260(4 Pt 1):E651-E661, 1991 2018128
- Vanda Pharmaceuticals Inc.: HETLIOZ® (tasimelteon) capsules, full prescribing information. Washington, DC, Vanda Pharmaceuticals Inc., 2014. Available at: <http://www.hetlitz.com/pdf/HetlitzPI.pdf>. Accessed October 30, 2016.
- Vayer P, Mandel P, Maitre M: Gamma-hydroxybutyrate, a possible neurotransmitter. *Life Sci* 41(13):1547-1557, 1987 2887998
- Winrow CJ, Gotter AL, Cox CD, et al: Promotion of sleep by suvorexant-a novel dual orexin receptor antagonist. *J Neurogenet* 25(1-2):52-61, 2011 21473737
- Wisden W, Stephens DN: Towards better benzodiazepines. *Nature* 401(6755):751-752, 1999 10548094
- Wong CG, Gibson KM, Snead OC 3rd: From the street to the brain: neurobiology of the recreational drug gamma-



hydroxybutyric acid. Trends Pharmacol Sci 25(1): 29-34, 2004  
14723976

Yang LP: Suvorexant: first global approval. Drugs 74(15):1817-1822, 2014 25227290

Youngstedt SD, Kripke DF, Elliott JA: Melatonin excretion is not related to sleep in the elderly. J Pineal Res 24(3):142-145, 1998 9551850

Zeitzer JM, Daniels JE, Duffy JF, et al: Do plasma melatonin concentrations decline with age? Am J Med 107(5):432-436, 1999 10569297

Zhdanova IV, Wurtman RJ, Regan MM, et al: Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab 86(10): 4727-4730, 2001 11600532

## CHAPTER 44

# Psychostimulants and Wakefulness-Promoting Agents

Charles DeBattista, D.M.H., M.D.

**Amphetamine**, first discovered in 1887, and the subsequently developed stimulants have been used in clinical psychiatry with varying results. Beyond their use for attention-deficit/hyperactivity disorder (ADHD), stimulants have been used for symptomatic relief based on their effects on mood and hedonic drive. Research into the use of stimulants as adjunctive agents in the treatment of specific symptoms and syndromes has been increasing. Various common adjunctive psychotherapeutic uses for stimulants, such as depression, have not been well researched, whereas other indications, such as narcolepsy, are backed by considerable clinical data. In this chapter, I review the pharmacology of these medications and their indications (Tables 44-1 and 44-2).

**TABLE 44-1. FDA classifications of psychostimulants and wakefulness-promoting agents**

Agent	Schedule	Approved for	Medication type	Abuse potential
Amphetamine	II	ADHD, narcolepsy	Anorexiant/stimulant	Black box warning
Lisdexamfetamine	II	ADHD	Stimulant	Black box warning
Methylphenidate	II	ADHD, narcolepsy	Anorexiant/stimulant ("Mild stimulant")	Black box warning

*Note.* ADHD=attention-deficit/hyperactivity disorder; FDA=U.S. Food and Drug Administration; OSAHS=obstructive sleep apnea/hypopnea syndrome; SWSD=shift-work sleep disorder.

*Source.* Adapted from *Physicians' Desk Reference*, 60th Edition. Montvale, NJ, Medical Economics Company, 2006.

<b>Agent</b>	<b>Schedule</b>	<b>Approved for Medication type</b>	<b>Abuse potential</b>
Modafinil	IV	Excessive daytime sleepiness associated with narcolepsy, OSAHS, and SWSD	Wakefulness-promoting agent Reinforcing
Armodafinil	IV	Excessive daytime sleepiness associated with narcolepsy, OSAHS, and SWSD	Wakefulness-promoting agent Reinforcing

*Note.* ADHD=attention-deficit/hyperactivity disorder; FDA=U.S. Food and Drug Administration; OSAHS=obstructive sleep apnea/hypopnea syndrome; SWSD=shift-work sleep disorder.

*Source.* Adapted from *Physicians' Desk Reference*, 60th Edition. Montvale, NJ, Medical Economics Company, 2006.

**TABLE 44-2. Amphetamine and methylphenidate preparations**

<b>Stimulant</b>	<b>Time to effect</b>	<b>Peak (hours)</b>	<b>Duration (hours)</b>	<b>Dosing</b>
<b>Amphetamine preparations</b>				
Adderall <sup>a</sup>	~ 1 hour	3	6-9	bid
Adderall XR	1-2 hours	7	6-10	qd (or bid)
Dexedrine	1 hour	3	4-6	bid or tid
Dexedrine Spansules	1 hour	4	6-10	qd or bid
Desoxyn (methamphetamine)	40 minutes	1-3	4-24	qd, bid, or tid

*Note.* bid = twice daily; qd = once daily; tid = three times daily.

<sup>a</sup>Amphetamine/dextroamphetamine, 1:3 ratio.

<sup>b</sup>Laser hole in capsule allows passage of drug; osmotically active push layer expels drug.

<sup>c</sup>Rapid-release and continuous-release beads give biphasic response.

<b>Stimulant</b>	<b>Time to effect</b>	<b>Peak (hours)</b>	<b>Duration (hours)</b>	<b>Dosing</b>
Vyvanse (lisdexamfetamine)	~ 1 hour	2	9	qd
<b>Methylphenidate preparations</b>				
Methylphenidate	15-30 minutes	1-2	4-5	bid or tid
Focalin (dexamethylphenidate)	15-30 minutes	1-2	4-5	bid or tid
Ritalin SR (tablet)	1-2 hours	5	8	qd or bid
Concerta <sup>b</sup>	1-2 hours	6-8	12	qd or bid
Metadate-CD <sup>c</sup>	1 hour	Biphasic: 1-2 and 4-5	6-8	qd or bid

*Note.* bid = twice daily; qd = once daily; tid = three times daily.

<sup>a</sup>Amphetamine/dextroamphetamine, 1:3 ratio.

<sup>b</sup>Laser hole in capsule allows passage of drug; osmotically active push layer expels drug.

<sup>c</sup>Rapid-release and continuous-release beads give biphasic response.

## Amphetamines

### Structure-Activity Relations

Structurally, amphetamine is phenylisopropylamine. Ultimate pharmacological action is determined by alterations to any of the three basic parts of the amphetamine molecule.

#### Amine Changes

In terms of affecting clinical utility, substitution at the amine group is the most common alteration. Methamphetamine (both L and D isomers), which is characterized by an additional methyl group attached to the amine, making it a secondary substituted amine, is more potent than amphetamine. Usefully, one may think of the amine group as enhancing stimulant-like properties.

#### Isopropyl Changes

An intact isopropyl side chain appears to be needed in order to maintain the potency of amphetamine. For example, changing the propyl to an ethyl chain creates phenylethylamine, an endogenous neuroamine (a metabolite of the monoamine oxidase inhibitor [MAOI] phenelzine) that has mood- and energy-enhancing properties but less potency and a much shorter half-life than amphetamine (Janssen et al. 1999).

## Aromatic Changes

Substitutions on the phenyl group are associated with a decrease in amphetamine-like properties. Interestingly, reduction of the phenyl to a cyclohexyl ring reduces the potency, but not the efficacy, of amphetamine properties. Unlike changes at the amine or isopropyl level, additions to the aromatic ring substantially alter the effects of the compound. The most common changes at the aromatic ring are of the methoxy type and are associated with hallucinogenic properties.

## Stereospecificity

In recent years there has been renewed interest in drugs that are pure stereoisomers, as opposed to racemic mixtures, especially with the release of dexamethylphenidate (the dextro isomer of methylphenidate) and escitalopram (the levo isomer of citalopram). In amphetamine isomers, it is true that the dextro form (i.e., dextro isomer, or dextroamphetamine) is almost twice as potent as the levo form (i.e., levo isomer, or levoamphetamine) in promoting wakefulness, but they are of equal potency in reducing cataplexy and rapid eye movement (REM) sleep ([Nishino and Mignot 1997](#)). The effect on dopamine reuptake is stereospecific; inhibition in rat brain, striatum, and hypothalamus has been found to be markedly different between the two isomers ([Ferris and Tang 1979](#)).

The clinical utility of stereospecificity is unclear. Urine levels of the levo isomer have been used to measure compliance in amphetamine-addicted patients prescribed dextroamphetamine for maintenance or detoxification; the logic is that the more levo isomer present in urine, the less compliance ([George and Braithwaite 2000](#)).

Perhaps the most clinically useful difference between amphetamine isomers involves their differential effects on reinforcement. Studies in rats have shown that the dextro isomer is four times more potent than the levo isomer in promoting lever pressing for intracranial stimulation ([Hunt and Atrens 1992](#)). However, that pure dextroamphetamine is better for the treatment of ADHD than, for example, the mixed salts of dextroamphetamine/amphetamine is neither obvious nor conclusively shown. In addition, the overall greater potency of the dextro form for central actions suggests that this form may have a higher potential for abuse.

## Pharmacological Profile

Amphetamines are noncatecholamine, sympathomimetic amines with central nervous system (CNS) stimulant activity that causes catecholamine efflux and inhibits the reuptake of these neurotransmitters (see subsection “Mechanism of Action” later in this section).

## Pharmacokinetics and Disposition

Amphetamine is highly lipid soluble and reaches peak levels in approximately 2 hours. Because of this lipid solubility, amphetamine has rapid distribution into

tissues and transit across the blood-brain barrier. The protein binding is highly variable, but the average volume of distribution ( $V_d$ ) is 5 L/kg.

The half-life of amphetamine is approximately 16–30 hours. On average, 30% of amphetamine is excreted unchanged.

## Mechanism of Action

The classic mechanism of action of amphetamine involves rapid diffusion directly into neuron terminals; through dopamine and norepinephrine transporters, amphetamine enters vesicles, causing release of dopamine and norepinephrine. The release of these neurotransmitters into the synapse mediates some of the psychological and motoric effects of amphetamine, including euphoria, increased energy, and locomotor activation.

## Side Effects and Toxicology

The side effects of amphetamines are predictable relative to their sympathomimetic pharmacology. The most common effects are nervousness, agitation, and decreased sleep. Serious adverse consequences have been observed with amphetamines and include arrhythmias, hyperpyrexia, rhabdomyolysis, and convulsions. Death, although uncommon, generally occurs only after the manifestation of one of these symptoms. Hallucinoses and psychosis are frequent complications of injected or inhaled amphetamines but are uncommon with oral intoxication.

Methamphetamine is more frequently associated with complications; because of its higher toxicity, it is not clear whether severe complications are dose dependent. For example, in a retrospective study of methamphetamine-related deaths in a large city, methamphetamine use was significantly associated with a higher risk of coronary artery disease, as well as a higher rate of subarachnoid hemorrhage, although it was of course impossible to determine whether the subjects were first-time users or chronic abusers ([Karch et al. 1999](#)). Of particular note in this study, however, was that blood levels of methamphetamine did not differ between the group in which methamphetamine was judged to be the cause of death and the group in which methamphetamine was detected but judged not to be related to the cause of death, suggesting that these toxicities are not necessarily dose dependent. Similarly, in one 5-year study, methamphetamine accounted for 43% of rhabdomyolysis cases in an emergency department setting.

Methamphetamine is more neurotoxic than amphetamine; it can cause destruction of dopaminergic neurons in the basal ganglia and thus is widely thought to increase the likelihood of future parkinsonism ([Guilarte 2001](#)). Although it is commonly believed that MDMA (3,4-methylenedioxy-*N*-methamphetamine; “Ecstasy”) is toxic primarily to serotonergic neurons ([Sprague et al. 1998](#)), evidence shows that it is also toxic to dopaminergic neurons ([Ricaurte et al. 2002](#)).

Seizures are fairly common in amphetamine abuse scenarios, especially with the more potent methamphetamine and hallucinogenic analogs.

Stimulant psychosis—often referred to as *paranoid psychosis*—is also common in amphetamine abuse scenarios because of the overwhelming presentation of the eponymous symptom. Visual hallucinations are also disproportionately common with amphetamine psychosis. Psychosis is often seen together with stereotypy. In humans, stereotypy can take many forms but usually is expressed as pacing, searching, or examining minute details.

## Drug-Drug Interactions

A comprehensive review found that drug interactions with amphetamine were mostly pharmacodynamic in nature ([Markowitz and Patrick 2001](#)); however, because a small portion of amphetamine metabolism occurs via the cytochrome P450 (CYP) 2D6 isoenzyme, those drugs that inhibit 2D6 metabolism can, theoretically, have the effect of increasing the plasma level of amphetamine.

---

## Lisdexamfetamine

---

Lisdexamfetamine dimesylate, a prodrug that on absorption is metabolized to dextroamphetamine and L-lysine, was approved in 2007 for the treatment of ADHD. Food does not affect absorption of lisdexamfetamine, but acidification of the urine results in more rapid clearance.

Two small studies in children found good efficacy and tolerability for lisdexamfetamine in the treatment of ADHD. A 4-week randomized, double-blind, forced-dose, parallel-group study compared lisdexamfetamine 30, 50, or 70 mg/day with placebo in children (ages 6–12 years) with ADHD ([Biederman et al. 2007b](#)). Efficacy, as measured by scores on the ADHD Rating Scale—Version IV (ADHD-RS-IV), the Conners Parent Rating Scale (CPR), and the Clinical Global Impression-Improvement (CGI-I) scale, was statistically superior to that of placebo for all dosages tested. A randomized, double-blind, placebo-controlled crossover study compared lisdexamfetamine with placebo and extended-release mixed amphetamine salts (Adderall XR) in 52 children (ages 6–12 years) with ADHD in an analog classroom setting ([Biederman et al. 2007a](#)). The study found comparable efficacy and safety for the active medications and superiority over placebo as measured by scores on the CGI-I scale and the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)–Department subscale.

In 420 adults, a 4-week forced-dose (30, 50, or 70 mg/day) study found lisdexamfetamine to have significantly greater efficacy over placebo as measured by ADHD-RS scores. Human liability studies have also found lower abuse-related drug-likeness scores compared with immediate-release D-amphetamine at equivalent dosages ([Najib 2009](#)).

In 2014, lisdexamfetamine was approved for the treatment of binge-eating disorder in adults. The registration trials involved more than 700 patients with moderate to severe binge-eating disorder. In a Phase II trial, subjects were randomly assigned to 30, 50, or 70 mg/day lisdexamfetamine or placebo for 3 weeks

and maintained at this dosage for an additional 8 weeks. Compared with placebo, the 50-mg/day and 70-mg/day dosages were more effective in reducing the total number of binge-eating days, were more likely to result in a remission of symptoms, and produced greater global improvement ([McElroy et al. 2015a](#)). Subsequent to that study, two Phase III trials have evaluated the efficacy and safety of lisdexamfetamine (target dosage of 50 or 70 mg/day as tolerated) versus placebo in adults ages 18–55 years with binge-eating disorder. Lisdexamfetamine at both dosages was more effective than placebo in reducing the total number of binge days. The active-treatment groups showed a reduction in binge-eating days from an average of 5 days/week to 1 day/week (versus a reduction to about 2 days/week in the placebo group). Compared with subjects who received placebo, those who received active treatment experienced greater overall improvement, as measured by the CGI-I score ([McElroy et al. 2016](#)).

Several preliminary studies suggested that lisdexamfetamine might be useful as an adjunctive treatment for major depressive disorder. [Trivedi et al. \(2013\)](#) found that 20–50 mg of lisdexamfetamine added to escitalopram for 6 weeks was superior to placebo in treating residual symptoms of depression. However, two subsequent Phase III randomized controlled trials failed to demonstrate a significant benefit for lisdexamfetamine over placebo in the adjunctive treatment of major depressive disorder. Still, there is some evidence that lisdexamfetamine may be more effective than placebo in treating executive function deficits in patients with major depressive disorder ([Madhoo et al. 2014](#)) and that it may have a role in the treatment of bipolar depression ([McElroy et al. 2015b](#)).

---

## Methylphenidate

---

### Structure–Activity Relations

Although methylphenidate has two chiral centers, only one contributes to its clinical effect. The D- and L-threo enantiomers are in a racemic mixture, although a single-isomer form of methylphenidate, dexamethylphenidate [(*R,R*)-(+)], is currently being marketed under the brand name Focalin. There are some differences in the pharmacological parameters of the two isomers, as described in the following subsection.

### Pharmacokinetics and Disposition

Methylphenidate is almost totally absorbed on oral administration (as is the single isomer dexamethylphenidate), although it is absorbed at a faster rate in the presence of food ([Chan et al. 1983](#)). Methylphenidate has low protein binding (15%) and is fairly short acting; the effects last approximately 4 hours, with a half-life of 3 hours. The primary means of clearance is through the urine, in which 90% is excreted.



## Mechanism of Action

Although it is both a norepinephrine and a dopamine reuptake inhibitor, methylphenidate appears to exert its effects primarily through its action on dopamine neurobiology. It blocks the dopamine transporter (DAT) and increases extracellular dopamine. The amount of extracellular dopamine increase varies greatly among individuals depending on the extent of both DAT blockade and baseline dopamine release.

## Side Effects and Toxicology

The common side effects of methylphenidate are similar to those of amphetamine and include nervousness, insomnia, and anorexia, as well as dose-related systemic effects such as increased heart rate and blood pressure. Overdose may lead to seizures, dysrhythmias, or hyperthermia ([Klein-Schwartz 2002](#)). At therapeutic dosages, discontinuation symptoms tend to be slight, but with chronic abuse, symptoms similar to those in amphetamine withdrawal, including lethargy, depression, and paranoia, can occur ([Klein-Schwartz 2002](#)).

## Drug-Drug Interactions

Although theoretically a substrate of CYP2D6, methylphenidate was found not to have any significant metabolism in humans via this enzyme ([DeVane et al. 2000](#)). The prescribing information ([Novartis 2007](#)) does cite methylphenidate's potential ability to inhibit the metabolism of warfarin, some antiepileptic agents, and tricyclic antidepressants (TCAs), and therefore caution should be observed. However, a review found that methylphenidate is relatively safe and has minimal drug-drug interactions, with the exception of concomitant MAOI use ([Markowitz and Patrick 2001](#)).

---

## Modafinil

---

Modafinil is the first U.S. Food and Drug Administration (FDA)-designated "wakefulness-promoting agent"; it is approved by the FDA for the treatment of excessive sleepiness associated with narcolepsy, sleep apnea, and residual sleepiness after standard treatment for shift-work sleep disorder ([Cephalon Inc. 2008](#)). As described below, modafinil does little to prevent or alter sleep when one is trying to do so; however, it appears to permit more stable wakefulness (i.e., reduced sleep propensity) when one is attempting to stay awake in the presence of elevated sleep pressure.

## Structure-Activity Relations

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) exists in racemic form. Both stereoisomers appear to have the same activity in animals.

## Pharmacokinetics and Disposition

Modafinil, the primary metabolite of adrafinil, lacks many of the side effects found in adrafinil, such as increased liver enzymes, anxiety, and stomach pain. Modafinil is rapidly absorbed but slowly cleared. It has fairly high protein binding (60%) and a  $V_d$  of 0.8 L/kg. Its half-life is 11–14 hours.

The metabolism of modafinil is complex. In contrast to excretion of amphetamines, less than 10% of modafinil is excreted unchanged.

Metabolism is primarily via CYP3A4/5. It has been reported that modafinil also has in vitro capacity to induce CYP3A4 ([Robertson et al. 2000](#)), especially gastrointestinal 3A4. A clinically significant reduction of triazolam has been reported ([Robertson et al. 2002](#)).

## Mechanism of Action

The precise mechanism by which modafinil exerts its wakefulness-promoting effect in patients with excessive sleepiness due to narcolepsy is not yet known. Modafinil, given its efficacy in narcolepsy, is not surprisingly observed to increase c-fos activity of hypocretin cells, as well as in the tuberomammillary nucleus (which is primarily histaminergic), striatum, and cingulate cortex at higher dosages ([Scammell et al. 2000](#)). Additionally, in rats, an increase in histamine release in the anterior hypothalamus is seen ([Ishizuka et al. 2003](#)). However, modafinil's wakefulness-promoting effects were not decreased in histamine knockout mice ([Bonaventure et al. 2007](#)).

What may be an important aspect of the pharmacology of modafinil is its lack of effect on the neuroendocrine system. A comparison of healthy volunteers who were sleep deprived for 36 hours with those who received modafinil during sleep deprivation found no difference in cortisol, melatonin, or growth hormone levels ([Brun et al. 1998](#)).

## Side Effects and Toxicology

Modafinil appears to be well tolerated, with the most frequent side effects being headache and nausea. Side effects have been found to increase with dosages from 100 to 600 mg/day, and very high dosages (800 mg/day) have been found to be associated with higher rates of tachycardia and hypertension ([Wong et al. 1999](#)). Overall, only 5% of the patients in Phase III trials discontinued modafinil because of side effects ([Cephalon Inc. 2008](#)).

Modafinil appears to be fairly safe at high dosages. Reports indicate that 32 patients have safely taken 1,000 mg/day for more than 50 days; one individual safely took 1,200 mg/day for 21 consecutive days. Two patients took 4,000 mg and 4,500 mg, respectively, in a single dose and experienced only transient (<24 hours)

agitation and insomnia with mild elevations in heart rate and blood pressure ([Cephalon Inc. 2008](#)). There have been no reports of seizures with modafinil.

During the attempts to obtain FDA approval of modafinil for the treatment of ADHD, concerns arose over the possibility that modafinil may carry a risk of Stevens-Johnson syndrome. Three cases of drug-induced rash were reported during clinical trials ([U.S. Food and Drug Administration 2007](#)).

The package insert notes a risk of “serious rash, including Stevens-Johnson syndrome,” in adults and children and cautions that modafinil is not indicated for children. The insert cites a rash incidence of 0.8% in pediatric patients, with one case of possible Stevens-Johnson syndrome and one case of multiorgan hypersensitivity reported, and concludes with the statement that although there are no known predictive factors, benign rashes do occur, and modafinil should be discontinued if rash develops.

## Drug-Drug Interactions

As described earlier in this section, modafinil induces CYP3A4/5 and thus conceivably could lower the plasma concentrations of medications with substantial 3A4/5 metabolism. However, it is not clear if this induction is substantial only on the gastrointestinal cytochrome and is thus relevant only for other drugs undergoing significant first-pass metabolism.

Modafinil inhibits CYP2C19 in vitro ([Robertson et al. 2000](#)). It is prudent to assume that the effect of modafinil on the cytochrome system is not well characterized and to be vigilant for these potential drug-drug interactions.

---

## Armodafinil

---

Armodafinil, properly *l*-(*R*)-modafinil (or  $[-]$ -*R*)-modafinil), is the longer-acting isomer of racemic modafinil. In 2007, it received FDA approval for the same indications as modafinil—specifically, excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS) as an adjunct to standard treatment, and shift-work sleep disorder (SWSD).

Armodafinil and racemic modafinil produce comparable peak plasma concentrations, although the peak for armodafinil occurs later than that for modafinil and is maintained for 6–14 hours postdose ([Dinges et al. 2006](#)).

Published data on armodafinil are still limited. Two 12-week double-blind studies using armodafinil 150 mg as an adjunct to continuous positive airway pressure (CPAP), both in patients who were otherwise stable except for some residual sleepiness ([Hirshkowitz et al. 2007](#)) and in patients who were still symptomatic ([Roth et al. 2006](#)), found improvements in wakefulness measures. Armodafinil also significantly improved the quality of episodic secondary memory (i.e., the ability to recall unrehearsed information). Whether this effect was due directly to the medication, to improved wakefulness, or to decreased hypoxia (as a function of

being more awake) is unclear. However, armodafinil did not adversely affect the CPAP or any other physiological parameters.

A 12-week double-blind study of armodafinil in narcolepsy found improvements similar to those seen with modafinil. These included improved wakefulness (as measured by the Maintenance of Wakefulness Test), improved Clinical Global Impression of Change (CGI-C) scores, and improvement in memory and attention. Armodafinil 150 mg/day and 250 mg/day were similarly effective ([Harsh et al. 2006](#)).

In SWSD, armodafinil 150 mg/day was tested against placebo in a 12-week study, showing significant prolongation of time to sleep onset and an improvement in overall clinical condition by CGI-C. Armodafinil had no effect on daytime sleep polysomnography ([Roth et al. 2005](#)).

---

## Clinical Uses of Stimulants and Wakefulness-Promoting Agents

---

Although stimulants have been used for many years in a number of clinical scenarios, double-blind, randomized controlled trials examining their safety, efficacy, and effectiveness in neurobehavioral disorders other than ADHD are relatively rare. Most of the support for their use comes from open-label studies and case series. Randomized trials of modafinil for neurobehavioral disorders with symptoms of sleepiness and fatigue are beginning to be published.

### Attention-Deficit/Hyperactivity Disorder

Multiple double-blind, placebo-controlled studies have shown the efficacy of stimulants for ADHD, and their use is well investigated in both adults and children ([Greenhill et al. 2002](#); [Wilens et al. 2002](#)). Some studies are aimed at showing the superiority of one preparation relative to another, although this approach is not always fruitful; for example, one study comparing various single-dose amphetamine preparations with one another and with placebo over 8 weeks found that they were all superior to placebo. However, immediate-release amphetamines had a faster onset but shorter duration of action; spansules, although much slower to take effect than the others, lasted several hours longer ([James et al. 2001](#)).

With respect to individual stimulants, all appear to be equally efficacious in the treatment of ADHD, but they have been reported to have different time courses. In a double-blind, double-control (placebo and methylphenidate) study, the mixed amphetamine salts of Adderall were found to exert their effects rapidly but to dissipate quickly over the course of the day, although Adderall lasted longer than methylphenidate ([Swanson et al. 1998](#)). Interestingly, higher doses of Adderall lasted longer than lower doses, indicating a dose-dependent effect in duration of action not found with methylphenidate. Thus, although stimulants may appear to be of equal efficacy overall, there is considerable variability in individual response to each stimulant.

The decision to choose amphetamines or methylphenidate for the treatment of ADHD is often based on the clinician's preference and degree of experience with the medication. At least one important blinded crossover study found that in performance tasks, both drugs were generally equally efficacious ([Efron et al. 1997](#)).

Modafinil is not FDA approved for the treatment of ADHD. A 4-week double-blind study with an 8-week open-label extension found modafinil to be efficacious across all ADHD rating subscales for the duration of the open-label extension ([Boellner et al. 2006](#)). Interestingly, 10% of the 220 children studied lost an average of 3 kg, while 4% gained the same amount. Another such double-blind study found significant efficacy with dosages of 300 mg/day, although heavier children ( $\geq 30$  kg) required 400 mg/day ([Biederman et al. 2006](#)). A pooled analysis of three trials (638 patients) found that modafinil produced similar and impressive improvements in ADHD rating scales between stimulant-naïve and prior-stimulant subgroups relative to placebo ([Wigal et al. 2006](#)). As in other studies, insomnia and headache were the most common, but infrequent, side effects. A 9-week trial ([Biederman et al. 2005](#)) found that almost half of patients (mean age 10 years, mean dosage 368 mg/day) were much or very much improved, and efficacy was seen in both inattentive and hyperactive subgroups and both school and home ratings. Some small but controlled trials ([Rugino and Samsock 2003](#); [Turner et al. 2004](#)) found efficacy with modafinil, and in one study ([Taylor and Russo 2000](#)), equivalence to dextroamphetamine was shown. Modafinil is currently indicated only for the treatment of excessive sleepiness associated with narcolepsy, OSAHS, and SWSD.

## Stroke and Traumatic Brain Injury

The results from studies on the effects of stimulants in patients who had strokes or traumatic brain injury are mixed. Although small early studies showed some superiority of amphetamine to placebo in improving motor function poststroke ([Crisostomo et al. 1988](#); [Walker-Batson et al. 1995](#)), a double-blind study found that 10 mg/day of amphetamine combined with physiotherapy in geriatric stroke patients was not superior to placebo plus physiotherapy in improving activities of daily living or motor function 5 weeks later ([Sonde et al. 2001](#)). Neither was amphetamine found to be superior to placebo in improving somatosensory training outcomes ([Knecht et al. 2001](#)). Modafinil also has not been consistently effective in the treatment of fatigue associated with traumatic brain injury ([Jha et al. 2008](#)). In contrast, relative to placebo, dextroamphetamine 10 mg/day significantly improved language recovery in poststroke aphasic patients when immediately coupled with a session of speech therapy; this effect was seen as quickly as within 1 week ([Walker-Batson et al. 2001](#)). A review lamented the lack of good data in brain-injured patients but did note that available data suggest that the bulk of stimulant efficacy may lie with its improvements in mood and cognitive processing ([Whyte et al. 2002](#)).

Although there is a dearth of placebo-controlled studies, there are some interesting reports in which stimulants were compared with antidepressants in patients with poststroke depression. One such study, comparing methylphenidate

with TCAs, found similar and significant response to both drugs, although the stimulant worked faster ([Lazarus et al. 1994](#)).

Modafinil has been reported to have some therapeutic efficacy in some types of brain injury. Two double-blind studies by the same group ([Saletu et al. 1990, 1993](#)) found modafinil effective in improving cognition and accelerating improvement in patients with alcoholic brain syndrome. In addition, there is some evidence that modafinil may help with cognition in patients with traumatic brain injury ([Dougall et al. 2015](#); [Maksimowski and Tampi 2016](#)).

## Cocaine and Stimulant Abuse

It may not be surprising that a double-blind study showed sustained-release dextroamphetamine to be superior to placebo in reducing cocaine use ([Grabowski et al. 2001](#)). However, similarly designed studies by the same authors did not find this effect with methylphenidate ([Grabowski et al. 1997](#)) or with risperidone ([Grabowski et al. 2000](#)). A double-blind, placebo-controlled study found that modafinil did not increase the euphoria or craving for cocaine; it may, in fact, have blunted the euphoria ([Dackis et al. 2003](#)). A double-blind, placebo-controlled study of 62 patients found that modafinil-treated patients had a longer duration of cocaine abstinence (>3 weeks), with no dropouts due to adverse events ([Dackis et al. 2005](#)). Likewise, a 48-day double-blind trial found that under controlled laboratory conditions, modafinil significantly attenuated self-administration and effects of cocaine ([Hart et al. 2008](#)). However, a large randomized controlled study of modafinil in the treatment of 210 subjects with DSM-IV-TR ([American Psychiatric Association 2000](#))-defined cocaine dependence did not find modafinil generally efficacious in improving abstinence from cocaine use ([Dackis et al. 2012](#)), although there was a trend for male patients receiving a modafinil dosage of 400 mg/day to be less likely to use cocaine. More study is needed to determine which, if any, patients with cocaine dependence might benefit from modafinil treatment.

## Alcohol Use Disorder

Basic research suggests that amphetamine appears to have an unexpected effect in alcohol use disorder. In rats, amphetamines reduced alcohol consumption during choice trials; this reduction was specific to alcohol intake, because amphetamine administration had no effect on rodents' intake of water ([Yu et al. 1997](#)). This effect of amphetamine on alcohol consumption may involve the neurobiology of reward systems. Much more research is needed to identify the mechanisms by which stimulants affect alcohol intake.

## Narcolepsy

Stimulants have traditionally been used for the treatment of excessive sleepiness associated with narcolepsy. Narcolepsy is characterized by excessive sleepiness that is typically associated with cataplexy and other REM sleep phenomena such as sleep



paralysis and hypnagogic hallucinations. Modafinil's approval for treatment of excessive sleepiness in narcolepsy was based on substantial evidence from large multicenter clinical trials ([Broughton et al. 1997](#); [U.S. Modafinil in Narcolepsy Multicenter Study Group 1998, 2000](#)). Modafinil is less disruptive of sleep than amphetamines and is rated as having a lower abuse potential ([Shelton et al. 1995](#)) (see [Table 44-1](#)). One study found that taking an extra dose (200 mg) at midday improved wakefulness in patients with narcolepsy without causing insomnia at night ([Schwartz et al. 2004](#)). Importantly, cataplexy—the sudden occurrence of muscle weakness in association with experiencing laughter, anger, or surprise—is responsive to amphetamines but not to modafinil ([Shelton et al. 1995](#)).

## Fatigue

The use of stimulants for the treatment of fatigue syndromes may seem intuitive, but evidence from large-scale controlled clinical trials to warrant this use is scant. In one of the only double-blind, placebo-controlled studies, men with HIV, depression, and fatigue had significantly less fatigue with dextroamphetamine (73% response) ([Wagner and Rabkin 2000](#)). Tolerance, dependence, and abuse were not observed, even across a 6-month open phase. A double-blind study of methylphenidate and pemoline in a similar group of 144 patients with HIV who had severe fatigue found both stimulants effective in improving fatigue and quality of life ([Breitbart et al. 2001](#)). [Rabkin et al. \(2011\)](#) found that a significant majority of HIV patients—including those with comorbid hepatitis C—reported an improvement in fatigue with armodafinil. Likewise, in a Phase III trial of modafinil treatment in 631 patients with cancer-related fatigue, [Jean-Pierre et al. \(2010\)](#) found that modafinil was more effective than placebo in helping patients with severe fatigue. However, modafinil did not separate from placebo in cancer patients with mild or moderate fatigue at baseline. Similarly, in a Phase III study of armodafinil 150 mg/day for 8 weeks in the treatment of cancer-related fatigue in multiple myeloma patients, armodafinil failed to separate from placebo ([Berenson et al. 2015](#)). In addition, no advantage was found for armodafinil in a controlled study of the treatment of brain radiation-related fatigue ([Page et al. 2015](#)).

Two controlled trials ([Adler et al. 2003](#); [Högl et al. 2002](#)) found modafinil effective in reducing excessive sleepiness in Parkinson's disease. Findings from open-label studies of modafinil for fatigue in multiple sclerosis ([Rammohan et al. 2002](#)) and myotonic dystrophy ([Damian et al. 2001](#)) suggest modafinil's utility in management of fatigue. A small double-blind crossover study of modafinil in myotonic dystrophy found a reduction in fatigue but no improvement on activity measures ([Wintzen et al. 2007](#)). This result would be consistent with modafinil's rather selective effect on wakefulness and minimal impact on motor or autonomic parameters. In the same vein, studies of modafinil in patients with fibromyalgia ([Schwartz et al. 2007](#)) and of armodafinil in patients with sarcoidosis ([Lower et al. 2013](#)) did find that the medications were useful in treating the fatigue associated with these disorders.

## Obstructive Sleep Apnea/Hypopnea Syndrome

There are two placebo-controlled studies of modafinil in the treatment of residual sleepiness in patients with DSM-IV-TR-defined obstructive sleep apnea ([Kingshott et al. 2001](#); [Pack et al. 2001](#)). The studies show modafinil's efficacy in treating the residual daytime sleepiness experienced by some OSAHS patients who were compliant in their use of CPAP treatment.

Importantly, modafinil's use was studied in—and should be limited to—the treatment of OSAHS only after CPAP has been instituted and optimized. OSAHS carries significant cardiovascular risks if the airway collapse during sleep is not treated appropriately with CPAP and related therapies. It is conceivable that lessened daytime sleepiness from use of modafinil might fool the patient into thinking that CPAP is unnecessary, thus posing a risk via the untreated underlying OSAHS.

## Obesity

That amphetamines are anorectic is well known; however, the extent of the effect may be overstated. [Bray and Greenway \(1999\)](#) summarized the studies of obesity treatments, wherein they cited a large review of more than 200 short-term (3-month) double-blind studies of various noradrenergic agents, including amphetamine and amphetamine derivatives. Patients taking stimulants were twice as likely as those taking placebo to lose 1 lb/week; however, the percentage of patients who lost 3 lb/week was quite small (10%). A small study found that high doses of amphetamine (30 mg) decreased overall caloric intake but did so primarily through a decrease in fat consumption; carbohydrate consumption actually increased ([Foltin et al. 1995](#)). This mild effect on appetite is important when considering the use of stimulants in elderly patients who lack both energy and motivation and have poor appetite.

## Depression

As described earlier in this chapter, the only large-scale randomized controlled trials of a stimulant in the treatment of depression have involved lisdexamfetamine. Whereas early controlled studies suggested a benefit from adjunctive lisdexamfetamine ([Trivedi et al. 2013](#)) in the treatment of depression, subsequent Phase III trials failed to demonstrate the efficacy of lisdexamfetamine in the treatment of residual depressive symptoms after selective serotonin reuptake inhibitor (SSRI) treatment.

Beyond the lisdexamfetamine data, the bulk of the evidence for the utility of stimulants in the treatment of depression derives from case series by [Feighner et al. \(1985\)](#) and [Fawcett et al. \(1991\)](#), which suggested the efficacy of stimulants combined with MAOIs and MAOI/TCA combinations as well as their safety in not causing hypertensive or hyperthermic crises, and case series by [Stoll et al. \(1996\)](#) and [Metz and Shader \(1991\)](#), in which a combination of stimulant and SSRI was used. Another case series argued for amphetamine's ability to augment an antidepressant effect in patients with only partial response, although the effects



were, not unexpectedly, primarily in improving fatigue and apathy ([Masand et al. 1998](#)).

In an open-label trial of depressed cancer patients, both amphetamine and methylphenidate were reported to improve depressive symptoms to the same extent, and effects were seen within 2 days. In this series, stimulants did not cause anorexia; in fact, they improved appetite in more than half of the patients studied ([Olin and Masand 1996](#)), suggesting that these agents are not contraindicated solely on the basis of concerns about anorexia.

In a review, [Orr and Taylor \(2007\)](#) noted the paucity of high-quality data and suggested a possible role for stimulants in depression, particularly as adjunctive agents, in specific patient subgroups.

The utility of modafinil in depressive states is still not well characterized, the majority of evidence being either anecdotal or retrospective. More work is likely forthcoming, but there are two studies that bear some examination. The mood-altering properties of modafinil were studied in 32 normal volunteers in a double-blind crossover inpatient study ([Taneja et al. 2007](#)). Modafinil had positive results on general mood, especially on alertness and energy measures, but also had a negative effect on feeling calm (i.e., increased anxiety).

A double-blind, placebo-controlled trial ([Dunlop et al. 2007](#)) examining the effects of modafinil initiated at the outset of treatment with an SSRI in depressed patients with fatigue found no difference in the primary outcome measure of the Epworth Sleepiness Scale but found some improvement in the hypersomnia items of the 31-item Hamilton Rating Scale for Depression. Two other controlled trials ([DeBattista et al. 2003](#); [Fava et al. 2005](#)) and two open-label trials ([DeBattista et al. 2001](#); [Menza et al. 2000](#)) suggest that modafinil may have some utility as an augmentation agent to antidepressants in depressed patients with fatigue or excessive sleepiness.

Both modafinil and armodafinil have shown some preliminary benefit in the treatment of bipolar depression. [Frye et al. \(2007\)](#) found that the addition of modafinil at dosages of 100–200 mg/day for 6 weeks to a standard mood stabilizer was more effective than the addition of placebo in 85 patients with bipolar depression. In a larger randomized controlled multicenter study ([Calabrese et al. 2010](#)), 257 patients with bipolar depression on either lithium or valproate were randomly assigned to receive augmentation treatment with 150 mg/day armodafinil or placebo. Armodafinil appeared to help some—but not all—patients with bipolar depression, and the differences between groups did not reach statistical significance. Likewise, a study of 399 bipolar depressed patients randomly assigned to receive adjunctive armodafinil or placebo for 8 weeks failed to demonstrate armodafinil's benefit on the primary outcome measure (mean change from baseline on the 30-Item Inventory of Depressive Symptomatology—Clinician-Rated [IDS-C30] total score) ([Frye et al. 2015](#)). However, armodafinil was efficacious on a number of secondary measures, including IDS-C30 remission and Global Assessment of Functioning.

# Negative Symptoms and Cognitive Deficits in Schizophrenia

Whereas positive symptoms of schizophrenia are often responsive to antipsychotics, negative symptoms and cognitive deficits are often not ([Tandon 2011](#)). Because the negative symptoms and cognitive impairments of schizophrenia are frequently more disabling than the positive symptoms, there has been interest in developing effective treatments for these symptoms and deficits. A number of studies have explored the efficacy of modafinil and armodafinil in the treatment of negative symptoms and cognitive deficits in schizophrenia, with mixed results. For example, whereas some studies have found that modafinil or armodafinil improves negative symptoms ([Arbabi et al. 2012](#); [Kane et al. 2010](#)) and working memory ([Scoriels et al. 2012](#)) in some schizophrenic patients, other studies have found no benefit ([Bobo et al. 2011](#); [Pierre et al. 2007](#); [Sevy et al. 2005](#)). Despite these mixed results, modafinil has been well tolerated in most studies in schizophrenia. By contrast, stimulants such as dextroamphetamine may worsen positive symptoms of schizophrenia and have been less commonly studied in the treatment of negative symptoms and cognitive impairments. Further study is required to determine the role of stimulants and wakefulness-promoting agents in schizophrenia.

---

## Conclusion

---

The safety and efficacy of stimulants for the treatment of ADHD have been established. Modafinil and armodafinil are also firmly established as efficacious wakefulness-promoting agents in narcolepsy, sleep apnea, and shift work sleep disorder. The utility of these drugs in other areas is being examined. Although there is intense interest in the potential use of stimulants and modafinil in other psychiatric and neurobehavioral conditions, controlled studies on their safety and efficacy are limited. It is unclear why stimulants have not been extensively investigated for clinical utility for indications other than the treatment of ADHD. The approval of armodafinil, as the newest of the wakefulness-promoting compounds, may perhaps spur further research. Well-designed large-scale controlled trials are needed to define and characterize the role of stimulants and modafinil in various psychiatric illnesses. It is hoped that this will be an area of continued interest and development, from the elucidation of the molecular mechanisms of stimulants and modafinil to the demonstration through controlled trials of their potential clinical safety and benefits.

---

## References

---

Adler CH, Caviness JN, Hentz JG, et al: Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord* 18(3):287-293, 2003 12621632

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000
- Arbabi M, Bagheri M, Rezaei F, et al: A placebo-controlled study of the modafinil added to risperidone in chronic schizophrenia. *Psychopharmacology (Berl)* 220(3):591-598, 2012 21947320
- Berenson JR, Yellin O, Shamasunder HK, et al: A phase 3 trial of armodafinil for the treatment of cancer-related fatigue for patients with multiple myeloma. *Support Care Cancer* 23(6):1503-1512, 2015 25370889
- Biederman J, Swanson JM, Wigal SB, et al: Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible-dose study. *Pediatrics* 116(6):e777-e784, 2005 16322134
- Biederman J, Swanson JM, Wigal SB, et al; Modafinil ADHD Study Group: A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. *J Clin Psychiatry* 67(5): 727-735, 2006 16841622
- Biederman J, Boellner SW, Childress A, et al: Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. *Biol Psychiatry* 62(9):970-976, 2007a 17631866
- Biederman J, Krishnan S, Zhang Y, et al: Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther* 29(3):450-463, 2007b 17577466
- Bobo WV, Woodward ND, Sim MY, et al: The effect of adjunctive armodafinil on cognitive performance and psychopathology in antipsychotic-treated patients with schizophrenia/schizoaffective disorder: a randomized, double-blind, placebo-controlled trial. *Schizophr Res* 130(1-3):106-113, 2011 21641776
- Boellner SW, Earl CQ, Arora S: Modafinil in children and adolescents with attention-deficit/hyperactivity disorder: a preliminary 8-week, open-label study. *Curr Med Res Opin* 22(12):2457-2465, 2006 17257460
- Bonaventure P, Letavic M, Dugovic C, et al: Histamine H3 receptor antagonists: from target identification to drug leads. *Biochem Pharmacol* 73(8):1084-1096, 2007 17129577
- Bray GA, Greenway FL: Current and potential drugs for treatment of obesity. *Endocr Rev* 20(6):805-875, 1999 10605627
- Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J: A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. *Arch Intern Med* 161(3):411-420, 2001 11176767
- Broughton RJ, Fleming JA, George CF, et al: Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 49(2):444-451, 1997 9270575
- Brun J, Chamba G, Khalfallah Y, et al: Effect of modafinil on plasma melatonin, cortisol and growth hormone rhythms, rectal temperature and performance in healthy subjects during a 36 h sleep deprivation. *J Sleep Res* 7(2):105-114, 1998 9682182
- Calabrese JR, Ketter TA, Youakim JM, et al: Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized,

- multicenter, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry* 71(10):1363-1370, 2010 20673554
- Cephalon Inc: Provigil (modafinil) tablets: prescribing information. Frazer, PA, Cephalon, Inc., March 2008. Available at: <http://www.provigil.com>. Accessed December 2008.
- Chan YP, Swanson JM, Soldin SS, et al: Methylphenidate hydrochloride given with or before breakfast, II: effects on plasma concentration of methylphenidate and ritalinic acid. *Pediatrics* 72(1):56-59, 1983 6866592
- Crisostomo EA, Duncan PW, Propst M, et al: Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. *Ann Neurol* 23(1):94-97, 1988 3345072
- Dackis CA, Lynch KG, Yu E, et al: Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. *Drug Alcohol Depend* 70(1):29-37, 2003 12681523
- Dackis CA, Kampman KM, Lynch KG, et al: A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 30(1):205-211, 2005 15525998
- Dackis CA, Kampman KM, Lynch KG, et al: A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *J Subst Abuse Treat* 43(3):303-312, 2012 22377391
- Damian MS, Gerlach A, Schmidt F, et al: Modafinil for excessive daytime sleepiness in myotonic dystrophy. *Neurology* 56(6):794-796, 2001 11274321
- DeBattista C, Solvason HB, Kendrick E, et al: Modafinil as an adjunctive agent in the treatment of fatigue and hypersomnia associated with major depression, in New Research Program and Abstracts of the 154th Annual Meeting of the American Psychiatric Association, May 9, 2001, New Orleans, LA, USA Abstract NR532, 144, 2001
- DeBattista C, Doghramji K, Menza MA, et al; Modafinil in Depression Study Group: Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. *J Clin Psychiatry* 64(9): 1057-1064, 2003 14628981
- DeVane CL, Markowitz JS, Carson SW, et al: Single-dose pharmacokinetics of methylphenidate in CYP2D6 extensive and poor metabolizers. *J Clin Psychopharmacol* 20(3):347-349, 2000 10831022
- Dinges DF, Arora S, Darwish M, Niebler GE: Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. *Curr Med Res Opin* 22(1):159-167, 2006 16393442
- Dougall D, Poole N, Agrawal N: Pharmacotherapy for chronic cognitive impairment in traumatic brain injury. *Cochrane Database Syst Rev* (12):CD009221, 2015 26624881
- Dunlop BW, Crits-Christoph P, Evans DL, et al: Coadministration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 27(6):614-619, 2007 18004129
- Efron D, Jarman F, Barker M: Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 100(6):E6, 1997 9382907
- Fava M, Thase ME, DeBattista C: A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake

- inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry* 66(1):85-93, 2005 15669893
- Fawcett J, Kravitz HM, Zajecka JM, Schaff MR: CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. *J Clin Psychopharmacol* 11(2):127-132, 1991 2056139
- Feighner JP, Herbstein J, Damlouji N: Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. *J Clin Psychiatry* 46(6):206-209, 1985 3997787
- Ferris RM, Tang FL: Comparison of the effects of the isomers of amphetamine, methylphenidate and deoxypipradrol on the uptake of l-[3H]norepinephrine and [3H] dopamine by synaptic vesicles from rat whole brain, striatum and hypothalamus. *J Pharmacol Exp Ther* 210(3):422-428, 1979 39160
- Foltin RW, Kelly TH, Fischman MW: Effect of amphetamine on human macronutrient intake. *Physiol Behav* 58(5):899-907, 1995 8577886
- Frye MA, Grunze H, Suppes T, et al: A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 164(8):1242-1249, 2007 17671288
- Frye MA, Amchin J, Bauer M, et al: Randomized, placebo-controlled, adjunctive study of armodafinil for bipolar I depression: implications of novel drug design and heterogeneity of concurrent bipolar maintenance treatments. *Int J Bipolar Disord* 3(1):34, 2015 26330288
- George S, Braithwaite RA: Using amphetamine isomer ratios to determine the compliance of amphetamine abusers prescribed dextedrine. *J Anal Toxicol* 24(3):223-227, 2000 10774542
- Grabowski J, Roache JD, Schmitz JM, et al: Replacement medication for cocaine dependence: methylphenidate. *J Clin Psychopharmacol* 17(6):485-488, 1997 9408812
- Grabowski J, Rhoades H, Silverman P, et al: Risperidone for the treatment of cocaine dependence: randomized, double-blind trial. *J Clin Psychopharmacol* 20(3):305-310, 2000 10831016
- Grabowski J, Rhoades H, Schmitz J, et al: Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J Clin Psychopharmacol* 21(5):522-526, 2001 11593078
- Greenhill LL, Pliszka S, Dulcan MK, et al: American Academy of Child and Adolescent Psychiatry: Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 41 (2 suppl):26S-49S, 2002 11833633
- Guilarte TR: Is methamphetamine abuse a risk factor in parkinsonism? *Neurotoxicology* 22(6):725-731, 2001 11829406
- Harsh JR, Hayduk R, Rosenberg R, et al: The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin* 22(4):761-774, 2006 16684437
- Hart CL, Haney M, Vosburg SK, et al: Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology* 33(4):761-768, 2008 17568397
- Hirshkowitz M, Black JE, Wesnes K, et al: Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med* 101(3):616-627, 2007 16908126
- Högl B, Saletu M, Brandauer E, et al: Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-

- controlled polygraphic trial. *Sleep* 25(8): 905-909, 2002 12489899
- Hunt GE, Atrens DM: Reward summation and the effects of pimozide, clonidine, and amphetamine on fixed-interval responding for brain stimulation. *Pharmacol Biochem Behav* 42(4):563-577, 1992 1513839
- Ishizuka T, Sakamoto Y, Sakurai T, Yamatodani A: Modafinil increases histamine release in the anterior hypothalamus of rats. *Neurosci Lett* 339(2):143-146, 2003 12614915
- James RS, Sharp WS, Bastain TM, et al: Double-blind, placebo-controlled study of single-dose amphetamine formulations in ADHD. *J Am Acad Child Adolesc Psychiatry* 40(11):1268-1276, 2001 11699800
- Janssen PA, Leysen JE, Megens AA, Awouters FH: Does phenylethylamine act as an endogenous amphetamine in some patients? *Int J Neuropsychopharmacol* 2(3): 229-240, 1999 11281991
- Jean-Pierre P, Morrow GR, Roscoe JA, et al: A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. *Cancer* 116(14):3513-3520, 2010 20564068
- Jha A, Weintraub A, Allshouse A, et al: A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil* 23(1):52-63, 2008 18219235
- Kane JM, D'Souza DC, Patkar AA, et al: Armodafinil as adjunctive therapy in adults with cognitive deficits associated with schizophrenia: a 4-week, double-blind, placebo-controlled study. *J Clin Psychiatry* 71(11):1475-1481, 2010 20816042
- Karch SB, Stephens BG, Ho CH: Methamphetamine-related deaths in San Francisco: demographic, pathologic, and toxicologic profiles. *J Forensic Sci* 44(2):359-368, 1999 10097363
- Kingshott RN, Vennelle M, Coleman EL, et al: Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 163(4):918-923, 2001 11282766
- Klein-Schwartz W: Abuse and toxicity of methylphenidate. *Curr Opin Pediatr* 14(2):219-223, 2002 11981294
- Knecht S, Imai T, Kamping S, et al: D-amphetamine does not improve outcome of somatosensory training. *Neurology* 57(12):2248-2252, 2001 11756605
- Lazarus LW, Moberg PJ, Langsley PR, Lingam VR: Methylphenidate and nortriptyline in the treatment of poststroke depression: a retrospective comparison. *Arch Phys Med Rehabil* 75(4):403-406, 1994 8172499
- Lower EE, Malhotra A, Surdulescu V, Baughman RP: Armodafinil for sarcoidosis-associated fatigue: a double-blind, placebo-controlled, crossover trial. *J Pain Symptom Manage* 45(2):159-169, 2013 22917711
- Madhoo M, Keefe RS, Roth RM, et al: Lisdexamfetamine dimesylate augmentation in adults with persistent executive dysfunction after partial or full remission of major depressive disorder. *Neuropsychopharmacology* 39(6):1388-1398, 2014 24309905
- Maksimowski MB, Tampi RR: Efficacy of stimulants for psychiatric symptoms in individuals with traumatic brain injury. *Ann Clin Psychiatry* 28(3):156-166, 2016 27490831
- Markowitz JS, Patrick KS: Pharmacokinetic and pharmacodynamic drug interactions in the treatment of attention-deficit hyperactivity disorder. *Clin Pharmacokinet*

- 40(10):753-772, 2001 11707061
- Masand PS, Anand VS, Tanquary JF: Psychostimulant augmentation of second generation antidepressants: a case series. *Depress Anxiety* 7(2):89-91, 1998 9614599
- McElroy SL, Hudson JI, Mitchell JE, et al: Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry* 72(3):235-246, 2015a 25587645
- McElroy SL, Martens BE, Mori N, et al: Adjunctive lisdexamfetamine in bipolar depression: a preliminary randomized, placebo-controlled trial. *Int Clin Psychopharmacol* 30(1):6-13, 2015b 25340384
- McElroy SL, Hudson J, Ferreira-Cornwell MC, et al: Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology* 41(5):1251-1260, 2016 26346638
- Menza MA, Kaufman KR, Castellanos A: Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry* 61(5):378-381, 2000 10847314
- Metz A, Shader RI: Combination of fluoxetine with pemoline in the treatment of major depressive disorder. *Int Clin Psychopharmacol* 6(2):93-96, 1991 1960383
- Najib J: The efficacy and safety profile of lisdexamfetamine dimesylate, a prodrug of d-amphetamine, for the treatment of attention-deficit/hyperactivity disorder in children and adults. *Clin Ther* 31(1):142-176, 2009 19243715
- Nishino S, Mignot E: Pharmacological aspects of human and canine narcolepsy. *Prog Neurobiol* 52(1):27-78, 1997 9185233
- Novartis: Ritalin LA (methylphenidate hydrochloride) extended-release capsules: prescribing information. East Hanover, NJ, Novartis, April 2007. Available at: [http://www.pharma.us.novartis.com/product/pi/pdf/ritalin\\_la.pdf](http://www.pharma.us.novartis.com/product/pi/pdf/ritalin_la.pdf). Accessed December 2008.
- Olin J, Masand P: Psychostimulants for depression in hospitalized cancer patients. *Psychosomatics* 37(1):57-62, 1996 8600496
- Orr K, Taylor D: Psychostimulants in the treatment of depression: a review of the evidence. *CNS Drugs* 21(3):239-257, 2007 17338594
- Pack AI, Black JE, Schwartz JR, Matheson JK: Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med* 164(9):1675-1681, 2001 11719309
- Page BR, Shaw EG, Lu L, et al: Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. *Neuro-oncol* 17(10):1393-1401, 2015 25972454
- Pierre JM, Peloian JH, Wirshing DA, et al: A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry* 68(5):705-710, 2007 17503979
- Rabkin JG, McElhiney MC, Rabkin R: Treatment of HIV-related fatigue with armodafinil: a placebo-controlled randomized trial. *Psychosomatics* 52(4):328-336, 2011 21777715
- Rammohan KW, Rosenberg JH, Lynn DJ, et al: Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry* 72(2): 179-183, 2002 11796766
- Ricaurte GA, Yuan J, Hatzidimitriou G, et al: Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"). *Science* 297(5590):2260-2263, 2002 12351788



- Robertson P, DeCory HH, Madan A, Parkinson A: In vitro inhibition and induction of human hepatic cytochrome P450 enzymes by modafinil. *Drug Metab Dispos* 28(6):664-671, 2000 10820139
- Robertson PJr, Hellriegel ET, Arora S, Nelson M: Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* 71(1):46-56, 2002 11823757
- Roth T, Czeisler CA, Walsh JK, et al: Randomized, double-blind, placebo-controlled study of armodafinil for the treatment of excessive sleepiness associated with chronic shift work sleep disorder (abstract no. 161). *Neuropsychopharmacology* 30:S140, 2005
- Roth T, White D, Schmidt-Nowara W, et al: Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther* 28(5):689-706, 2006 16861091
- Rugino TA, Samsock TC: Modafinil in children with attention-deficit hyperactivity disorder. *Pediatr Neurol* 29(2):136-142, 2003 14580657
- Saletu B, Saletu M, Grünberger J, et al: On the treatment of the alcoholic organic brain syndrome with an alpha-adrenergic agonist modafinil: double-blind, placebo-controlled clinical, psychometric and neurophysiological studies. *Prog Neuropsychopharmacol Biol Psychiatry* 14(2): 195-214, 1990 1968672
- Saletu B, Saletu M, Grünberger J, et al: Treatment of the alcoholic organic brain syndrome: double-blind, placebo-controlled clinical, psychometric and electroencephalographic mapping studies with modafinil. *Neuropsychobiology* 27(1):26-39, 1993 8100044
- Scammell TE, Estabrooke IV, McCarthy MT, et al: Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci* 20(22):8620-8628, 2000 11069971
- Schwartz JR, Nelson MT, Schwartz ER, Hughes RJ: Effects of modafinil on wakefulness and executive function in patients with narcolepsy experiencing late-day sleepiness. *Clin Neuropharmacol* 27(2):74-79, 2004 15252267
- Schwartz TL, Rayancha S, Rashid A, et al: Modafinil treatment for fatigue associated with fibromyalgia. *J Clin Rheumatol* 13(1):52, 2007 17278955
- Scoriels L, Barnett JH, Soma PK, et al: Effects of modafinil on cognitive functions in first episode psychosis. *Psychopharmacology (Berl)* 220(2):249-258, 2012 21909634
- Sevy S, Rosenthal MH, Alvir J, et al: Double-blind, placebo-controlled study of modafinil for fatigue and cognition in schizophrenia patients treated with psychotropic medications. *J Clin Psychiatry* 66(7):839-843, 2005 16013898
- Shelton J, Nishino S, Vaught J, et al: Comparative effects of modafinil and amphetamine on daytime sleepiness and cataplexy of narcoleptic dogs. *Sleep* 18(10): 817-826, 1995 8746387
- Sonde L, Nordström M, Nilsson CG, et al: A double-blind placebo-controlled study of the effects of amphetamine and physiotherapy after stroke. *Cerebrovasc Dis* 12(3):253-257, 2001 11641592
- Sprague JE, Everman SL, Nichols DE: An integrated hypothesis for the serotonergic axonal loss induced by 3,4-methylenedioxymethamphetamine. *Neurotoxicology* 19(3):427-441, 1998 9621349
- Stoll AL, Pillay SS, Diamond L, et al: Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* 57(2):72-76, 1996 8591972



- Swanson JM, Wigal S, Greenhill LL, et al: Analog classroom assessment of Adderall in children with ADHD. *J Am Acad Child Adolesc Psychiatry* 37(5):519-526, 1998 9585654
- Tandon R: Antipsychotics in the treatment of schizophrenia: an overview. *J Clin Psychiatry* 72 (suppl 1):4-8, 2011 22217436
- Taneja I, Haman K, Shelton RC, Robertson D: A randomized, double-blind, crossover trial of modafinil on mood. *J Clin Psychopharmacol* 27(1):76-79, 2007 17224718
- Taylor FB, Russo J: Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *J Child Adolesc Psychopharmacol* 10(4):311-320, 2000 11191692
- Trivedi MH, Cutler AJ, Richards C, et al: A randomized controlled trial of the efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with residual symptoms of major depressive disorder after treatment with escitalopram. *J Clin Psychiatry* 74(8):802-809, 2013 24021497
- Turner DC, Clark L, Dowson J, et al: Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 55(10):1031-1040, 2004 15121488
- U.S. Food and Drug Administration: Provigil (Modafinil): Follow-up to Hypersensitivity Reactions in the Pediatric Population. Pediatric Advisory Committee. November 28, 2007. Available at: [http://www.fda.gov/ohrms/dockets/AC/07/slides/2007-4325s2\\_12\\_Modafinil,%20Villalba,%20MD%20\(FDA\).pdf](http://www.fda.gov/ohrms/dockets/AC/07/slides/2007-4325s2_12_Modafinil,%20Villalba,%20MD%20(FDA).pdf). Accessed December 2008.
- U.S. Modafinil in Narcolepsy Multicenter Study Group: Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol* 43(1):88-97, 1998 9450772
- U.S. Modafinil in Narcolepsy Multicenter Study Group: Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 54:1166-1175, 2000 10720292
- Wagner GJ, Rabkin R: Effects of dextroamphetamine on depression and fatigue in men with HIV: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 61(6):436-440, 2000 10901342
- Walker-Batson D, Smith P, Curtis S, et al: Amphetamine paired with physical therapy accelerates motor recovery after stroke. Further evidence. *Stroke* 26(12):2254-2259, 1995 7491646
- Walker-Batson D, Curtis S, Natarajan R, et al: A double-blind, placebo-controlled study of the use of amphetamine in the treatment of aphasia. *Stroke* 32(9):2093-2098, 2001 11546902
- Whyte J, Vaccaro M, Grieb-Neff P, Hart T: Psychostimulant use in the rehabilitation of individuals with traumatic brain injury. *J Head Trauma Rehabil* 17(4):284-299, 2002 12105998
- Wigal SB, Biederman J, Swanson JM, et al: Efficacy and safety of modafinil film-coated tablets in children and adolescents with or without prior stimulant treatment for attention-deficit/hyperactivity disorder: pooled analysis of 3 randomized, double-blind, placebo-controlled studies. *Prim Care Companion J Clin Psychiatry* 8(6): 352-360, 2006 17245457
- Wilens TE, Spencer TJ, Biederman J: A review of the pharmacotherapy of adults with attention-deficit/hyperactivity disorder. *J Atten Disord* 5(4):189-202, 2002 11967475

- Wintzen AR, Lammers GJ, van Dijk JG: Does modafinil enhance activity of patients with myotonic dystrophy? A double-blind placebo-controlled crossover study. *J Neurol* 254(1):26-28, 2007 17285226
- Wong YN, Simcoe D, Hartman LN, et al: A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol* 39(1):30-40, 1999 9987698
- Yu YL, Fisher H, Sekowski A, Wagner GC: Amphetamine and fenfluramine suppress ethanol intake in ethanol-dependent rats. *Alcohol* 14(1):45-48, 1997 9014023

---

This chapter is an update and revision of Ballas CA, Evans DL, Dinges DF: "Psychostimulants and Wakefulness-Promoting Agents," in *The American Psychiatric Publishing Textbook of Psychopharmacology*, 4th Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, American Psychiatric Publishing, 2009, pp. 843-860.

## CHAPTER 45

# **Electroconvulsive Therapy and Other Neuromodulation Therapies**

William M. McDonald, M.D.

Thomas W. Meeks, M.D.

Linda L. Carpenter, M.D.

W. Vaughn McCall, M.D., M.S.

Charles F. Zorumski, M.D.

Over the past several decades, electroconvulsive therapy (ECT) has been proven to be perhaps the most effective somatic treatment for mood disorders ([Kellner et al. 2012](#)). The continued use of ECT spurred more systematic research on its indications, techniques to maximize efficacy and minimize side effects, and understanding ECT's mechanism of action. In this chapter,

we review the history of ECT, the preclinical and clinical data on the mechanism of action of ECT, and the relevant literature related to the efficacy and side-effect burden of ECT. We also offer practical guidelines for the administration of ECT in treating various psychiatric disorders, including appropriate patient selection, stimulus settings and electrode placement, pretreatment medical evaluation, and management of the patient during acute, continuation, and maintenance courses of ECT. Finally, we discuss recent developments with nonconvulsive therapies such as transcranial magnetic stimulation (TMS) in relation to their efficacy in depression treatment and their utility as part of the neuromodulatory treatments.

---

## **Electroconvulsive Therapy**

---

### **History**

The development of ECT occurred at a time when few somatic treatments were available for psychiatric disorders and physicians were attempting to find treatments for severely ill psychotic patients. In 1935, Manfred Sakel (1900–1957) induced hypoglycemic episodes in psychiatric patients (using insulin shock therapy), and in the same year Lazlo Meduna (1896–1964) injected patients with pentylenetetrazol to induce convulsions in order to treat psychosis. Three years later, the Italian psychiatrists Ugo Cerletti (1877–1963) and Lucio Bini (1908–1964) used electroshock treatments to induce seizures. This treatment proved safer and easier to administer than chemically

induced seizures and replaced other methods of inducing seizures.

Modern psychopharmacology began with the discovery of lithium (1949) and iproniazid (1957) for the treatment of mood disorders and the synthesis of the first antipsychotic, chlorpromazine (1952); the first tricyclic antidepressant, imipramine (1959); and the first benzodiazepine, chlordiazepoxide (1960). The development of psychotropic medications was associated with a decline in the use of ECT from the 1960s to the 1980s, at which point the use of ECT began to increase, with data showing that more than 36,000 U.S. patients received ECT in 1986 ([Thompson et al. 1994](#)). However, the percentage of U.S. hospitals providing ECT declined by an estimated 43% between 1993 and 2009 ([Case et al. 2013](#)). Studies in Canada and Denmark have reported relatively stable rates of ECT use over the last 15–30 years ([Munk-Olsen et al. 2006](#); [Rapoport et al. 2006](#)), whereas decreasing rates of use have been reported in the United Kingdom and Australia ([Plakiotis et al. 2012](#); [Scott 2012](#)). The results of the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study ([Rush et al. 2009](#)) and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) program ([Lieberman et al. 2005](#)) confirmed the limited effectiveness of psychopharmacology for major mental disorders and supported the continued clinical relevance of ECT for those patients whose symptoms do not respond to medication management ([Insel and Wang 2009](#); [McCall 2007](#)).

Since the 1980s, the safety of ECT has improved significantly with the introduction of sophisticated cardiopulmonary and electroencephalographic monitoring, the development of better anesthetic agents, and the adoption of the brief-pulse stimulus machine. Today, ECT is

arguably the fastest, most effective treatment for mood disorders. ECT is also one of the safest procedures performed under general anesthesia, with a mortality rate reported at 0.002% or less ([Watts et al. 2011](#)).

## Mechanism of Action

### Anticonvulsant Hypothesis

One of the most popular theories on the mechanism of action of ECT is that the antidepressant efficacy is directly correlated with the anticonvulsant effect of ECT. That is, the therapeutic effect of ECT is proportional to an increase in the seizure threshold during ECT. This theory is based on the fact that a course of ECT results in an increase in seizure threshold and a decrease in seizure duration ([Sackeim 1999](#)) and focuses on changes in neurotransmitter systems and intracellular biochemical processes related to the seizure threshold.

$\gamma$ -Aminobutyric acid (GABA) is the predominant inhibitory transmitter in the brain and is a target for multiple anticonvulsant drugs (e.g., barbiturates, benzodiazepines). Data from animal studies indicated increases in the threshold for bicuculline- and pentylenetetrazol-induced seizures following a series of electroconvulsive shock (ECS) treatments ([Nutt et al. 1981](#); [Płaźnik et al. 1989](#)). Because bicuculline and pentylenetetrazol act by inhibiting GABA<sub>A</sub> receptors, these findings suggest that ECT results in changes in GABAergic inhibition. Additionally, GABA levels increase in certain central nervous system (CNS) regions after ECS in laboratory animals ([Green et al. 1982](#)), and evidence from magnetic resonance spectroscopy indicates that ECT increases GABA levels in the occipital cortex in

humans ([Sanacora et al. 2003](#)). These changes in GABA levels suggest that there may be an increase in tonic inhibition after repeated seizures, and effects on GABA-mediated tonic inhibition are increasingly recognized as an important aspect of several neuroactive drugs ([Farrant and Nusser 2005](#)). In line with this research is the finding that the most consistent biological marker for ECT response has been increased frontal delta activity (i.e., postictal depression) shown on the electroencephalogram (EEG) after ECT ([Azuma et al. 2007](#); [Mayur 2006](#)), which is associated with decreased cerebral blood flow in the immediate postictal period ([Nobler et al. 1993](#)).

## **Antidepressant Medication and the Effects of Electroconvulsive Therapy on Mood Disorders**

The efficacy of anticonvulsants as mood stabilizers supports the anticonvulsant hypothesis; this hypothesis is appealing in that it can explain the therapeutic effects of ECT in both mania and depression ([Sackeim 1994, 1999](#)). Yet most antidepressants are not anticonvulsants, and researchers have investigated other common mechanisms of action for ECT and antidepressant medication to determine the therapeutic effects of ECT.

There are several common threads in the neurotransmitter changes induced by ECT and antidepressant medication. ECT, like antidepressant pharmacotherapy, has been reported to normalize hypothalamic-pituitary-adrenal (HPA) axis perturbations associated with major depressive disorder ([Yuuki et al. 2005](#)). However, a more productive area of research has focused on determining how a course of ECT affects biogenic amines. Of interest is the finding that certain

antidepressants cause  $\alpha_1$ -adrenergic receptor subsensitivity, and similar effects are observed with ECS ([Nutt and Glue 1993](#)). ECS has multiple other effects on the adrenergic system, including increased norepinephrine turnover, increased  $\alpha_1$ -adrenergic receptor sensitivity, and possibly decreased presynaptic  $\alpha_2$ -adrenergic receptor sensitivity. ECS also enhances the function of the serotonin system, producing increased behavioral responses to serotonin agonists and possibly increases in 5-hydroxytryptamine type 2 (5-HT<sub>2</sub>) receptor binding in the cerebral cortex ([Fochtmann 1994](#); [Nutt and Glue 1993](#); [Sackeim 1994](#)). Thus, 5-HT<sub>2</sub> receptor downregulation, like  $\alpha$ -adrenergic receptor subsensitivity, may be a mechanism common to several antidepressant treatments.

One of the more intriguing avenues for understanding the effects of ECT is the literature on the neurocircuitry of mood regulation and depression. This circuitry involves connections between and within regions of the prefrontal cortex, anterior cingulate gyrus, subgenual prefrontal cortex, anterior thalamus, and more traditional limbic structures (hippocampus and amygdala) ([Drevets 2000](#); [Seminowicz et al. 2004](#)). Evidence now indicates structural changes including cell loss (glia and possibly neurons) in several of these regions in subtypes of depression ([Harrison 2002](#)). It also appears that different antidepressant treatments may differentially affect metabolism in this circuit. Effective treatment with paroxetine appears to increase metabolism in frontal regions while decreasing metabolism in the hippocampus, whereas cognitive-behavioral therapy results in the opposite effects ([Goldapple et al. 2004](#); [Seminowicz et al. 2004](#)). ECT, in contrast, diminishes metabolism in both prefrontal cortex



and hippocampus ([Nobler et al. 2001](#)). Although it is too early to draw firm conclusions about these observations, it is intriguing that chronic deep brain stimulation (DBS) targeted toward the subgenual prefrontal region appears to be effective in a small sample of patients with treatment-resistant chronic depression ([Mayberg et al. 2005](#)), further implicating neurocircuitry changes in the biology of depression.

Evidence suggests that several antidepressant treatments, including ECS, have neurotrophic effects and result in neurogenesis in the dentate gyrus of adult rodents ([Madsen et al. 2000](#); [Malberg et al. 2000](#); [Scott et al. 2000](#)). These effects may result from changes in brain-derived neurotrophic factor (BDNF) and the receptor tyrosine kinase (TRK<sub>B</sub>) through which BDNF exerts its actions, as well as from the treatment's effects on the adenylate cyclase intracellular signaling system, including the downstream effector cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) ([Duman and Vaidya 1998](#); [Nestler et al. 2002](#); [Schloss and Henn 2004](#)).

Other evidence suggests that the new neurons produced in the dentate gyrus of adult rodents have the properties of functional neurons and participate in synaptic transmission ([Song et al. 2002](#)), suggesting that antidepressant treatments, including ECT, may ultimately enhance hippocampal function. Hippocampal changes appear to be accompanied by increases in local angiogenesis and blood flow in specific subregions of the hippocampus ([Hellsten et al. 2005](#); [Newton et al. 2006](#)). Whether effects on neurogenesis are important for the therapeutic effects of ECT and other antidepressant treatments remains speculative, although elegant studies in rodents provide

evidence that neurogenesis is important for at least some behavioral effects of medications ([Santarelli et al. 2003](#)). Whether similar neurotrophic effects occur with ECT in humans is uncertain. However, studies that used magnetic resonance spectroscopy to monitor regional changes in the glutamate-to-glutamine ratio (Glx), a marker of local intracellular excitatory transmitter metabolism ([Hasler et al. 2007](#)), indicated that depressed subjects have low Glx values that increase to normal values with effective ECT ([Michael et al. 2003](#); [Pfleiderer et al. 2003](#)). Changes in Glx in depression treated with ECT may reflect alterations in glial function in the circuitry underlying depression.

Recent efforts to identify mechanisms contributing to the effects of ECT and antidepressant drugs have included the use of microarrays to study gene expression in multiple brain regions. Although these studies are in their infancy, some evidence indicates that rapidly acting treatments like ECT result in changes primarily in the catecholaminergic system, whereas treatments that act more slowly, such as fluoxetine, act predominantly on the serotonergic system. These studies also show strong effects of ECT on BDNF and transcripts encoding proteins involved in hippocampal synaptic plasticity ([Conti et al. 2007](#)). Follow-up studies examining protein expression and downstream functional effects will be important in determining their relevance to ECT's clinical actions.

## Indications and Efficacy

### Depression

The summary statement by the American Psychiatric Association Task Force on Electroconvulsive Therapy

([American Psychiatric Association 2001](#)) has supported the efficacy and safety of ECT. A meta-analysis of randomized controlled trials (RCTs) performed by the [UK ECT Review Group \(2003\)](#) confirmed the following about the efficacy of ECT for major depressive disorder:

- ECT is more efficacious than sham ECT (shown in six RCTs; effect size = 0.91).
- ECT is more efficacious than antidepressant pharmacotherapy (18 RCTs; effect size = 0.80).
- Aspects of ECT associated with a positive response include higher total dose and bilateral electrode placement (although many studies likely underdosed patients with unilateral ECT).

Given these data, ECT should no longer be considered a treatment of last resort ([Beale and Kellner 2000](#); [Kellner et al. 2005](#)). Instead, ECT should be viewed as a potential first-line treatment when a rapid clinical response is essential in severely ill patients (e.g., those with active suicidal ideation, catatonia, or a compromised medical condition related to depression such as dehydration or malnutrition), when the patient has a history of a positive response to ECT, or when the patient (or surrogate decision maker) requests ECT over other treatment options.

ECT exerts its antidepressant effects more rapidly than pharmacotherapy does, and research has confirmed a rapid resolution of suicidal ideation with ECT ([Kellner et al. 2005](#); [Patel et al. 2006](#)). [Beale and Kellner \(2000\)](#) argued that delaying the use of ECT until multiple medication trials have failed does not take into account the tolerability and efficacy of modern ECT and may lead to needless suffering on the part of the patient. They pointed out that

antidepressant treatment algorithms place ECT as a tertiary treatment (e.g., [Rush and Thase 1997](#)) instead of recommending that ECT practitioners be consulted early in the treatment process to determine whether ECT would be appropriate therapy.

Surveys show that patients who have received ECT rate it as a highly effective treatment ([Parker et al. 2001](#)) and that 85% of the patients who have received ECT would agree to a second course of ECT if needed ([Bernstein et al. 1998](#)). ECT-related relief of depressive symptoms also has been associated with long-term improvements in health-related quality of life, an increasingly important outcome measure in medical research ([McCall et al. 2006](#)).

**Predictors of response.** Positive predictors of response include increasing age ([Dombrovski et al. 2005](#); [O'Connor et al. 2001](#)) and the presence of psychotic or catatonic symptoms ([Birkenhäger et al. 2005](#); [Buchan et al. 1992](#); [Petrides et al. 2001](#)). Several studies have reported that patients with longer current episodes of depression ([Dombrovski et al. 2005](#)) or personality disorders (e.g., borderline personality disorder) ([Feske et al. 2004](#); [Parker et al. 2001](#); [Rasmussen 2015](#)) are less likely to respond to ECT. Medication resistance also has been found to correlate with lack of response to ECT ([Heijnen et al. 2010](#); [Sackeim et al. 2001a](#)).

Patients with depression complicated by dysthymia (i.e., double depression) appear to respond to ECT to the same extent that patients without dysthymia do ([Prudic et al. 1993](#)). Attempts to link subtypes of depression (e.g., melancholic vs. atypical, unipolar depression vs. depression associated with bipolar disorder) to ECT response generally have not identified differences. However, response by

session 3 of ECT may predict long-term efficacy in relieving depression ([Tsuchiyama et al. 2005](#)).

Among persons with comorbid major depressive disorder and posttraumatic stress disorder (PTSD), those with impaired suppression on the dexamethasone suppression test responded better to ECT than did those with normal or excessive suppression ([Watts and Groft 2010](#)). Genetic variants related to dopamine functioning (catechol-*O*-methyltransferase and dopamine type 2 receptors) also may play a role as moderators of response to ECT ([Anttila et al. 2008](#)).

[Coffey et al. \(1989\)](#) found that elderly patients referred for ECT had a greater number of structural abnormalities observed on magnetic resonance imaging (MRI) scans of the brain (e.g., deep white matter, basal ganglia, and periventricular hyperintensities) compared with age-matched control subjects. Although age is positively correlated with response to ECT, these white matter abnormalities, in addition to medial temporal lobe atrophy, may decrease the response to ECT in an individual older patient ([Hickie et al. 1995](#); [Oudega et al. 2011](#); [Steffens et al. 2001](#)) and increase the risk of interictal delirium ([Figiel et al. 1990](#)).

## Mania

Anecdotal reports and case studies suggest that ECT is beneficial in the treatment of mania associated with bipolar disorder ([Fink 2001, 2006](#)). In a prospective controlled trial, [Small et al. \(1988\)](#) compared the efficacy of ECT with that of lithium in the treatment of mania. Patients who received ECT improved more during the first 8 weeks of treatment than did patients who received lithium.

Nevertheless, after 8 weeks of treatment, ECT and lithium were comparable in efficacy.

A double-blind RCT of bifrontal and bitemporal ECT in acute mania also confirmed the efficacy of ECT in mania ([Hiremani et al. 2008](#)). In addition, patients with mixed symptoms of depression and mania responded particularly well to ECT ([Gruber et al. 2000](#); [Medda et al. 2010, 2014](#); [Valentí et al. 2008](#); [Vieta 2005](#)). Given the benefit of anticonvulsant medications in treating mania and the evidence that ECT may exert its therapeutic effect by raising the seizure threshold ([Sackeim 1999](#)), the efficacy of ECT for mania is not surprising. Catatonia secondary to mania represents another clinical scenario in which ECT may offer advantages in efficacy and rapidity of response compared with pharmacotherapy ([Taylor and Fink 2003](#)).

Challenges specific to treating mania with ECT include the following:

- Concomitant use of anticonvulsants, which may interfere with seizure induction in ECT
- Reports of prolonged seizures and delirium when ECT is given with lithium ([Sadananda et al. 2013](#); [Sartorius et al. 2005](#)), although other researchers have reported safe coadministration of ECT and lithium ([Dolenc and Rasmussen 2005](#); [Thirthalli et al. 2011](#))
- Decreased likelihood that manic (vs. depressed) patients will voluntarily consent to ECT treatment

Despite a rapid increase in studies evaluating alternative mood-stabilizing medications, including newer anticonvulsants and atypical antipsychotics, there is a relative lack of research comparing the potential benefits of ECT in the acute and maintenance treatment of bipolar

disorder ([Fink 2001](#); [Keck et al. 2000](#)). This is regrettable given the advantages of ECT as a mood stabilizer that can effectively treat both the manic and the depressed phases of the illness. ECT has been given safely to children with intractable mania ([Hill et al. 1997](#)) and to patients with dementia and comorbid mania ([McDonald and Thompson 2001](#)). ECT also may have an important role in the treatment of mania during pregnancy, given the potential teratogenic effects of many anticonvulsant medications as well as the potential harm to both the mother and the fetus from a prolonged affective episode ([Spodniakova et al. 2014](#)).

It is unclear whether unilateral ECT is as effective as bilateral ECT in the treatment of mania. [Hiremani et al. \(2008\)](#) found both bifrontal and bitemporal ECT to be effective for mania with equivalent side-effect burden, although patients had a more rapid improvement with bifrontal electrode placement. Future research is needed to clarify the role of ECT in the treatment of mania, although clear evidence indicates that ECT is an effective treatment and should be included in any algorithm of therapy for treatment-resistant, severely disabling, catatonic, or delirious mania ([Jacobowski et al. 2013](#); [Nivoli et al. 2012](#)).

## Schizophrenia

With the introduction of clozapine and the atypical antipsychotics, ECT has become a third-line treatment for schizophrenia in the United States, but ECT may be a first-line treatment for schizophrenia in some Eastern Hemisphere countries such as India and China (e.g., [McDonald 2012](#)). ECT continues to have an important role in the treatment of acute psychotic episodes, catatonic schizophrenia, and neuroleptic malignant syndrome

([Matheson et al. 2010](#); [Pompili et al. 2013](#); [Tharyan and Adams 2005](#)). Case reports of ECT in more chronic and treatment-resistant cases support the role of ECT in the treatment of schizophrenia ([Biedermann et al. 2011](#); [Chanpattana and Kramer 2003](#); [Chanpattana and Sackeim 2010](#); [Cupina et al. 2013](#); [Pawelczyk et al. 2014](#); [Pompili et al. 2013](#)).

ECT is particularly beneficial in the treatment of positive symptoms of schizophrenia and is less effective in decreasing negative symptoms ([Chanpattana and Sackeim 2010](#); [Pawelczyk et al. 2014](#)). ECT also has been shown to be effective in augmenting antipsychotic treatment in treatment-resistant schizophrenia ([Painuly and Chakrabarti 2006](#); [Ravanić et al. 2009](#)). A randomized trial found bilateral ECT to be effective as an add-on to clozapine for treatment-refractory psychosis in schizophrenia, with a 50% response rate in this difficult-to-treat population ([Petrides et al. 2015](#)).

ECT combined with antipsychotic therapy also may be effective in the management of aggressive behavior in patients with schizophrenia ([Hirose et al. 2001](#)) as well as for maintenance treatment of schizophrenia ([Chanpattana et al. 1999](#)).

There has been research to support bifrontal (as opposed to bitemporal) electrode placement as providing better treatment response and tolerability in schizophrenia, although the data are limited ([Phutane et al. 2013](#)).

Catatonic schizophrenia is very responsive to ECT ([Fink 2013](#); [van Waarde et al. 2010](#)), and ECT can be an important treatment when benzodiazepines are ineffective and symptoms do not respond to antipsychotics or when antipsychotics are relatively contraindicated because of an



unclear diagnosis of catatonia versus neuroleptic malignant syndrome ([Rosebush and Mazurek 2010](#)).

The recommendations of the American Psychiatric Association Task Force on Electroconvulsive Therapy ([American Psychiatric Association 2001](#)) state that ECT is an effective treatment for schizophrenia in the following clinical conditions: 1) during acute onset of symptoms, 2) when the catatonic subtype of schizophrenia is present, and 3) when there is a history of a positive response to ECT.

## **Other Medical and Psychiatric Disorders**

ECT can be a lifesaving treatment for patients with catatonia regardless of the etiology, including catatonia resulting from a medical disease (e.g., systemic lupus erythematosus), neuroleptic malignant syndrome, schizophrenia, autism spectrum disorders, bipolar disorder, and major depressive disorder ([Luchini et al. 2015](#); [Rosebush and Mazurek 2010](#)). Patients with developmental delay complicated by catatonia and self-injurious behavior have shown improvements in catatonic symptoms and self-injurious behavior with ECT ([Wachtel et al. 2013](#)), as have patients with developmental delay and comorbid mood symptoms ([Aziz et al. 2001](#); [van Waarde et al. 2001](#)).

A recent matched case-control study of more than 40,000 patients with PTSD and major depressive disorder (MDD) found that compared with antidepressant therapy alone, ECT combined with antidepressants was associated with a significant reduction in PTSD and MDD symptoms as well as a decrease in completed suicides and cardiovascular and all-cause mortality ([Ahmadi et al. 2016](#)). Citing a case report of a decrease in PTSD symptoms when traumatic events were recalled immediately prior to each ECT session ([Gahr et al. 2014](#)), [Andrade et al. \(2016\)](#) hypothesized that

ECT is effective because the treatment impairs reconsolidation of reactivated, emotionally aversive memories.

Limited evidence suggests that ECT may relieve symptoms associated with obsessive-compulsive disorder (OCD) ([A.Y. Liu et al. 2014](#); [Maletzky et al. 1994](#); [Thomas and Kellner 2003](#)) and schizophrenia complicated by OCD ([Lavin and Halligan 1996](#)).

Because the administration of ECT raises the seizure threshold, ECT can interrupt status epilepticus ([Cline and Roos 2007](#); [Fink et al. 1999](#); [Lisanby et al. 2001](#); [Shin et al. 2011](#)) and treat intractable seizures ([Regenold et al. 1998](#)).

Case reports and retrospective reviews have found that ECT can alleviate behavioral and psychological symptoms of dementia, including associated depression, psychosis, and agitation; such patients would be at increased risk for delirium during the acute course of ECT, but the limited existing evidence does not indicate significant worsening of the underlying dementia ([X. Liu et al. 2014](#); [Rodríguez-Sosa et al. 2013](#); [Tang et al. 2014](#); [Ujkaj et al. 2012](#)).

ECT is effective in treating psychosis and depression in patients with Huntington's disease ([Cusin et al. 2013](#)). ECT also has been shown to be an effective treatment for the motor symptoms of Parkinson's disease ([Faber and Trimble 1991](#); [Kellner et al. 1994](#); [Rasmussen and Abrams 1991](#)), and a meta-analysis of five studies confirmed that ECT acutely improves global motor functioning in patients with Parkinson's disease, with a notable effect size of 1.68 ([Fregni et al. 2005](#)). These reports have included patients with and without psychiatric illnesses; ECT improves the motor symptoms of Parkinson's disease independently of its effects on the patient's mood. Favorable predictors of response include advanced age, severe disability (on-off

syndromes), and painful dyskinesias. Reductions in the symptoms of Parkinson's disease tend to occur during the first several sessions of ECT. However, the effects of ECT are not permanent and usually last from several days to several months, although prolonged improvement has been reported in a few patients. Maintenance ECT also has been shown to be effective for up to 4 years in treating the motor symptoms of Parkinson's disease ([Aarsland et al. 1997](#); [Wengel et al. 1998](#)).

Autoimmune disorders with comorbid depression and psychosis have been successfully treated with ECT, including anti-*N*-methyl-D-aspartate receptor encephalitis ([Kuppuswamy et al. 2014](#)) and systemic lupus erythematosus ([Tan and Tan 2013](#)).

ECT may exert some analgesic effects independent of its effects on mood, as evidenced in a trial with positive results that used ECT to treat fibromyalgia ([Usui et al. 2006](#)). ECT has also been shown to be effective in the treatment of both mood symptoms and pain in patients with complex regional pain syndromes ([McDaniel 2003](#)).

## **Electroconvulsive Therapy Use During Pregnancy**

According to a joint report by the American Psychiatric Association and the American College of Obstetricians and Gynecologists ([Yonkers et al. 2009](#)), ECT is an effective, safe treatment for women who experience severe manic and/or depressive symptoms during pregnancy. As with pharmacotherapy, ethical concerns limit randomized prospective trials to assess the efficacy and safety of ECT in pregnancy, although ECT has been safely used in all three trimesters ([Rabheru 2001](#)).

A review of 339 case reports from 1941 to 2007 identified 25 cases of fetal complications during ECT (of which fewer than 50% were deemed possibly or likely related to ECT) and 20 cases of maternal complications (of which 90% were deemed possibly or likely related to ECT) ([Anderson and Reti 2009](#)). The efficacy rates for ECT in these case reports were in keeping with efficacy rates for ECT in nonpregnant patients (61% for schizophrenia, 84% for depression).

The risks of administering ECT during pregnancy have been reviewed by [Rabheru \(2001\)](#). Possible strategies for mitigating risk of ECT during pregnancy include obstetrics consultation and performance of the procedure in facilities equipped to deal with obstetrical emergencies. Physiological issues in pregnancy that could affect risks include delayed gastric emptying, aortocaval compression causing placental insufficiency, uterine restriction on respiratory ventilation when supine, and seizure-induced elevations in oxytocin with subsequent premature uterine contractions. Use of antacids, adequate hydration, elevation of the right hip, and availability of tocolytic therapy if needed are strategies to address these respective pregnancy-specific issues in ECT administration ([Saatcioglu and Tomruk 2011](#)).

## Stimulus Dosing in Electroconvulsive Therapy for the Treatment of Depression

Questions about the proper management of the electrical stimulus have been central to the science and practice of ECT. Cerletti and Bini modeled ECT on the success of

pharmacologically induced convulsive therapy and assumed that the stimulus should be convulsive. Interestingly, the first ECT session in 1938 involved two subconvulsive stimulations before Cerletti and Bini increased the stimulus intensity to produce a convulsion ([Endler 1988](#)). Thus, the first ECT session was a “titrated” ECT session involving the serial application of increasing stimulus intensities passing from the subconvulsive range through the convulsive threshold. Issues in stimulus dosing that have been considered since that time include the following:

- Whether the stimulus should be subconvulsive or convulsive
- What the optimal stimulus waveform is
- If a convulsive stimulus is desired, to what degree the stimulus intensity should be in excess of the convulsive threshold
- Which physiological parameters, if any, provide useful feedback to continuously refine stimulus dosing throughout the ECT course

## **Convulsive, Subconvulsive, and Sham Stimulation**

The use of nonconvulsive electrical stimulation to treat psychiatric disorders preceded the introduction of ECT by decades. Most of the treatments involved administering static electricity to parts of the body including but not limited to the head ([Grover 1924](#)). The availability of commercial ECT devices did not lead to the immediate replacement of subconvulsive stimulation with convulsive stimulation. Instead, some practitioners used the devices to deliver lengthy (several minutes long) subconvulsive cranial stimulation. However, it became clear that subconvulsive

stimulation was associated with a *poorer* outcome than conventional psychotherapy in patients in the depressive/anxious spectrum, and the practice of treating patients with subconvulsive stimuli decreased ([Hargrove et al. 1953](#)). Now, many years later, the use of repetitive transcranial magnetic stimulation (rTMS) has reopened the question of whether subconvulsive stimuli are an effective treatment for depression; these data are reviewed in a later section (see “Subconvulsive Stimulation Therapies: rTMS and VNS”). The elements of modified ECT (including muscle relaxation and general anesthesia) were described early in the history of ECT. The wide-scale adoption of these modifications raised new questions as to whether seizure is central to the antidepressive efficacy of ECT or whether anesthesia alone would be just as effective. The Northwick Park trial ([Johnstone et al. 1980](#)) and the Leicestershire trial ([Brandon et al. 1984](#)) are examples of two “sham” ECT studies in which anesthesia alone was compared with real ECT. It was convincingly demonstrated that real ECT is more efficacious, especially for the most severe forms of depression ([Brandon et al. 1984](#); [Johnstone et al. 1980](#)). The efficacy of ECT was clearly linked to the production of a seizure. Neither the use of anesthesia alone without the electrical stimulus nor the use of subconvulsive stimuli appears to have real benefit in the treatment of depression.

## **Stimulus Waveform**

Given that a convulsive stimulus is necessary for the antidepressive effects of ECT, a nearly infinite number of variations are available for formulating the stimulus waveform. The earliest ECT devices delivered a sinusoidal stimulus. Other waveforms available on early ECT devices included the “chopped” sine wave, the unidirectional pulse

square wave, and the alternating brief-pulse square wave. Although some investigators suspected that sine wave stimuli might produce slightly better antidepressive effects compared with brief-pulse stimuli, that idea became untenable when a randomized study showed that sine wave ECT produced more memory side effects than brief-pulse ECT, irrespective of the placement of the stimulating electrodes ([Weiner et al. 1986b](#)).

This finding of greater cognitive side effects with sine wave ECT was replicated in an efficacy study using a prospective cohort design, which showed that compared with brief-pulse stimulation, sine wave stimulation was associated with a slowing of reaction time that persisted for at least 6 months after ECT ([Sackeim et al. 2007](#)). The more severe cognitive side effects produced by sinusoidal stimuli may be explained by the slower rise time for each sine wave cycle as compared with the brief-pulse cycle. Consequent to the slower rise time, much of the sine wave stimulus is subconvulsive and thus presumably adds nothing to the therapeutic effect of ECT, adding only to cognitive side effects. The steep rise in the brief-pulse waveform allows for the entire stimulus to be above the convulsive threshold (suprathreshold). Because much of the sine wave stimulus is nonproductive, being in the subconvulsive range, it would be predicted that brief-pulse stimuli would be more efficient, requiring a stimulus of smaller magnitude to produce a seizure. *Standard* brief-pulse stimuli are defined by a pulse duration of 1-2 milliseconds, whereas *ultrabrief*-pulse stimuli are defined by a pulse duration of less than 0.50 millisecond. In [1980](#), [Weiner](#) showed that standard brief-pulse stimuli could induce a seizure with only one-third of the energy required with sine wave stimuli. Standard brief-pulse ECT devices have currently replaced

sine wave devices in the United States ([Farah and McCall 1993](#)).

Devices using ultrabrief-pulse stimuli have the advantage of improving the efficiency of seizure induction. [Abrams \(2002\)](#) estimated that it takes only about 0.25 millisecond to initiate neuronal depolarization, and that longer pulse widths are inefficient and waste electrical charge. The total energy output of these ultrabrief-pulse modalities is the same as the total energy output of the standard brief-pulse widths; thus, as the stimulus pulse widths are shortened, the stimulus trains are lengthened. Ultrabrief-pulse widths may have an advantage because shorter pulse widths and longer pulse trains have been shown to elicit seizures with a smaller electrical charge and therefore may have fewer cognitive side effects ([Sackeim et al. 2008](#)).

Several recent studies have assessed the efficacy and side-effect profile of brief-pulse versus ultrabrief-pulse width right-unilateral ECT. In a prospective study comparing ultrabrief-pulse right-unilateral ECT (0.3 millisecond;  $n=74$ ) versus brief-pulse right-unilateral ECT (1.0 millisecond;  $n=22$ ) in depressed patients, [Loo et al. \(2008\)](#) found similar depression response rates in the two groups (albeit a slower rate of response in the ultrabrief-pulse right-unilateral ECT group), with better cognitive outcomes in the ultrabrief group. In a prospective randomized trial of high-dose right-unilateral ECT in 87 depressed inpatients, [Spaans et al. \(2013b\)](#) found that patients receiving ultrabrief-pulse ECT were significantly less likely to achieve remission—and required significantly more treatments to do so—compared with patients receiving brief-pulse ECT. A retrospective study in 150 subjects pooled from three research samples found that fewer treatments were needed with brief-pulse than with



ultrabrief-pulse right-unilateral ECT and that remission rates were significantly higher with brief-pulse ECT ([Loo et al. 2013](#)). Generally, researchers have found that ultrabrief-pulse right-unilateral ECT produced fewer neurocognitive effects (specifically on autobiographical memory) compared with brief-pulse treatment ([Loo et al. 2008](#); [Mayur et al. 2013](#); [Verwijk et al. 2012](#)) or that side effects for the two types were similar ([Spaans et al. 2013b](#)).

The data on pulse width and bilateral ECT are also evolving. In a retrospective study of bilateral ECT in which 65 patients with major depressive disorder received a pulse width of either 0.5 millisecond (brief) or 0.25 millisecond (ultrabrief), the two groups had similar response and remission rates ([Niemantsverdriet et al. 2011](#)). In a prospective randomized trial in which 64 patients received treatment with a course of either bifrontal ultrabrief-pulse (0.3 millisecond) ECT at 1.5 times the seizure threshold or right-unilateral ultrabrief-pulse ECT at 6 times the seizure threshold, the two patient groups showed equivalent response rates, with no changes in cognition in either group ([Sienaert et al. 2010](#)).

However, a randomized trial of 90 depressed patients who were treated with either right-unilateral ECT at 6 times the seizure threshold or bilateral ECT at 2.5 times the seizure threshold, using either a traditional brief pulse (1.5 milliseconds) or an ultrabrief pulse (0.3 millisecond), found that the remission rate with ultrabrief-pulse bilateral ECT was significantly lower than that with brief-pulse bilateral ECT (35% vs. 65%). Ultrabrief- and brief-pulse right-unilateral ECT (remission rates of 73% and 59%, respectively) were as effective as brief-pulse bilateral ECT (65%) but produced fewer cognitive side effects. Of the four treatment groups, ultrabrief-pulse right-unilateral ECT was

associated with the fewest cognitive side effects ([Sackeim et al. 2008](#)).

A recent systematic review concluded that brief-pulse right-unilateral ECT was “slightly” more efficacious than ultrabrief-pulse right-unilateral ECT in treating depression and required fewer treatment sessions but was also associated with more cognitive side effects ([Tor et al. 2015](#)). Other groups have reviewed the data and argued against the use of ultrabrief-pulse right-unilateral ECT, stating that the evidence does not support its selection over brief-pulse right-unilateral ECT ([Spaans et al. 2013a](#)) or over brief-pulse bilateral ECT at 2.5 times the initial seizure threshold ([McCormick et al. 2009](#)) as the first-line treatment. Clinicians considering the use of brief-pulse right-unilateral versus ultrabrief-pulse right-unilateral ECT versus bilateral ECT should take into account clinical factors such as baseline cognitive or neurological status and the severity of psychiatric symptoms, as well as practical issues such as the potential for increased length of the treatment course with brief-pulse treatments ([Galletly et al. 2012, 2014](#)).

The picture with ultrabrief-pulse *bilateral* ECT is less clear, and further research may be needed to determine the relative efficacy of ultrabrief-pulse versus standard brief-pulse bilateral ECT. Some have argued that brief-pulse right-unilateral ECT should be used when a faster speed of response is required, and that brief-pulse bilateral ECT should be used until more research data has accumulated in support of the efficacy of ultrabrief-pulse bilateral ECT ([Loo et al. 2012](#)).

## **Magnitude of the Stimulus Dose**

The consensus regarding the need for convulsive (as opposed to subconvulsive) stimuli and brief-pulse

waveforms would seem to make stimulus dosing in ECT a straightforward process, except for the question of the degree to which the stimulus should exceed the convulsive threshold. For years, ECT practitioners were satisfied that the answer to this question was found in the work of [Ottosson \(1962\)](#), who compared routine ECT with ECT modified by pretreatment with intravenous lidocaine. He found that seizures induced by lidocaine-modified ECT were shorter than those induced by routine ECT and observed an inverse relation between seizure duration and antidepressant effect. From this work, it was widely accepted that stimulus doses producing seizures lasting at least 25 seconds have an antidepressant effect ([American Psychiatric Association 1978](#)).

Initially, ECT was administered with bilateral (typically bitemporal) electrode placement. In [1949](#), [Goldman](#) introduced right-unilateral ECT and placed the stimulating electrodes over the right hemisphere instead of the mesial temporal lobes in an attempt to reduce the direct stimulation of language areas and thereby minimize cognitive side effects. Although right-unilateral ECT was associated with fewer cognitive side effects, most studies showed that bilateral ECT had a marked therapeutic advantage over unilateral ECT for depression ([d'Elia and Raotma 1975](#)).

The clinical wisdom that bilateral ECT was more effective than right-unilateral ECT in treating depression came into question with the work of Sackeim's research group. [Sackeim et al. \(1993\)](#) reported that when the electrical stimulus was just barely above the convulsive threshold, ECT with right-unilateral electrode placement was not efficacious, despite the production of electrographic seizures typically in excess of 25 seconds. However, as the

electrical dose was progressively increased, response rates in right-unilateral ECT improved significantly and approached those of bilateral ECT. In contrast, bilateral ECT was fully efficacious regardless of whether the electrical stimulus was minimally above or 2.5 times the seizure threshold, but excess memory side effects accrued at the higher stimulus dose.

There is a dose-response relationship in right-unilateral ECT only to the extent that the stimulus dose exceeds the convulsive threshold for a given patient; the absolute magnitude of the stimulus dose has no independent influence on this relationship. The efficacy of right-unilateral ECT follows a nearly linear relationship to the degree that the stimulus dose exceeds the seizure threshold, at least through 12 times the seizure threshold ([McCall et al. 2000](#)). This relationship is analogous to the patient-specific dose-response relationship in the pharmacological treatment of depression with tricyclic antidepressants: serum blood levels are more important than the absolute oral dose in determining both efficacy and side effects.

These findings led to the following conclusions:

- With standard brief-pulse stimulation delivered with right-unilateral electrode placement, the stimulus should be substantially above the convulsive threshold in order to ensure the effectiveness of ECT.
- With standard brief-pulse stimulation delivered with bilateral electrode placement, the stimulus should not be excessively above the convulsive threshold in order to avoid undue cognitive side effects.

The convulsive threshold varies by a factor of at least 40 in large patient samples; thus, the mean threshold for a group of patients may not inform the threshold for an individual ([Sackeim et al. 1991](#)). It is clear that the convulsive threshold is related to age, sex, race, choice of stimulating electrode placement, and, perhaps, cranial dimensions ([Chung 2006](#); [Colenda and McCall 1996](#); [Sackeim et al. 1991](#)) and even volume of cerebrospinal fluid estimated on MRI ([van Waarde et al. 2013](#)). Still, these factors predict only a small amount of the variance in the convulsive threshold, and statistical models to predict the convulsive threshold, including age-based dosing approaches, may not yield an accurate estimate of the threshold ([Colenda and McCall 1996](#); [Tiller and Ingram 2006](#)). In addition, a primary factor for an individual patient may be medications that affect the seizure threshold (e.g., benzodiazepines, anticonvulsants), which are difficult to account for in any algorithm estimating the seizure threshold.

## Seizure Morphology

The report of [Sackeim et al. \(1993\)](#) that threshold right-unilateral ECT produced seizures of 25 seconds or longer without antidepressant efficacy cast into doubt the clinical wisdom that the stimulus dose was therapeutic if the electrographic seizure lasted at least 25 seconds. Investigators have sought to find a physiological marker of treatment adequacy to replace seizure duration. The most promising candidate is seizure morphology. [Ottoosson \(1962\)](#) reported that lidocaine changed the shape of ECT seizures, as well as shortening their duration. Lidocaine-modified seizures, in addition to being less efficacious than standard

ECT seizures, were characterized by loss of spike activity and poor postictal suppression.

Seizure morphology varies according to ECT technique. That is, greater seizure intensity correlates with ECT techniques that progress from lower efficacy (with right-unilateral electrode placement and low stimulus intensity) to higher efficacy (with bilateral placement and high stimulus intensity) ([Krystal et al. 1993](#)). Electrode placement and stimulus intensity have independent and additive effects on seizure morphology. Seizures of greater intensity are characterized by higher peak ictal amplitudes, greater stereotypy of the ictal discharge, greater symmetry and coherence between the left and the right cerebral hemispheres, and more profound postictal suppression. Preliminary evidence suggests that greater seizure intensity is predictive of a greater likelihood of response and/or a faster response ([McCall et al. 1993](#); [Nobler et al. 1993](#)).

The natural extension of this reasoning leads to the hope that seizure morphology could guide decisions about stimulus intensity as the course of ECT progresses. For example, if seizure intensity is low in the middle of the treatment course, then the treatment technique should be changed (by switching electrode placement and/or increasing the stimulus intensity) in order to optimize the clinical outcome. Manufacturers of ECT devices now incorporate automated measures of seizure intensity into the ECT chart recorder, and the accompanying owner's manual instructs the practitioner to increase the stimulus intensity if the seizure morphology appears to be degraded. The unstated implication is that degraded seizure morphology is a problem and that increasing the stimulus intensity will fix the problem. This instruction might have

merit if stimulus intensity were the primary determinant of seizure morphology, but other factors, such as age, baseline convulsive threshold, and other intrinsic patient characteristics, likely play an equal role in determining seizure expression ([McCall et al. 1996, 1998](#)). For example, greater seizure durations coupled with greater seizure regularity as shown by electroencephalography at the second ECT session are predictive of a better antidepressive outcome at the conclusion of the ECT course, and this relation is independent of the choice of stimulus electrode placement ([Kimball et al. 2009](#)).

Seizure morphology is little influenced by increasing the stimulus intensity above 2.5 times the seizure threshold. Therefore, it is premature to recommend stimulus dosing on the basis of seizure morphology. The importance of seizure morphology in predicting clinical outcome is far from being understood, and more work is needed if seizure morphology is to become a practical tool for governing ECT technique. Peak heart rate has been proposed as an alternative physiological measure of treatment adequacy, with higher heart rates perhaps indicating better clinical outcomes ([Swartz 2000](#)). Again, this approach has yet to be widely accepted.

## **Integrating the Science of Stimulus Dosing With the Choice of Electrode Placement**

**Estimating the convulsive threshold.** The recent advances in knowledge pertaining to stimulus dosing led to the conclusion that standard brief-pulse right-unilateral ECT should be initiated with a stimulus known to be at least five times the seizure threshold, whereas standard brief-pulse bilateral ECT should be initiated with a stimulus

about 50% above the seizure threshold. Choosing between these two strategies requires consideration of both efficacy and side effects. However, ultrabrief-pulse right-unilateral ECT should be considered for patients who are at risk for cognitive complications from ECT (e.g., Parkinson's disease).

[McCall et al. \(2000\)](#) conducted a randomized comparison of low-dose (1.5 times the seizure threshold) bilateral ECT ( $n=37$ ) and high-dose (8 times the seizure threshold) right-unilateral ECT ( $n=40$ ). Again, depression remission rates were not significantly different for right-unilateral electrode placement (60%) versus bilateral placement (73%), and memory effects were likewise similar. This study can be criticized for lacking sufficient power to detect small but meaningful effects. However, that concern was addressed in a subsequent study ([Sackeim et al. 2009](#)) in which 319 patients who were randomly assigned to receive either standard brief-pulse right-unilateral ECT administered at 6 times the seizure threshold or bilateral ECT administered at 1.5 times the seizure threshold. Although differences between the antidepressant effects of the two treatments were again indistinguishable, the extent of autobiographical memory loss was greater in the bilateral ECT group.

[Kellner et al. \(2010\)](#) conducted a multicenter double-blind, controlled trial in which 230 individuals with major depressive disorder were randomly assigned to one of three electrode placements: bifrontal at 1.5 times the seizure threshold, bitemporal at 1.5 times the seizure threshold, and right unilateral at 6 times the seizure threshold. The investigators found that the three electrode placements were statistically equivalent, with remission rates of 61% with bifrontal, 64% with bitemporal, and 55% with right-unilateral electrode placement. Notably, the patients



treated with bitemporal electrode placement had greater improvement in depression early in the course of treatment. In this study, the investigators used an extensive neuropsychological battery, including measures of autobiographical memory, and found few differences among the three electrode placements on a variety of neuropsychological instruments.

The bulk of the evidence thus suggests that it is desirable to set the stimulus dose as a proportion of the convulsive threshold. The convulsive threshold of each patient should be identified, preferably by measuring convulsive threshold early in the ECT course. The most accurate means of measuring the convulsive threshold for a given patient is empirical observation through use of stimulus “titration” at the initial treatment session—a technique in which an intentionally subconvulsive stimuli is first administered, followed by administration of successively larger stimuli until a seizure is produced. This approach applies to both right-unilateral and bilateral electrode placement.

If ECT practitioners agree with the above reasoning and use this stimulus dosing technique, they should ascertain the convulsive threshold at the first ECT session. However, some ECT researchers have argued against titration of stimulus doses with unilateral ECT and instead have encouraged practitioners to use fixed high doses of unilateral ECT ([Abrams 2002](#)) or fixed moderate doses of bilateral ECT ([Kellner 2001](#)). In fact, an admittedly dated survey of ECT practitioners from 1993 showed that only a minority performed titration of the stimulus dose ([Farah and McCall 1993](#)). The reasons for this are unclear, but possible explanations include concerns that 1) the subconvulsive stimulation inherent in stimulus titration might be medically dangerous, 2) the subconvulsive

stimulation might add to the memory side effects, or 3) the production of a barely suprathreshold seizure with right-unilateral placement would constitute ineffective treatment, thus rendering the first treatment a wasted effort.

Subconvulsive stimulation transiently slows the heart rate, and if a subconvulsive stimulation is administered to patients who have received a  $\beta$ -blocker and no anticholinergic drug, substantial asystole is a risk ([McCall et al. 1994](#)). However, atropine pretreatment eliminates this risk. The possibility of excess acute cognitive side effects with subconvulsive stimuli has been examined and discounted ([Prudic et al. 1994](#)). The possibility of a sluggish antidepressive response when right-unilateral stimulus doses are titrated to a level moderately above the seizure threshold, however, is a reasonable concern that must be weighed against the benefits associated with assessing the seizure threshold to determine the most therapeutic dose for ECT. Of course, an initial titrated suprathreshold bilateral stimulus would be closer to the therapeutic dose (of 1.5-2.5 times the seizure threshold), and the cognitive benefits of ensuring that the dose is not suprathreshold (i.e., >3 times the seizure threshold) are more straightforward.

**Alternatives to estimating the convulsive threshold.** [Abrams \(2002\)](#) suggested that the most efficient method of administering right-unilateral ECT is to use 100% of the maximum device capacity and a pulse width of 0.25-0.50 millisecond and recommended changing to bilateral ECT if the patient does not improve sufficiently. This strategy takes advantage of the cognitive sparing of shorter pulse widths and the efficacy of right-unilateral ECT at high doses. The disadvantages of this strategy are that it

is not adjusted to the individual's seizure threshold and that more cognitive side effects without therapeutic benefit are possible.

Alternatively, twice-weekly bilateral ECT could be initiated using the half-age method ([Abrams 2002](#)). In the half-age method, the age of the patient is divided by 2; the resulting number is the percentage of the device's maximal output with which the patient is first treated (e.g., a 50-year-old would be treated at 25% of the machine's maximal output). The half-age method has been shown to be a reasonable estimate for the therapeutic stimulation in patients receiving bitemporal ECT ([Petrides et al. 2009](#)). As stated earlier, characteristics other than age can influence an individual's seizure threshold, including multiple medications (e.g., benzodiazepines, valproic acid) that the patient may be taking or anesthetic medications such as propofol. For these reasons, this calculation may be problematic.

[Kellner \(2001\)](#) recommended an alternative fixed-dose strategy that involves starting with 75% of the maximal output for right-unilateral ECT and 30%–60% of maximal output for bilateral ECT. Again, these estimates do not provide the individualized dosing that can be achieved with dose titration.

**Choosing an electrode placement and stimulus dose.** As noted earlier, a comparison of the three most commonly used electrode placements found no significant difference in the efficacy or side-effect profiles of right-unilateral at 6 times the seizure threshold, bitemporal at 1.5 times the seizure threshold, or bifrontal electrode placement at 1.5 times the seizure threshold ([Kellner et al. 2010](#)). The absolute response rate, however, favored

bitemporal ECT over the other two electrode placements, and bitemporal ECT was noted to have a faster onset of response. Additionally, bitemporal ECT is associated with reduction of suicidal intent ([Kellner et al. 2005](#)). Therefore, those patients with the most serious complications of major depressive disorder or mania (i.e., active suicidal behavior with intent, catatonia, psychosis) should be considered for brief-pulse bitemporal ECT at 1.5–2.5 times the stimulus threshold. Consideration of high-dose (10 times the seizure threshold) brief-pulse right-unilateral ECT is appropriate given concerns about a particular patient's vulnerability to the cognitive side effects of ECT. No clear guidelines are available for use of right-unilateral ECT in schizophrenia or mania, although some evidence supports bifrontal over bitemporal ECT in schizophrenia ([Phutane et al. 2013](#)) and acute mania ([Hiremani et al. 2008](#)).

In patients who have a treatment-resistant mood or psychotic disorder without an acute danger to themselves, starting with right-unilateral electrode placement should be considered. Again, the decision to start brief-pulse or ultrabrief-pulse ECT can be individualized to the particular patient. The dosing could start with moderately suprathreshold dosing (5–6 times the seizure threshold) and be increased to 10–12 times the seizure threshold without a significant response after 5–6 treatments depending on patient tolerance.

Other situations favoring the use of titrated right-unilateral ECT (with its potential cognition-sparing effects) include treatment of depressed patients with comorbid dementia or other neurological conditions (e.g., Parkinson's disease). The treatment in these patients should minimize even transient memory side effects and may include starting at a very conservative unilateral dose (i.e., five

times the seizure threshold) and increasing the dose as tolerated.

# Electroconvulsive Therapy

## Treatment Procedure

### **Pretreatment Medical Evaluation**

Although no medical condition represents an absolute contraindication for ECT, several clinical conditions may increase the risk of complications from ECT:

- Recent myocardial infarction or unstable cardiac conditions
- Any illness that increases intracranial pressure (e.g., brain tumor)
- Recent cerebral infarction, particularly hemorrhagic infarction
- Aneurysm or vascular malformation
- American Society of Anesthesiology physical status classification level 4 or 5
- Severe pulmonary disease

When treating high-risk patients with ECT, clinicians must evaluate the effects of ECT on cerebral and cardiac physiology and review data from the extant ECT literature to help develop individual risk-benefit ratios ([American Psychiatric Association 2001](#); [Saito 2005](#); [Sundsted et al. 2014](#)). All patients should undergo a thorough medical and neuropsychiatric review before beginning a course of ECT. Particular emphasis should be placed on diseases affecting the CNS and the cardiovascular system. The pre-ECT

evaluation should include a physical examination, a detailed neurological examination, a mental status examination, a medical history, and a review of systems. The patient's mental status should be evaluated before initiation of ECT and monitored closely before administration of ECT at every session thereafter.

## **Electroconvulsive Therapy Administration**

In the United States, the standard anesthetic agent used for ECT is methohexital, a short-acting barbiturate with minimal anticonvulsant effects. Methohexital is given in a dose of approximately 0.75–1.0 mg/kg; one alternative is propofol, given in a dose of approximately 0.75–1.5 mg/kg. Concerns regarding the use of propofol include the fact that it is associated with shorter seizures than methohexital and increases the number of missed seizures (i.e., delivery of an electrical stimulus without induction of a seizure) ([Swaim et al. 2006](#)). However, seizure duration has not been correlated with clinical efficacy, and trials comparing the use of methohexital with the use of propofol have not shown significant differences in the antidepressant efficacy of ECT ([Avramov et al. 1995](#)). Propofol was associated with improved hemodynamic stability and equivalent improvement in depressive symptoms in trials comparing the two anesthetic agents ([Geretsegger et al. 2007](#)).

One strategy to lengthen seizures is to change to the anesthetic etomidate (0.15–0.3 mg/kg), which is associated with significantly longer seizures ([Stadtland et al. 2002](#)), and, in one retrospective naturalistic study, was associated with a significantly shorter treatment course ([Swaim et al. 2006](#)).

Another strategy is to add the ultra-short-acting narcotics remifentanil or alfentanil to methohexital or propofol and

decrease the dose of the methohexital or propofol. These opiates are potentially proconvulsant, suppress the hemodynamic response to the seizure, and can provide anesthesia in lieu of lower doses of methohexital or propofol ([Locala et al. 2005](#); [Vishne et al. 2005](#)).

Immediately after the patient is anesthetized, a muscle relaxant is administered intravenously. Succinylcholine, at doses of 0.75–1.5 mg/kg, is a widely used depolarizing neuromuscular blocking agent. In patients with musculoskeletal disease, a nondepolarizing agent such as rocuronium can be considered. Anticholinergic agents, such as atropine or glycopyrrolate, are used to prevent ECT-induced bradycardia and to minimize airway secretions. Glycopyrrolate does not cross the blood–brain barrier and therefore may be associated with less postictal confusion than atropine in the elderly. When a  $\beta$ -blocker is added to control the ECT-induced rise in blood pressure and heart rate, use of an anticholinergic agent should be considered because the initial response to the ECT stimulus is bradycardia. Atropine (0.4–1.0 mg) or glycopyrrolate (0.2–0.4 mg) can be given either intramuscularly 30 minutes before the ECT treatment or intravenously at the time of treatment.

Regarding dosing of the electrical stimulus, the titration or *method-of-limits* approach involves use of a table with incremental increases in the electrical energy to determine the minimal amount of energy necessary to produce a seizure (i.e., seizure threshold) as monitored by electroencephalography. Typically, a seizure lasting 30–90 seconds occurs during treatment. Seizures lasting longer than 3 minutes should be terminated by administering an anticonvulsant (e.g., a second dose of methohexital or propofol or a short-acting benzodiazepine such as

midazolam). Patients usually are alert and oriented 20–45 minutes after receiving an ECT treatment.

Although anticonvulsant medications should be minimized, if possible, during the ECT course, there is evidence that continuing or starting antidepressant medication during the course of ECT for major depressive disorder may enhance the overall antidepressant response ([Sackeim et al. 2009](#)).

## Management of Electroconvulsive Therapy–Related Side Effects

### Postictal Agitation

Postictal agitation can be a significant problem, with the potential for causing injury to both the patient and the nursing staff caring for the patient ([Augoustides et al. 2002](#)). Postictal agitation is difficult to predict in an individual patient and must be differentiated from status epilepticus. Postictal agitation is characterized by random flailing movements of the patient (in contrast to the rhythmic convulsions of a seizure) and by the fact that the patient does not lose consciousness or manifest the fixed gaze of a patient experiencing a grand mal seizure.

Several strategies exist for treating postictal agitation, and most involve intravenous access. Midazolam or methohexital will often sedate the patient and can be very effective. Additionally, propofol can be used to manage postictal agitation ([Tzabazis et al. 2013](#)). Intravenous haloperidol has been associated with ventricular ectopy ([Greene et al. 2000](#)) and should be used only in patients with cardiac monitors. One of the atypical antipsychotics



with an intramuscular formulation can be effective, with a more benign cardiac profile compared with haloperidol. Dexmedetomidine has been used to treat severe postictal agitation ([Bryson et al. 2013](#); [Cohen and Stewart 2013](#); [O'Brien et al. 2010](#)).

Preventive measures also can be taken. First, the use of a dissolvable atypical antipsychotic medication such as olanzapine at least 10 minutes prior to ECT can be very effective and does not require administration of any additional liquids ([Hermida et al. 2016](#)). Second, current drug use should be reviewed. Lithium has been associated with postictal agitation and prolonged seizures ([el-Mallakh 1988](#); [Jha et al. 1996](#); [Sadananda et al. 2013](#); [Sartorius et al. 2005](#)) and should be discontinued throughout the ECT course or withheld both the night before and the morning of ECT treatments. Use of the anesthetic agent etomidate is also associated with postictal agitation ([Freeman 2009](#)). Additionally, carbidopa has been associated with postictal delirium and should be withheld the morning of ECT treatment ([Nymeyer and Grossberg 1997](#)).

Postictal agitation has been linked to increased serum lactate levels, and some have argued that increasing the succinylcholine dose to decrease ictal muscle activity and subsequent rises in serum lactate levels can help minimize postictal agitation ([Auriacombe et al. 2000](#)). Another strategy therefore may be to increase the succinylcholine dose if any muscle movement occurs during the seizure. However, care should be taken, because another potential cause of postictal agitation is the patient awakening from anesthesia with latent paralysis of the respiratory muscles. Patients describe this experience as very frightening and may question continuing ECT.

## **Interictal Delirium**

Interictal delirium that develops during a course of ECT can persist on days when the patient does not receive a treatment. This side effect is observed primarily in elderly patients and increases in incidence with advancing age ([Figiel et al. 1990](#)). ECT-induced interictal delirium is associated with prolonged hospitalization and an increased risk of falls. Among the elderly, additional risk factors for interictal delirium are 1) Parkinson's disease, 2) Alzheimer's disease, 3) one or more cardiovascular risk factors, and 4) preexisting structural changes in the caudate nucleus observed on brain scans. Patients who develop postictal confusion are likely to have greater retrograde amnesia in the weeks and months after ECT ([Sobin et al. 1995](#)).

The incidence of delirium during a course of ECT can vary dramatically depending on the ECT technique used. As a rule, ECT-induced interictal delirium is a short-lived, reversible side effect if identified early. Once delirium has been identified, ECT treatments should be withheld until it resolves. Subsequent treatments should be administered less frequently and/or at a lower electrical charge.

## **Cardiovascular Side Effects**

ECT is associated with an increased risk of cardiovascular complications in elderly patients who have, or who are at risk for, cardiovascular disease. Studies have found widely varying rates of cardiac complications in elderly patients receiving ECT. The retrospective design of the studies, the lack of continuous cardiovascular monitoring, and the different definitions of what constitutes a cardiac complication probably account for the discrepancies in the

results. Despite these inconsistencies, most studies have found a correlation between cardiac complications and older age. ECT often produces transient systemic hypertension and abrupt transitions in cardiac rate, which can result in myocardial ischemia or arrhythmias. The increased incidence of cardiac complications among elderly patients is probably associated with the increased rate of preexisting cardiac conditions such as hypertension, coronary artery disease, and arrhythmias. On the basis of these observations, several authors have recommended the use of prophylactic cardiac medications to dampen cardiovascular responses during ECT in elderly patients who have (or are at risk for) cardiovascular disease.

Research has documented that labetalol (a medication with both  $\alpha$ - and  $\beta$ -adrenergic-blocking activity), esmolol (a shorter-acting  $\beta$ -blocker) ([Castelli et al. 1995](#); [Shrestha et al. 2007](#)), and nicardipine (a calcium channel blocker) ([Avramov et al. 1998](#); [Zhang et al. 2005](#)) can be safely used to attenuate the cardiac response during ECT.

It is recommended that adequate doses of an anticholinergic medication (intravenous atropine or glycopyrrolate) be used to decrease bradycardia induced by the initial stimulus ([Swartz and Saheba 1989](#)), and anticholinergic medications given before ECT also have been shown to increase cerebral oxygenation and perfusion during the seizure ([Rasmussen et al. 2007](#)). To help prevent ECT-induced hypotension, it is additionally recommended that all patients be adequately hydrated before undergoing ECT. If patients experience significant orthostatic hypotension in the recovery room, labetalol can be switched to the shorter-acting pure  $\beta$ -blocker esmolol.

The anesthetic agent propofol has been shown to have fewer cardiovascular effects than methohexital and can be

used in patients with preexisting cardiac conditions requiring an attenuated hemodynamic response during treatment ([Bailine et al. 2003](#)). As noted earlier, the trade-off is a shortening of the seizure length with the use of propofol.

## **Cognitive Side Effects**

The greatest area of concern with ECT among the lay public, patients, and their families is the potential development of adverse cognitive changes ([Rajagopal et al. 2013](#)). The medical community's concerns about cognitive side effects and the negative images of ECT in the media are important factors in determining the availability of ECT.

The technique by which ECT is administered influences the incidence and severity of cognitive side effects that may develop during a course of ECT. Specifically, electrode placement, the type of electrical waveform, the intensity of the electrical stimulus, and the frequency of ECT sessions all affect cognitive outcomes during ECT. Preexisting structural brain changes (e.g., white matter hyperintensities), medical illness, advancing age, low "cognitive reserve" (assessed in relation to education and occupation), and concomitant administration of certain psychotropic medications also may be risk factors for cognitive side effects from ECT ([McClintock et al. 2014](#); [Oudega et al. 2014](#)).

It is important to recognize that depression itself (especially late-life depression) often causes cognitive deficits, such that successful treatment of depression with ECT often actually improves some aspects of cognition in certain patients. [Hihn et al. \(2006\)](#) showed that prefrontally mediated aspects of cognition, such as attention and immediate encoding, improved during ECT treatment of

depression, whereas long-term memory functions remained impaired. In a review and meta-analysis of 84 studies of patients receiving ECT for depression (total  $N=2,981$ ) in which cognition was assessed with standardized tests, [Semkovska and McLoughlin \(2010\)](#) found that at 15 days post-ECT, several cognitive domains (processing speed, verbal working memory, and executive functioning) showed improvement relative to pre-ECT measures that was presumably attributable to resolution of cognition-impairing psychiatric symptoms.

The memory loss sometimes observed after ECT can be both anterograde and retrograde and has a temporal gradient, being most prominent around the time of treatment and continuing several weeks after the ECT course ([American Psychiatric Association 2001](#); [Sackeim et al. 2000](#)). Delayed recall is more affected than immediate recall, verbal more than visual, and unstructured (e.g., random word lists) more than contextualized (e.g., story recall) ([Semkovska and McLoughlin 2010](#)). In most patients, any anterograde or retrograde memory problems clear quickly after ECT ([Kellner et al. 2010](#); [O'Connor et al. 2001](#)). Episodic or autobiographical memory is particularly vulnerable to the effects of ECT, although autobiographical memory is also impaired by depression itself ([Fraser et al. 2008](#)).

Most evidence indicates that the degree of amnesia and global cognitive impairment incurred acutely during a course of ECT is greater with bitemporal ECT than with unilateral ECT ([Lisanby et al. 2000](#); [Semkovska and McLoughlin 2010](#)), although this conclusion has not been uniformly supported; a randomized trial comparing right-unilateral, bifrontal, and bitemporal ECT found only transient cognitive side effects, with no significant

differences among the three electrode placements ([Kellner et al. 2010](#)). Evidence also suggests that the degree of cognitive side effects increase with the number of treatments administered, the frequency of administration, and stimulus intensity ([Sackeim et al. 2000](#); [Shapira et al. 2000](#)), although not all reports have confirmed these latter points ([Semkovska and McLoughlin 2010](#)).

Some long-term data do not support the notion that these acute differences in cognition in studies of unilateral versus bilateral ECT persist when assessed weeks to months after an ECT course. Although unilateral ECT is associated with fewer memory problems, the cognitive deficits that occur show a dose relationship and increase as the stimulus dose is increased to 8–12 times the seizure threshold ([McCall et al. 2000](#); [Semkovska and McLoughlin 2010](#)). Research comparing bilateral and unilateral ECT has not addressed whether right-unilateral ECT given at a dose of 10–12 times the seizure threshold would cause more cognitive side effects than bilateral ECT given at a dose that is minimally above or 1.5 times the seizure threshold. *Bilateral* ECT in this context generally refers to *bitemporal* electrode placement, but in a meta-analysis of bifrontal ECT for depression, [Dunne and McLoughlin \(2012\)](#) reported less global cognitive impairment with *bifrontal* (vs. *bitemporal*) ECT, a finding on par with the overall global cognitive and amnestic effects of right-unilateral ECT.

The causes of the memory disturbance associated with ECT are multifactorial and likely include the effects of anesthetic drugs, electrode placement, stimulus waveform, generalized seizures, and electrical dose ([Sackeim et al. 2007](#)). Because cognitive effects associated with ECT are perhaps the primary (rational) barrier to more widespread use of a highly effective treatment modality, not surprisingly

researchers have started to explore ways to prevent or lessen these effects. In keeping with the possible cholinergic mechanisms of action of ECT-induced cognitive effects, at least three trials of acetylcholinesterase inhibitors (medications approved for treatment of certain dementias) have been reported in the literature, all small in sample size but all indicating benefit for general cognitive and/or memory-related test scores when the medications were administered during the acute phase of ECT ([Matthews et al. 2013](#); [Prakash et al. 2006](#); [Stryjer et al. 2012](#)). None of the trials reported any serious adverse events with these medications, which is notable in light of theoretical concerns that cholinesterase inhibitors could cause prolonged paralysis when given with the muscle paralytic succinylcholine, commonly used in ECT anesthesia, and concerns that these medications could prolong the bradycardia and/or asystole that may immediately follow the electrical dose administration.

Nonpharmacological efforts to mitigate cognitive side effects also may prove useful. [Choi et al. \(2011\)](#) reported positive early feasibility during ECT of a cognitive remediation intervention adapted from use among persons with mesial temporal lobe epilepsy.

## **Effects on Cerebral Physiology**

Immediately after an ECT treatment, the EEG shows generalized slowing of brain wave activity. This slowing tends to increase and persist longer after successive treatments. After a course of ECT is completed, slow-wave activity gradually decreases, and EEGs show a reversion to baseline activity within 3 months ([Weiner et al. 1986a](#)). Rarely, electroencephalographic abnormalities may persist for more than 3 months. Pre-existing

electroencephalographic abnormalities may increase the risk for developing prolonged abnormalities after ECT, but the clinical significance of these abnormalities is unknown. Findings from functional neuroimaging studies are consistent with post-ECT EEG findings of generalized slowing, especially in prefrontal regions. Evidence from several studies shows decreased cerebral perfusion and metabolism in frontal regions as well as decreased frontal connectivity with subcortical regions after a course of ECT ([Abbott et al. 2014a](#)); some postulate that this is a possible mechanism of action for the antidepressant effects of ECT, that is, quelling the “hyperconnectivity” that has been reported in frontal-subcortical circuits in major depressive disorder ([Bolwig 2014](#)).

## **Does Electroconvulsive Therapy Cause Brain Damage?**

Human autopsy studies of patients who have received ECT have shown no convincing evidence of irreversible brain damage when ECT was administered with current techniques ([Devanand et al. 1994](#); [Scalia et al. 2007](#); [Weiner 1984](#)). These findings are supported by a brain MRI study in which no significant structural brain changes were found immediately or 6 months after the completion of ECT ([Coffey et al. 1991](#)). In a study of six depressed patients, cerebrospinal fluid markers of neuronal/glial degeneration (tau protein, neurofilament, and S-100 beta protein) were measured before and after a successful course of ECT and showed no biochemical evidence of neuronal/glial damage or blood-brain barrier dysfunction ([Zachrisson et al. 2000](#)). In fact, emerging evidence supports quite the opposite of these commonly held beliefs and fears among the public.



ECS in animal studies has been associated with increased neurogenesis, synaptogenesis, angiogenesis, and gliogenesis, particularly in the hippocampus ([Bouckaert et al. 2014](#)). Human structural neuroimaging studies have identified increased gray matter volume and increased hippocampal volume following ECT, and magnetic resonance spectroscopy studies have reported increased chemical markers of neurogenesis ([Abbott et al. 2014b](#)).

## Prophylactic Somatic Treatment After Acute Response to Electroconvulsive Therapy

Although the short-term therapeutic benefits of ECT for depression have been clearly established, the 6-month relapse rate after ECT remains high ([Bourgon and Kellner 2000](#)). [Sackeim et al. \(1990\)](#) followed 58 patients for 1 year after ECT and found a relapse rate of 64% in patients with major depressive disorder (with and without psychotic features) in whom an adequate pre-ECT medication trial had failed. In contrast, the relapse rate in patients who had not received an adequate pre-ECT antidepressant trial was only 32%. Other clinical and demographic factors, including the presence of delusions, were not significant in predicting relapse. The adequacy of the post-ECT maintenance medication did not correlate with relapse rates. However, maintenance medications post-ECT were not standardized, and the evaluation of the pre-ECT medication trial was retrospective. The conclusion of this study is intuitively appealing: patients whose symptoms do not respond to antidepressant medication before ECT are those most likely

to relapse with maintenance medication after ECT. With relapse occurring in almost two-thirds of such patients within 1 year after ECT, the relapse rate is alarmingly high.

In a prospective randomized, double-blind trial, [Sackeim et al. \(2001a\)](#) compared three maintenance strategies: placebo, nortriptyline (target steady-state level=75–125 ng/mL), and nortriptyline plus lithium (target lithium steady-state level=0.5–0.9 mEq/L). Over the 24-week trial, the depression relapse rate was 84% with placebo, 60% with nortriptyline, and 39% with nortriptyline plus lithium, indicating a statistically significant advantage for combination therapy. In another prospective study, [Shapira et al. \(1995\)](#) found that patients who responded to an acute course of ECT and subsequently received maintenance therapy with lithium for 6 months had a relapse rate of only 36%. Of the 22 patients, the 8 who relapsed did so within the first 13 weeks. Clinical factors associated with relapse included a shorter duration of the index depressive episode, an additional depressive episode in the 12 months prior to ECT, and, again, failure of an adequate trial of antidepressant therapy before the ECT course.

The high relapse rates of depression in patients receiving antidepressant medications after a successful course of ECT have led clinicians to use alternative therapies, such as continuation and maintenance ECT, in patients who are at high risk for recurrence of their mood disorder. *Continuation ECT* is defined as ECT for up to 6 months after the acute ECT course (i.e., aimed at relapse prevention). Continuation ECT is differentiated from *maintenance ECT*, which is defined as ECT that continues for more than 6 months after the initial course (i.e., aimed at recurrence prevention).

The term *prophylactic ECT* is used to refer to any ECT treatments given as continuation or maintenance therapy. According to clinical guidelines, candidates for prophylactic ECT include patients who have recurring affective episodes that are responsive to ECT and/or who are resistant to, intolerant of, or noncompliant with antidepressant medications ([American Psychiatric Association 2001](#)). The debate over appropriate prophylactic treatment for patients who have acutely responded to ECT has focused on the clinical decision to either continue therapy with antidepressant medications or initiate maintenance ECT. The pivotal study in understanding this debate compared continuation psychopharmacology with nortriptyline and lithium with continuation ECT in 201 patients whose depression had remitted with an acute course of bilateral ECT ([Kellner et al. 2006](#)). No statistical difference was seen in relapse rates for the two groups, and more than half of the patients in each group relapsed. This study reported high relapse rates after an acute course of ECT, even with an aggressive pharmacological approach, but the relapse rates in both groups were significantly lower than relapse rates in patients in other studies who received placebo.

---

## **Other Neuromodulation Therapies**

---

Subconvulsive Stimulation  
Therapies: rTMS and VNS

To date, two types of subconvulsive therapies have received device approval from the U.S. Food and Drug Administration (FDA) for use in the treatment of depression: rTMS and vagus nerve stimulation (VNS).

## **Repetitive Transcranial Magnetic Stimulation**

The efficacy of TMS therapy is now well established and calls into question the axiom that subconvulsive stimuli cannot be therapeutic. TMS transiently entrains cortical oscillatory rhythms detected with surface EEG electrodes ([Brignani et al. 2008](#); [Johnson et al. 2010](#)). Interleaved imaging with TMS applied to prefrontal cortex shows that it immediately induces activation in subcortical limbic regions as well as cortical areas directly beneath the coil ([Li et al. 2004](#)). Other studies have found TMS-associated production of BDNF and cellular proliferation in the hippocampus ([Wang et al. 2014](#)), normalization of medial prefrontal-medial parietal default network connectivity ([Liston et al. 2014](#)), and modulation of oscillatory rhythms ([Ding et al. 2014](#); [Fuggetta and Noh 2013](#)). However, similar to many other antidepressant treatments, the putative mechanism of therapeutic action of TMS is not known.

At the time of this chapter's publication, five devices were cleared by the FDA for TMS treatment of major depressive disorder. Four of these (Deep TMS by Brainsway, Rapid2 by Magstim, MagVita by MagVenture, and NeuroSoft TMS) were cleared by the FDA under a regulatory pathway that required the manufacturer to document substantial equivalence with predicate TMS devices in adult patients who had failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

Neuronetics reported a significant effect for TMS treatment in a double-blind, sham-controlled multisite trial in 301 medication-free depressed patients ([O'Reardon et al. 2007](#)), albeit with a modest remission rate of 17% in active treatment compared with 8% in sham. In October 2008, the FDA approved NeuroStar TMS for patients with depression whose symptoms had failed to respond to antidepressant medication trials. In a study using the Neuronetics TMS devices and the same stimulation parameters, but with funding from the National Institute of Mental Health, [George et al. \(2010\)](#) replicated the positive results reported by the industry-sponsored trial. This trial confirmed the superiority of active TMS relative to sham TMS for symptoms of major depressive disorder in a blinded controlled trial involving 199 antidepressant drug-free patients with a remission rate of 14% in active treatment compared with 5% in sham. Despite these low remission rates in the sham-controlled studies, a multisite observational study conducted after FDA clearance in 307 outpatients with major depressive disorder found a 56.4% response rate and a 28.7% remission rate as assessed on the Patient Health Questionnaire ([Carpenter et al. 2012](#)). Also encouraging were the follow-up data on the 257 patients who completed a course of rTMS in this study ([Dunner et al. 2014](#)). Overall, the proportion of patients who had achieved remission at the conclusion of acute treatment was similar at 1-year follow-up, with about one-third receiving additional TMS.

The Brainsway randomized controlled trial ([Levkovitz et al. 2015](#)) in 212 patients with pharmacoresistant major depressive disorder also showed significantly higher remission rates for active TMS compared with sham (32.6% vs. 14.6%). These results were used to obtain regulatory

clearance for the Deep TMS device in 2013. FDA approvals for the Magstim, MagVenture, and NeuroSoft devices were granted on the basis of coils and stimulators that were similar to those in earlier TMS systems.

## **Vagus Nerve Stimulation**

Originally approved by the FDA for use in patients with treatment-resistant epilepsy, VNS therapy exerts its effect by applying intermittent subconvulsive electrical stimulation to the left vagus nerve. The left vagus nerve has autonomic connections to limbic and cortical areas that are known to be involved in mood regulation ([George et al. 2000](#); [Nemeroff et al. 2006](#)), and as previously discussed, a putative effect of ECT is to act as an anticonvulsant ([Sackeim 1999](#)) (see “Anticonvulsant Hypothesis” subsection earlier in this chapter). Studies of the effect of VNS on mood regulation in a small sample of patients with epilepsy reported a trend toward mood improvements ([Elger et al. 2000](#)) or showed a positive effect on mood that was no different from that seen in a group of epilepsy patients taking anticonvulsant medications alone ([Harden et al. 2000](#)). However, a 10-week open pilot study of 60 depressed nonepileptic patients showed a response rate of 31% and a remission rate of 15% ([Rush et al. 2000](#); [Sackeim et al. 2001b](#)), and the initial treatment response continued over the following 2 years ([Nahas et al. 2005](#)).

These pilot data served as the basis for a larger multicenter trial in 222 patients ([Rush et al. 2005a](#)). The study design included a 2-week single-blind recovery period after implantation (during which patients received no stimulation), followed by 10 weeks of masked active VNS treatment or sham treatment. At 10 weeks, response rates were 15% for the active-treatment group ( $n=112$ ) and 10%

for the sham-treatment group ( $n=110$ ) ( $P=0.251$ ). Although this study did not yield definitive evidence of short-term efficacy for adjunctive VNS in patients with treatment-resistant depression, the patients were subsequently followed for 1 year in a naturalistic study in which they received VNS and antidepressant treatments, both of which could be adjusted ([Rush et al. 2005b](#)). These flexible conditions should be kept in mind when considering the reported 1-year results—a response rate of 27% (55/202) and a remission rate of 16% (32/202). In another 1-year study, VNS patients showed significant improvement in comparison with a matched control group of patients with similar treatment-resistant depression who were receiving only medication ([George et al. 2005](#)). The FDA considered these data and approved the Cyberonics VNS Therapy System in 2005 for adjunctive long-term treatment of chronic or recurrent depression in adults who have not had adequate response to four or more adequate antidepressant treatments.

## Comparisons of VNS and TMS With Electroconvulsive Therapy

Studies directly comparing the antidepressant efficacy of TMS and ECT are limited. A comparative effectiveness review prepared for the U.S. Agency for Healthcare Research and Quality (AHRQ) included four trials comparing ECT with rTMS ([Gaynes et al. 2011](#)). Three trials rated “fair” in quality (defined as “susceptible to some bias but probably not sufficient to invalidate its results”) did not find a difference in response or remission rates between TMS and ECT ([Grunhaus et al. 2003](#); [Hansen et al.](#)



2011; Rosa et al. 2006). One study rated as “good” in quality (defined as “has the least bias, and results are considered to be valid”) was a multicenter trial comparing an average of 6 bilateral ECT sessions with a fixed course of 15 high-frequency TMS sessions in a mixed population of patients with unipolar and bipolar depression (McLoughlin et al. 2007). The investigators in this study found a 59% remission rate for patients in the ECT group, which was significantly higher than the rTMS remission rate (17%), and determined that ECT was more cost-effective. In the AHRQ analysis, Gaynes et al. (2011) concluded that they could not ascertain any true pattern of superiority between ECT and TMS because of the limited number of studies and the fact that the study methods and study populations were so heterogeneous.

Nine published trials have compared ECT with high-frequency TMS applied to the left prefrontal cortex, and in one trial, TMS was applied to the right side (see review by Janicak and Carpenter 2014). Although several reviews have not identified superiority of one treatment over the other for patients with pharmacoresistant depression, subsequent authors of meta-analyses have suggested that ECT may be more efficacious for patients with treatment-resistant and psychotic depression (Berlim et al. 2013; Ren et al. 2014). TMS is currently indicated only for nonpsychotic outpatients with unipolar depression, reflecting the fact that regulatory trial samples excluded those who had bipolar disorder, were acutely suicidal or psychotic, or required hospitalization. Because the FDA “label” and insurance eligibility specify these exclusions, the types of patients who receive TMS in many clinical practice settings are fundamentally different from those who receive ECT (i.e., in many psychiatric care settings, ECT is initiated



during an episode of hospitalization). Patients who are imminently suicidal, catatonic, or failing to thrive as a result of severe depression are not candidates for TMS or any other neuromodulatory treatment currently available, except ECT.

No efficacy studies have compared VNS with ECT. Although transcutaneous VNS devices may offer a noninvasive future option ([Fang et al. 2016](#)), the currently approved VNS therapy device requires surgery for initial implantation, for replacement of depleted batteries in the pulse generator, and for removal of device components in the face of clinical nonresponse or emergence of a contraindication associated with nonremovable ferromagnetic metal. VNS also may have a longer latency to onset of positive response than ECT, with some VNS patients requiring several months—and multiple changes in stimulation parameters—to show response. Patients whose symptoms do not respond or worsen while receiving VNS may be unable to transition to alternative noninvasive neuromodulation treatments that involve delivery of strong magnetic or electrical fields because of risk of injury from potential induction or conduction of current through VNS device components.

## Investigational Neuromodulation Techniques

Several neuromodulation procedures are being investigated in mood disorders. These procedures exert their therapeutic effect by depolarizing neurons and initiating action potentials or modulating cell firing rates

resulting in the induction of neuroplastic changes in neural networks ([Rossini et al. 2015](#)).

## **Magnetic Seizure Therapy and Focal Electrically Administered Seizure Therapy**

Convulsive magnetic seizure therapy (MST) and focal electrically administered seizure therapy (FEAST) are designed to induce seizures with more focal stimulation of the cortex than with ECT and potentially produce a therapeutic seizure with fewer cognitive side effects.

MST uses high-intensity, rapidly fluxed magnetic fields to produce seizure-inducing electrical currents in the brain. MST delivers a very-high-frequency stimulus (e.g., 100 Hz) that results in an electrical field that is more focal and superficial than that with ECT ([Deng et al. 2011](#)). The stimulus has less of a direct effect on the mesial temporal structures (e.g., hippocampus) and theoretically is associated with fewer cognitive side effects than is ECT. To date, only small nonrandomized trials have evaluated the efficacy of MST. MST was shown to be equivalent to ECT in one study ([Kayser et al. 2011](#)), although another study showed a less consistent response ([Fitzgerald et al. 2013](#)). Cognitive safety has been either equivalent to ([Fitzgerald et al. 2013](#); [Kayser et al. 2011](#)) or better than ECT ([Lisanby et al. 2003](#); [Polster et al. 2015](#)).

The electrical stimulus used in FEAST technology induces more focal seizures in the prefrontal cortex by changing the ECT bipolar pulse to a monopolar pulse by using a smaller anode (positive electrode) placed frontally and a larger cathode (negative electrode) on the vertex ([Nahas et al. 2013](#)). A single photon emission computed tomography scan of a patient receiving FEAST showed increases in

regional cerebral blood flow that were limited to the right prefrontal cortex, with postictal changes generalized bilaterally ([Chahine et al. 2014](#)). A small open-label study confirmed an antidepressant effect ([Nahas et al. 2013](#)), but future studies are needed to support the efficacy of this novel approach to convulsive therapy.

## **Transcranial Direct Current Stimulation**

Several other neuromodulation modalities are subconvulsive, including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation, cranial electrotherapy stimulation, low field magnetic stimulation with or without synchronization of pulses to intrinsic brain rhythms, DBS, and external trigeminal nerve stimulation; these hold promise both for the treatment of mood disorders and for elucidating the underlying biology of depression. We focus on two representative subconvulsive neuromodulation techniques under investigation: tDCS and DBS.

tDCS uses a constant low current (1-2 mA) applied continuously for 10-20 minutes through anodal and cathodal electrodes applied to the scalp with the goal of modulating the spontaneous firing rates of cells. tDCS differs from TMS in that it does not directly initiate action potentials and instead causes small changes in the membranes of cell bodies to modulate spontaneous firing rates and functional connectivity ([Polanía et al. 2011, 2012](#); [Rossini et al. 2015](#)). Two meta-analyses have found that tDCS was associated with moderate efficacy in major depressive disorder with no significant side effects ([Kalu et al. 2012](#); [Shiozawa et al. 2014](#)).

## **Deep Brain Stimulation**

Perhaps the neuromodulation procedure that has generated the most interest in both the scientific community and the lay public is DBS. DBS requires surgical implantation of a device system with intracranial placement of bilateral electrodes whose tips are precisely inserted into the targeted brain region. Extension wires tunneled from the electrodes are connected with bilateral pulse generators, similar to those used in VNS, implanted subcutaneously in the chest wall. Open-label studies showed initial promise for DBS as a therapeutic subconvulsive stimulus for depression ([Holtzheimer et al. 2012](#); [Malone et al. 2009](#); [Mayberg et al. 2005](#); [Schlaepfer et al. 2013](#)). However, when DBS was subsequently tested with stimulation at two different anatomical targets in large randomized, sham-controlled trials, antidepressant efficacy could not be confirmed. Both the Medtronic RECLAIM trial, which evaluated DBS to ventral capsule/ventral striatum ([Dougherty et al. 2015](#)), and the St. Jude Medical BROADEN trial, which investigated DBS targeted at subgenual cingulate cortex ([Morishita et al. 2014](#)), were halted because of a lack of separation between active and sham groups.

[Morishita et al. \(2014\)](#) performed a systematic review of 22 published reports of DBS trials for depression targeting six different anatomical sites: nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. They found that response rates across 22 trials were consistently reported in the range of 40%–70%, but only 3 of the trials were controlled, and results from the 2 industry-sponsored trials were not included, so they concluded that DBS for depression remains investigational.

The most recently reported clinical DBS data include two randomized discontinuation trials. The first trial was a double-blind crossover study in five previously implanted patients with treatment-resistant depression that had remitted with chronic DBS in the subcallosal cingulate gyrus ([Puigdemont et al. 2015](#)). A significant effect of DBS was seen, with more patients remaining in remission during the 3 months when active stimulation was continued compared with the 3 months when stimulation was off with sham programming procedures. The second trial was an open-label study in which DBS was delivered to the anterior limb of the internal capsule during a parameter optimization phase that lasted up to 1 year in a relatively large sample ( $N=25$ ) of depressed patients, yielding a 40% response rate ([Bergfeld et al. 2016](#)). Sixteen of the subjects subsequently entered a randomized crossover phase; the group had significantly higher depression severity scores during sham DBS than during active stimulation.

The efficacy of DBS therapy has not been compared with that of ECT, and the safety of ECT for patients who have already been implanted with a DBS system has not been established. The main risk is induction of electrical currents by ECT, leading to damage of the implanted DBS components, interference with intended stimulation, undesirable stimulation effects, or neurological injury. Although DBS has not received regulatory approval to treat depression, the Medtronic Reclaim DBS device was granted U.S. FDA humanitarian device exemption status for the treatment of chronic, severe, treatment-resistant obsessive-compulsive disorder as an alternative to anterior capsulotomy. Several DBS devices are also approved for Parkinson's disease and essential tremor. Some published articles highlight ethical considerations for DBS in the

treatment of psychiatric disorders ([Saleh and Fontaine 2015](#); [Unterrainer and Oduncu 2015](#)). In light of the potentially significant risks associated with surgical implantation of DBS electrodes and the lack of biomarkers to guide optimal targets for stimulation, incorporation of this treatment modality into standard psychiatric practice awaits further efficacy and safety data from large controlled trials.

---

## Conclusion

---

More than 80 years have passed since ECT was first used in the treatment of psychiatric disorders. The scientific evidence for the safety and efficacy of ECT has grown exponentially, and no available medical treatment is as effective in treating debilitating, life-threatening symptoms including treatment-resistant depression, mania, catatonia, and psychosis. Other neuromodulation techniques, both convulsive and subconvulsive, hold promise for elucidating neuroanatomical pathways and expanding the range of available treatments for mood disorders. Further research is needed to determine which biomarkers and patient variables are associated with response to each of these treatments. However, for patients with severe treatment-resistant mood disorders and schizophrenia, ECT remains the gold standard.

---

## References

---

- Aarsland D, Larsen JP, Waage O, et al: Maintenance electroconvulsive therapy for Parkinson's disease. *Convuls Ther* 13(4):274-277, 1997 9437571
- Abbott CC, Gallegos P, Rediske N, et al: A review of longitudinal electroconvulsive therapy: neuroimaging investigations. *J Geriatr Psychiatry Neurol* 27(1):33-46, 2014a 24381234
- Abbott CC, Jones T, Lemke NT, et al: Hippocampal structural and functional changes associated with electroconvulsive therapy response. *Transl Psychiatry* 4:e483, 2014b 25405780
- Abrams R: Stimulus titration and ECT dosing. *J ECT* 18(1):3-9, discussion 14-15, 2002 11925511
- Ahmadi N, Moss L, Simon E, et al: Efficacy and long term clinical outcome of comorbid posttraumatic stress disorder and major depressive disorder after electroconvulsive therapy. *Depress Anxiety* 33(7):640-647, 2016 26555786
- American Psychiatric Association: Electroconvulsive Therapy: Report of the Task Force on Electroconvulsive Therapy of the American Psychiatric Association. Washington, DC, American Psychiatric Association, 1978
- American Psychiatric Association: The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging, 2nd Edition. Washington, DC, American Psychiatric Association, 2001
- Anderson EL, Reti IM: ECT in pregnancy: a review of the literature from 1941 to 2007. *Psychosom Med* 71(2):235-242, 2009 19073751
- Andrade C, McCall WV, Youssef NA: Electroconvulsive therapy for post-traumatic stress disorder: efficacy, mechanisms and a hypothesis for new directions. *Expert Rev Neurother* 16(7):749-753, 2016 27095363
- Anttila S, Huuhka K, Huuhka M, et al: Catechol-O-methyltransferase (COMT) polymorphisms predict

- treatment response in electroconvulsive therapy. *Pharmacogenomics* J 8(2):113-116, 2008 17700596
- Augoustides JG, Greenblatt E, Abbas MA, et al: Clinical approach to agitation after electroconvulsive therapy: a case report and literature review. *J ECT* 18(4):213-217, 2002 12468998
- Auriacombe M, Rénéric JP, Usandizaga D, et al: Post-ECT agitation and plasma lactate concentrations. *J ECT* 16(3):263-267, 2000 11005048
- Avramov MN, Husain MM, White PF: The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. *Anesth Analg* 81(3):596-602, 1995 7653829
- Avramov MN, Stool LA, White PF, et al: Effects of nicardipine and labetalol on the acute hemodynamic response to electroconvulsive therapy. *J Clin Anesth* 10(5): 394-400, 1998 9702620
- Aziz M, Maixner DF, DeQuardo J, et al: ECT and mental retardation: a review and case reports. *J ECT* 17(2):149-152, 2001 11417928
- Azuma H, Fujita A, Sato K, et al: Postictal suppression correlates with therapeutic efficacy for depression in bilateral sine and pulse wave electroconvulsive therapy. *Psychiatry Clin Neurosci* 61(2):168-173, 2007 17362434
- Bailine SH, Petrides G, Doft M, et al: Indications for the use of propofol in electroconvulsive therapy. *J ECT* 19(3):129-132, 2003 12972980
- Beale MD, Kellner CH: ECT in treatment algorithms: no need to save the best for last. *J ECT* 16(1):1-2, 2000 10735326
- Bergfeld IO, Mantione M, Hoogendoorn ML, et al: Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 73(5):456-464, 2016 27049915



- Berlim MT, Van den Eynde F, Daskalakis ZJ: Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. *Depress Anxiety* 30(7): 614-623, 2013 23349112
- Bernstein HJ, Beale MD, Burns C, Kellner CH: Patient attitudes about ECT after treatment. *Psychiatric Annals* 28(9):524-527, 1998
- Biedermann F, Pfaffenberger N, Baumgartner S, et al: Combined clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia: clinical and cognitive outcomes. *J ECT* 27(4):e61-e62, 2011 22124226
- Birkenhäger TK, van den Broek WW, Mulder PG, et al: One-year outcome of psychotic depression after successful electroconvulsive therapy. *J ECT* 21(4):221-226, 2005 16301881
- Bolwig TG: Neuroimaging and electroconvulsive therapy: a review. *J ECT* 30(2):138-142, 2014 24800687
- Bouckaert F, Sienaert P, Obbels J, et al: ECT: its brain enabling effects: a review of electroconvulsive therapy-induced structural brain plasticity. *J ECT* 30(2):143-151, 2014 24810772
- Bourgon LN, Kellner CH: Relapse of depression after ECT: a review. *J ECT* 16(1):19-31, 2000 10735328
- Brandon S, Cowley P, McDonald C, et al: Electroconvulsive therapy: results in depressive illness from the Leicestershire trial. *Br Med J (Clin Res Ed)* 288(6410):22-25, 1984 6418300
- Brignani D, Manganotti P, Rossini PM, et al: Modulation of cortical oscillatory activity during transcranial magnetic stimulation. *Hum Brain Mapp* 29(5):603-612, 2008 17557296
- Bryson EO, Briggs MC, Pasculli RM, et al: Treatment-resistant postictal agitation after electroconvulsive

- therapy (ECT) controlled with dexmedetomidine. *J ECT* 29(2):e18, 2013 23519216
- Buchan H, Johnstone E, McPherson K, et al: Who benefits from electroconvulsive therapy? Combined results of the Leicester and Northwick Park trials. *Br J Psychiatry* 160:355-359, 1992 1562861
- Carpenter LL, Janicak PG, Aaronson ST, et al: Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. *Depress Anxiety* 29(7):587-596, 2012 22689344
- Case BG, Bertollo DN, Laska EM, et al: Declining use of electroconvulsive therapy in United States general hospitals. *Biol Psychiatry* 73(2):119-126, 2013 23059049
- Castelli I, Steiner LA, Kaufmann MA, et al: Comparative effects of esmolol and labetalol to attenuate hyperdynamic states after electroconvulsive therapy. *Anesth Analg* 80(3):557-561, 1995 7864425
- Chahine G, Short B, Spicer K, et al: Regional cerebral blood flow changes associated with focal electrically administered seizure therapy (FEAST). *Brain Stimulat* 7(3):483-485, 2014 24795198
- Chanpattana W, Kramer BA: Acute and maintenance ECT with flupenthixol in refractory schizophrenia: sustained improvements in psychopathology, quality of life, and social outcomes. *Schizophr Res* 63(1-2):189-193, 2003 12892873
- Chanpattana W, Sackeim HA: Electroconvulsive therapy in treatment-resistant schizophrenia: prediction of response and the nature of symptomatic improvement. *J ECT* 26(4):289-298, 2010 20375701
- Chanpattana W, Chakrabhand ML, Sackeim HA, et al: Continuation ECT in treatment-resistant schizophrenia: a controlled study. *J ECT* 15(3):178-192, 1999 10492856

- Choi J, Lisanby SH, Medalia A, et al: A conceptual introduction to cognitive remediation for memory deficits associated with right unilateral electroconvulsive therapy. *J ECT* 27(4):286-291, 2011 22080239
- Chung KF: Determinants of seizure threshold of electroconvulsive therapy in Chinese. *J ECT* 22(2):100-102, 2006 16801823
- Cline JS, Roos K: Treatment of status epilepticus with electroconvulsive therapy. *J ECT* 23(1):30-32, 2007 17435572
- Coffey CE, Figiel GS, Djang WT, et al: White matter hyperintensity on magnetic resonance imaging: clinical and neuroanatomic correlates in the depressed elderly. *J Neuropsychiatry Clin Neurosci* 1(2):135-144, 1989 2521054
- Coffey CE, Weiner RD, Djang WT, et al: Brain anatomic effects of electroconvulsive therapy: a prospective magnetic resonance imaging study. *Arch Gen Psychiatry* 48(11):1013-1021, 1991 1747016
- Cohen MB, Stewart JT: Treatment of post-electroconvulsive therapy agitation with dexmedetomidine. *J ECT* 29(2):e23-e24, 2013 23519222
- Colenda CC, McCall WV: A statistical model predicting the seizure threshold for right unilateral ECT in 106 patients. *Convuls Ther* 12(1):3-12, 1996 8777650
- Conti B, Maier R, Barr AM, et al: Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. *Mol Psychiatry* 12(2):167-189, 2007 17033635
- Cupina D, Patil S, Loo C: Chronic catatonic schizophrenia treated successfully with right unilateral ultrabrief pulse electroconvulsive therapy: case report. *J ECT* 29(2):134-136, 2013 23303422
- Cusin C, Franco FB, Fernandez-Robles C, et al: Rapid improvement of depression and psychotic symptoms in

- Huntington's disease: a retrospective chart review of seven patients treated with electroconvulsive therapy. *Gen Hosp Psychiatry* 35(6):678.e3-678.e5, 2013 23541803
- d'Elia G, Raotma H: Is unilateral ECT less effective than bilateral ECT? *Br J Psychiatry* 126:83-89, 1975 1092400
- Deng ZD, Lisanby SH, Peterchev AV: Electric field strength and focality in electroconvulsive therapy and magnetic seizure therapy: a finite element simulation study. *J Neural Eng* 8(1):016007, 2011 21248385
- Devanand DP, Dwork AJ, Hutchinson ER, et al: Does ECT alter brain structure? *Am J Psychiatry* 151(7):957-970, 1994 8010381
- Ding L, Shou G, Yuan H, et al: Lasting modulation effects of rTMS on neural activity and connectivity as revealed by resting-state EEG. *IEEE Trans Biomed Eng* 61(7):2070-2080, 2014 24686227
- Dolenc TJ, Rasmussen KG: The safety of electroconvulsive therapy and lithium in combination: a case series and review of the literature. *J ECT* 21(3):165-170, 2005 16127306
- Dombrovski AY, Mulsant BH, Haskett RF, et al: Predictors of remission after electroconvulsive therapy in unipolar major depression. *J Clin Psychiatry* 66(8):1043-1049, 2005 16086621
- Dougherty DD, Rezai AR, Carpenter LL, et al: A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol Psychiatry* 78(4):240-248, 2015 25726497
- Drevets WC: Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog Brain Res* 126:413-431, 2000 11105660
- Duman RS, Vaidya VA: Molecular and cellular actions of chronic electroconvulsive seizures. *J ECT* 14(3):181-193, 1998 9773357

- Dunne RA, McLoughlin DM: Systematic review and meta-analysis of bifrontal electroconvulsive therapy versus bilateral and unilateral electroconvulsive therapy in depression. *World J Biol Psychiatry* 13(4):248-258, 2012 22098115
- Dunner DL, Aaronson ST, Sackeim HA, et al: A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. *J Clin Psychiatry* 75(12):1394-1401, 2014 25271871
- el-Mallakh RS: Complications of concurrent lithium and electroconvulsive therapy: a review of clinical material and theoretical considerations. *Biol Psychiatry* 23(6):595-601, 1988 3281716
- Elger G, Hoppe C, Falkai P, et al: Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res* 42(2-3):203-210, 2000 11074193
- Endler NS: The origins of electroconvulsive therapy (ECT).. *Convuls Ther* 4(1):5-23, 1988 11940939
- Faber R, Trimble MR: Electroconvulsive therapy in Parkinson's disease and other movement disorders. *Mov Disord* 6(4): 293-303, 1991 1758447
- Fang J, Rong P, Hong Y, et al: Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder. *Biol Psychiatry* 79(4):266-273, 2016 25963932
- Farah A, McCall WV: Electroconvulsive therapy stimulus dosing: a survey of contemporary practices. *Convuls Ther* 9(2):90-94, 1993 11941196
- Farrant M, Nusser Z: Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. *Nat Rev Neurosci* 6(3):215-229, 2005 15738957
- Feske U, Mulsant BH, Pilkonis PA, et al: Clinical outcome of ECT in patients with major depression and comorbid

- borderline personality disorder. *Am J Psychiatry* 161(11):2073-2080, 2004 15514409
- Figiel GS, Coffey CE, Djang WT, et al: Brain magnetic resonance imaging findings in ECT-induced delirium. *J Neuropsychiatry Clin Neurosci* 2(1):53-58, 1990 2136061
- Fink M: Treating bipolar affective disorder. ECT is effective. *BMJ* 322(7282):365-366, 2001 11229383
- Fink M: ECT in therapy-resistant mania: does it have a place? *Bipolar Disord* 8(3):307-309, 2006 16696837
- Fink M: Rediscovering catatonia: the biography of a treatable syndrome. *Acta Psychiatr Scand Suppl* (441):1-47, 2013 23215963
- Fink M, Kellner CH, Sackeim HA: Intractable seizures, status epilepticus, and ECT. *J ECT* 15(4):282-284, 1999 10614038
- Fitzgerald PB, Hoy KE, Herring SE, et al: Pilot study of the clinical and cognitive effects of high-frequency magnetic seizure therapy in major depressive disorder. *Depress Anxiety* 30(2):129-136, 2013 23080404
- Fochtmann LJ: Animal studies of electroconvulsive therapy: foundations for future research. *Psychopharmacol Bull* 30(3):321-444, 1994 7878180
- Fraser LM, O'Carroll RE, Ebmeier KP: The effect of electroconvulsive therapy on autobiographical memory: a systematic review. *J ECT* 24(1):10-17, 2008 18379329
- Freeman SA: Post-electroconvulsive therapy agitation with etomidate. *J ECT* 25(2):133-134, 2009 19494736
- Fregni F, Simon DK, Wu A, et al: Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. *J Neurol Neurosurg Psychiatry* 76(12):1614-1623, 2005 16291882
- Fuggetta G, Noh NA: A neurophysiological insight into the potential link between transcranial magnetic stimulation, thalamocortical dysrhythmia and neuropsychiatric disorders. *Exp Neurol* 245:87-95, 2013 23063603

- Gahr M, Schönfeldt-Lecuona C, Spitzer M, et al: Electroconvulsive therapy and posttraumatic stress disorder: first experience with conversation-based reactivation of traumatic memory contents and subsequent ECT-mediated impairment of reconsolidation. *J Neuropsychiatry Clin Neurosci* 26(3):E38-E39, 2014 25093782
- Galletly C, Paterson T, Burton C: A report on the introduction of ultrabrief pulse width ECT in a private psychiatric hospital. *J ECT* 28(1):59, 2012 22343583
- Galletly C, Clarke P, Paterson T, et al: Practical considerations in the use of ultrabrief ECT in clinical practice. *J ECT* 30(1):10-14, 2014 24080538
- Gaynes BN, Lux LJ, Lloyd SW, et al: Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Rockville, MD, Agency for Healthcare Research and Quality, 2011
- George MS, Sackeim HA, Rush AJ, et al: Vagus nerve stimulation: a new tool for brain research and therapy. *Biol Psychiatry* 47(4):287-295, 2000 10686263
- George MS, Rush AJ, Marangell LB, et al: A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry* 58(5):364-373, 2005 16139582
- George MS, Lisanby SH, Avery D, et al: Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 67(5):507-516, 2010 20439832
- Geretsegger C, Nickel M, Judendorfer B, et al: Propofol and methohexital as anesthetic agents for electroconvulsive therapy: a randomized, double-blind comparison of electroconvulsive therapy seizure quality, therapeutic efficacy, and cognitive performance. *J ECT* 23(4):239-243, 2007 18090696
- Goldapple K, Segal Z, Garson C, et al: Modulation of cortical-limbic pathways in major depression: treatment-

- specific effects of cognitive behavior therapy. Arch Gen Psychiatry 61(1):34-41, 2004 14706942
- Goldman D: Brief stimulus electric shock therapy. J Nerv Ment Dis 110(1):36-45, 1949 18132845
- Green AR, Sant K, Bowdler JM, et al: Further evidence for a relationship between changes in GABA concentration in rat brain and enhanced monoamine-mediated behavioural responses following repeated electroconvulsive shock. Neuropharmacology 21(10):981-984, 1982 7145036
- Greene YM, McDonald WM, Duggan J, et al: Ventricular ectopy associated with low-dose intravenous haloperidol and electroconvulsive therapy. J ECT 16(3):309-311, 2000 11005056
- Grover BB: Handbook of Electrotherapy for Practitioners and Students. Philadelphia, PA, Davis, 1924
- Gruber NP, Dilsaver SC, Shoaib AM, et al: ECT in mixed affective states: a case series. J ECT 16(2):183-188, 2000 10868328
- Grunhaus L, Schreiber S, Dolberg OT, et al: A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. Biol Psychiatry 53(4):324-331, 2003 12586451
- Hansen PE, Ravnkilde B, Videbech P, et al: Low-frequency repetitive transcranial magnetic stimulation inferior to electroconvulsive therapy in treating depression. J ECT 27(1):26-32, 2011 20351570
- Harden CL, Pulver MC, Ravdin LD, et al: A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav 1(2):93-99, 2000 12609137
- Hargrove EA, Bennett AE, Ford FR: The value of subconvulsive electrostimulation in the treatment of some emotional disorders. Am J Psychiatry 109(8):612-616, 1953 13030820



- Harrison PJ: The neuropathology of primary mood disorder. *Brain* 125(pt 7):1428-1449, 2002 12076995
- Hasler G, van der Veen JW, Tumonis T, et al: Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 64(2):193-200, 2007 17283286
- Heijnen WT, Birkenhäger TK, Wierdsma AI, et al: Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. *J Clin Psychopharmacol* 30(5):616-619, 2010 20814336
- Hellsten J, West MJ, Arvidsson A, et al: Electroconvulsive seizures induce angiogenesis in adult rat hippocampus. *Biol Psychiatry* 58(11):871-878, 2005 16043138
- Hermida AP, Janjua AU, Tang Y, et al: Use of orally disintegrating olanzapine during electroconvulsive therapy for prevention of postictal agitation. *J Psychiatr Pract* 22(6):459-462, 2016 27824778
- Hickie I, Scott E, Mitchell P, et al: Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiatry* 37(3):151-160, 1995 7727623
- Hihn H, Baune BT, Michael N, et al: Memory performance in severely depressed patients treated by electroconvulsive therapy. *J ECT* 22(3):189-195, 2006 16957535
- Hill MA, Courvoisie H, Dawkins K, et al: ECT for the treatment of intractable mania in two prepubertal male children. *Convuls Ther* 13(2):74-82, 1997 9253527
- Hiremani RM, Thirthalli J, Tharayil BS, et al: Double-blind randomized controlled study comparing short-term efficacy of bifrontal and bitemporal electroconvulsive therapy in acute mania. *Bipolar Disord* 10(6):701-707, 2008 18837864

- Hirose S, Ashby CR Jr, Mills MJ: Effectiveness of ECT combined with risperidone against aggression in schizophrenia. *J ECT* 17(1):22-26, 2001 11281510
- Holtzheimer PE, Kelley ME, Gross RE, et al: Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* 69(2):150-158, 2012 22213770
- Insel TR, Wang PS: The STAR\*D trial: revealing the need for better treatments. *Psychiatr Serv* 60(11):1466-1467, 2009 19880463
- Jacobowski NL, Heckers S, Bobo WV: Delirious mania: detection, diagnosis, and clinical management in the acute setting. *J Psychiatr Pract* 19(1):15-28, 2013 23334676
- Janicak PG, Carpenter LL: The efficacy of transcranial magnetic stimulation for major depression: a review of the evidence. *Psychiatric Annals* 44(6):284-292, 2014
- Jha AK, Stein GS, Fenwick P: Negative interaction between lithium and electroconvulsive therapy—a case-control study. *Br J Psychiatry* 168(2):241-243, 1996 8837918
- Johnson JS, Hamidi M, Postle BR: Using EEG to explore how rTMS produces its effects on behavior. *Brain Topogr* 22(4):281-293, 2010 19915972
- Johnstone EC, Deakin JF, Lawler P, et al: The Northwick Park electroconvulsive therapy trial. *Lancet* 2(8208-8209):1317-1320, 1980 6109147
- Kalu UG, Sexton CE, Loo CK, et al: Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychol Med* 42(9):1791-1800, 2012 22236735
- Kayser S, Bewernick BH, Grubert C, et al: Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. *J Psychiatr Res* 45(5):569-576, 2011 20951997

- Keck PE Jr, Mendlwicz J, Calabrese JR, et al: A review of randomized, controlled clinical trials in acute mania. *J Affect Disord* 59 (suppl 1):S31-S37, 2000 11121825
- Kellner CH: Towards the modal ECT treatment. *J ECT* 17(1):1-2, 2001 11281507
- Kellner CH, Beale MD, Pritchett JT, et al: Electroconvulsive therapy and Parkinson's disease: the case for further study. *Psychopharmacol Bull* 30(3):495-500, 1994 7878188
- Kellner CH, Fink M, Knapp R, et al: Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. *Am J Psychiatry* 162(5):977-982, 2005 15863801
- Kellner CH, Knapp RG, Petrides G, et al: Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry* 63(12):1337-1344, 2006 17146008
- Kellner CH, Knapp R, Husain MM, et al: Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry* 196(3):226-234, 2010 20194546
- Kellner CH, Greenberg RM, Murrough JW, et al: ECT in treatment-resistant depression. *Am J Psychiatry* 169(12):1238-1244, 2012 23212054
- Kimball JN, Rosenquist PB, Dunn A, et al: Prediction of antidepressant response in both 2.25xthreshold RUL and fixed high dose RUL ECT. *J Affect Disord* 112(1-3): 85-91, 2009 18539340
- Krystal AD, Weiner RD, McCall WV, et al: The effects of ECT stimulus dose and electrode placement on the ictal electroencephalogram: an intraindividual crossover study. *Biol Psychiatry* 34(11):759-767, 1993 8292679
- Kuppuswamy PS, Takala CR, Sola CL: Management of psychiatric symptoms in anti-NMDAR encephalitis: a

- case series, literature review and future directions. *Gen Hosp Psychiatry* 36(4):388-391, 2014 24731834
- Lavin MR, Halligan P: ECT for comorbid obsessive-compulsive disorder and schizophrenia. *Am J Psychiatry* 153(12):1652-1653, 1996 8942468
- Levkovitz Y, Isserles M, Padberg F, et al: Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry* 14(1):64-73, 2015 25655160
- Li X, Tenebäck CC, Nahas Z, et al: Interleaved transcranial magnetic stimulation/functional MRI confirms that lamotrigine inhibits cortical excitability in healthy young men. *Neuropsychopharmacology* 29(7):1395-1407, 2004 15100699
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353(12):1209-1223, 2005 16172203
- Lisanby SH, Maddox JH, Prudic J, et al: The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry* 57(6):581-590, 2000 10839336
- Lisanby SH, Bazil CW, Resor SR, et al: ECT in the treatment of status epilepticus. *J ECT* 17(3):210-215, 2001 11528315
- Lisanby SH, Luber B, Schlaepfer TE, et al: Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology* 28(10):1852-1865, 2003 12865903
- Liston C, Chen AC, Zebley BD, et al: Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry* 76(7):517-526, 2014 24629537

- Liu AY, Rajji TK, Blumberger DM, et al: Brain stimulation in the treatment of late-life severe mental illness other than unipolar nonpsychotic depression. *Am J Geriatr Psychiatry* 22(3):216-240, 2014 23891366
- Liu X, Cui H, Wei Q, et al: Electroconvulsive therapy on severe obsessive-compulsive disorder comorbid depressive symptoms. *Psychiatry Investig* 11(2):210-213, 2014 24843380
- Locala JA, Irefin SA, Malone D, et al: The comparative hemodynamic effects of methohexital and remifentanyl in electroconvulsive therapy. *J ECT* 21(1):12-15, 2005 15791171
- Loo CK, Sainsbury K, Sheehan P, et al: A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT. *Int J Neuropsychopharmacol* 11(7):883-890, 2008 18752719
- Loo CK, Katalinic N, Martin D, et al: A review of ultrabrief pulse width electroconvulsive therapy. *Ther Adv Chronic Dis* 3(2):69-85, 2012 23251770
- Loo CK, Garfield JB, Katalinic N, et al: Speed of response in ultrabrief and brief pulse width right unilateral ECT. *Int J Neuropsychopharmacol* 16(4):755-761, 2013 22963997
- Luchini F, Medda P, Mariani MG, et al: Electroconvulsive therapy in catatonic patients: efficacy and predictors of response. *World J Psychiatry* 5(2):182-192, 2015 26110120
- Madsen TM, Treschow A, Bengzon J, et al: Increased neurogenesis in a model of electroconvulsive therapy. *Biol Psychiatry* 47(12):1043-1049, 2000 10862803
- Malberg JE, Eisch AJ, Nestler EJ, et al: Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* 20(24):9104-9110, 2000 11124987
- Maletzky B, McFarland B, Burt A: Refractory obsessive compulsive disorder and ECT. *Convuls Ther* 10(1):34-42, 1994 8055290

- Malone DA Jr, Dougherty DD, Rezai AR, et al: Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 65(4):267-275, 2009 18842257
- Matheson SL, Green MJ, Loo C, et al: Quality assessment and comparison of evidence for electroconvulsive therapy and repetitive transcranial magnetic stimulation for schizophrenia: a systematic meta-review. *Schizophr Res* 118(1-3):201-210, 2010 20117918
- Matthews JD, Siefert CJ, Blais MA, et al: A double-blind, placebo-controlled study of the impact of galantamine on anterograde memory impairment during electroconvulsive therapy. *J ECT* 29(3):170-178, 2013 23519225
- Mayberg HS, Lozano AM, Voon V, et al: Deep brain stimulation for treatment-resistant depression. *Neuron* 45(5):651-660, 2005 15748841
- Mayur P: Ictal electroencephalographic characteristics during electroconvulsive therapy: a review of determination and clinical relevance. *J ECT* 22(3):213-217, 2006 16957539
- Mayur P, Byth K, Harris A: Autobiographical and subjective memory with right unilateral high-dose 0.3-millisecond ultrabrief-pulse and 1-millisecond brief-pulse electroconvulsive therapy: a double-blind, randomized controlled trial. *J ECT* 29(4):277-282, 2013 24263273
- McCall WV: What does Star\*D tell us about ECT? *J ECT* 23(1):1-2, 2007 17435561
- McCall WV, Shelp FE, Weiner RD, et al: Convulsive threshold differences in right unilateral and bilateral ECT. *Biol Psychiatry* 34(9):606-611, 1993 8292689
- McCall WV, Reid S, Ford M: Electrocardiographic and cardiovascular effects of subconvulsive stimulation during titrated right unilateral ECT. *Convuls Ther* 10(1): 25-33, 1994 8055289

- McCall WV, Robinette GD, Hardesty D: Relationship of seizure morphology to the convulsive threshold. *Convuls Ther* 12(3):147-151, 1996 8872402
- McCall WV, Sparks W, Jane J, et al: Variation of ictal electroencephalographic regularity with low-, moderate-, and high-dose stimuli during right unilateral electroconvulsive therapy. *Biol Psychiatry* 43(8):608-611, 1998 9564446
- McCall WV, Reboussin DM, Weiner RD, et al: Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Arch Gen Psychiatry* 57(5):438-444, 2000 10807483
- McCall WV, Prudic J, Olfson M, et al: Health-related quality of life following ECT in a large community sample. *J Affect Disord* 90(2-3):269-274, 2006 16412519
- McClintock SM, Choi J, Deng ZD, et al: Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. *J ECT* 30(2):165-176, 2014 24820942
- McCormick LM, Brumm MC, Benede AK, et al: Relative ineffectiveness of ultrabrief right unilateral versus bilateral electroconvulsive therapy in depression. *J ECT* 25(4):238-242, 2009 19384251
- McDaniel WW: Electroconvulsive therapy in complex regional pain syndromes. *J ECT* 19(4):226-229, 2003 14657776
- McDonald WM: New insights from China on the efficacy of ECT in schizophrenia. *J ECT* 28(4):203-204, 2012 23164724
- McDonald WM, Thompson TR: Treatment of mania in dementia with electroconvulsive therapy. *Psychopharmacol Bull* 35(2):72-82, 2001 12397888
- McLoughlin DM, Mogg A, Eranti S, et al: The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe

- depression: a multicentre pragmatic randomised controlled trial and economic analysis. *Health Technol Assess* 11(24):1-54, 2007 17580003
- Medda P, Perugi G, Zanello S, et al: Comparative response to electroconvulsive therapy in medication-resistant bipolar I patients with depression and mixed state. *J ECT* 26(2):82-86, 2010 19710623
- Medda P, Toni C, Perugi G: The mood-stabilizing effects of electroconvulsive therapy. *J ECT* 30(4):275-282, 2014 25010031
- Michael N, Erfurth A, Ohrmann P, et al: Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. *Psychol Med* 33(7):1277-1284, 2003 14580081
- Morishita T, Fayad SM, Higuchi MA, et al: Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. *Neurotherapeutics* 11(3):475-484, 2014 24867326
- Munk-Olsen T, Laursen TM, Videbech P, et al: Electroconvulsive therapy: predictors and trends in utilization from 1976 to 2000. *J ECT* 22(2):127-132, 2006 16801829
- Nahas Z, Marangell LB, Husain MM, et al: Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry* 66(9):1097-1104, 2005 16187765
- Nahas Z, Short B, Burns C, et al: A feasibility study of a new method for electrically producing seizures in man: focal electrically administered seizure therapy [FEAST]. *Brain Stimulat* 6(3):403-408, 2013 23518262
- Nemeroff CB, Mayberg HS, Kahl SE, et al: VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology* 31(7):1345-1355, 2006 16641939



- Nestler EJ, Barrot M, DiLeone RJ, et al: Neurobiology of depression. *Neuron* 34(1):13-25, 2002 11931738
- Newton SS, Girgenti MJ, Collier EF, et al: Electroconvulsive seizure increases adult hippocampal angiogenesis in rats. *Eur J Neurosci* 24(3):819-828, 2006 16930411
- Niemantsverdriet L, Birkenhäger TK, van den Broek WW: The efficacy of ultrabrief-pulse (0.25 millisecond) versus brief-pulse (0.50 millisecond) bilateral electroconvulsive therapy in major depression. *J ECT* 27(1):55-58, 2011 21343712
- Nivoli AM, Murru A, Goikolea JM, et al: New treatment guidelines for acute bipolar mania: a critical review. *J Affect Disord* 140(2):125-141, 2012 22100133
- Nobler MS, Sackeim HA, Solomou M, et al: EEG manifestations during ECT: effects of electrode placement and stimulus intensity. *Biol Psychiatry* 34(5):321-330, 1993 8399832
- Nobler MS, Oquendo MA, Kegeles LS, et al: Decreased regional brain metabolism after ECT. *Am J Psychiatry* 158(2):305-308, 2001 11156816
- Nutt DJ, Glue P: The neurobiology of ECT: animal studies, in *The Clinical Science of Electroconvulsive Therapy*. Edited by Coffey CE. Washington, DC, American Psychiatric Association, 1993, pp 213-234
- Nutt DJ, Cowen PJ, Green AR: Studies on the post-ictal rise in seizure threshold. *Eur J Pharmacol* 71(2-3):287-295, 1981 6113969
- Nymeyer L, Grossberg GT: Delirium in a 75-year-old woman receiving ECT and levodopa. *Convuls Ther* 13(2):114-116, 1997 9253532
- O'Brien EM, Rosenquist PB, Kimball JN, et al: Dexmedetomidine and the successful management of electroconvulsive therapy postictal agitation: a case report. *J ECT* 26(2):131-133, 2010 19710618
- O'Connor MK, Knapp R, Husain M, et al: The influence of age on the response of major depression to

- electroconvulsive therapy: a C.O.R.E. Report. *Am J Geriatr Psychiatry* 9(4):382-390, 2001 11739064
- O'Reardon JP, Solvason HB, Janicak PG, et al: Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 62(11):1208-1216, 2007 17573044
- Ottosson JO: Seizure characteristics and therapeutic efficiency in electroconvulsive therapy: an analysis of the antidepressive efficiency of grand mal and lidocaine-modified seizures. *J Nerv Ment Dis* 135:239-251, 1962 13940748
- Oudega ML, van Exel E, Wattjes MP, et al: White matter hyperintensities, medial temporal lobe atrophy, cortical atrophy, and response to electroconvulsive therapy in severely depressed elderly patients. *J Clin Psychiatry* 72(1):104-112, 2011 20816035
- Oudega ML, van Exel E, Wattjes MP, et al: White matter hyperintensities and cognitive impairment during electroconvulsive therapy in severely depressed elderly patients. *Am J Geriatr Psychiatry* 22(2):157-166, 2014 23567440
- Painuly N, Chakrabarti S: Combined use of electroconvulsive therapy and antipsychotics in schizophrenia: the Indian evidence. A review and a meta-analysis. *J ECT* 22(1):59-66, 2006 16633210
- Parker G, Roy K, Wilhelm K, et al: Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. *J Clin Psychiatry* 62(2): 117-125, 2001 11247097
- Patel M, Patel S, Hardy DW, et al: Should electroconvulsive therapy be an early consideration for suicidal patients? *J ECT* 22(2):113-115, 2006 16801826
- Pawelczyk T, Kołodziej-Kowalska E, Pawelczyk A, et al: Augmentation of antipsychotics with electroconvulsive therapy in treatment-resistant schizophrenia patients

with dominant negative symptoms: a pilot study of effectiveness. *Neuropsychobiology* 70(3):158–164, 2014 25358377

Petrides G, Fink M, Husain MM, et al: ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J ECT* 17(4):244–253, 2001 11731725

Petrides G, Braga RJ, Fink M, et al; CORE (Consortium for Research in ECT) Group: Seizure threshold in a large sample: implications for stimulus dosing strategies in bilateral electroconvulsive therapy: a report from CORE. *J ECT* 25(4):232–237, 2009 19972637

Petrides G, Malur C, Braga RJ, et al: Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry* 172(1):52–58, 2015 25157964

Pfleiderer B, Michael N, Erfurth A, et al: Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. *Psychiatry Res* 122(3):185–192, 2003 12694892

Phutane VH, Thirthalli J, Muralidharan K, et al: Double-blind randomized controlled study showing symptomatic and cognitive superiority of bifrontal over bitemporal electrode placement during electroconvulsive therapy for schizophrenia. *Brain Stimulat* 6(2):210–217, 2013 22560048

Plakiotis C, George K, O'Connor DW: Has electroconvulsive therapy use remained stable over time? A decade of electroconvulsive therapy service provision in Victoria, Australia. *Aust N Z J Psychiatry* 46(6):522–531, 2012 22375067

Plaźnik A, Kostowski W, Stefański R: The influence of antidepressive treatment on GABA-related mechanisms in the rat hippocampus: behavioral studies. *Pharmacol Biochem Behav* 33(4):749–753, 1989 2559414

- Polanía R, Nitsche MA, Paulus W: Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Hum Brain Mapp* 32(8):1236–1249, 2011 20607750
- Polanía R, Paulus W, Nitsche MA: Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum Brain Mapp* 33(10):2499–2508, 2012 21922602
- Polster JD, Kayser S, Bewernick BH, et al: Effects of electroconvulsive therapy and magnetic seizure therapy on acute memory retrieval. *J ECT* 31(1):13–19, 2015 24853650
- Pompili M, Lester D, Dominici G, et al: Indications for electroconvulsive treatment in schizophrenia: a systematic review. *Schizophr Res* 146(1–3):1–9, 2013 23499244
- Prakash J, Kotwal A, Prabhu H: Therapeutic and prophylactic utility of the memory-enhancing drug donepezil hydrochloride on cognition of patients undergoing electroconvulsive therapy: a randomized controlled trial. *J ECT* 22(3):163–168, 2006 16957530
- Prudic J, Sackeim HA, Devanand DP, Kiersky JE: The efficacy of ECT in double depression. *Depression* 1(1):38–44, 1993
- Prudic J, Sackeim HA, Devanand DP, et al: Acute cognitive effects of subconvulsive electrical stimulation. *Convuls Ther* 10(1):4–24, 1994 8055291
- Puigdemont D, Portella M, Pérez-Egea R, et al: A randomized double-blind crossover trial of deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a pilot study of relapse prevention. *J Psychiatry Neurosci* 40(4):224–231, 2015 25652752
- Rabheru K: The use of electroconvulsive therapy in special patient populations. *Can J Psychiatry* 46(8):710–719,

2001 11692973

- Rajagopal R, Chakrabarti S, Grover S: Satisfaction with electroconvulsive therapy among patients and their relatives. *J ECT* 29(4):283-290, 2013 23670027
- Rapoport MJ, Mamdani M, Herrmann N: Electroconvulsive therapy in older adults: 13-year trends. *Can J Psychiatry* 51(9):616-619, 2006 17007229
- Rasmussen KG: Do patients with personality disorders respond differentially to electroconvulsive therapy? A review of the literature and consideration of conceptual issues. *J ECT* 31(1):6-12, 2015 25054362
- Rasmussen K, Abrams R: Treatment of Parkinson's disease with electroconvulsive therapy. *Psychiatr Clin North Am* 14(4): 925-933, 1991 1771154
- Rasmussen P, Andersson JE, Koch P, et al: Glycopyrrolate prevents extreme bradycardia and cerebral deoxygenation during electroconvulsive therapy. *J ECT* 23(3):147-152, 2007 17804987
- Ravanić DB, Pantović MM, Milovanović DR, et al: Long-term efficacy of electroconvulsive therapy combined with different antipsychotic drugs in previously resistant schizophrenia. *Psychiatr Danub* 21(2):179-186, 2009 19556946
- Regenold WT, Weintraub D, Taller A: Electroconvulsive therapy for epilepsy and major depression. *Am J Geriatr Psychiatry* 6(2):180-183, 1998 9581214
- Ren J, Li H, Palaniyappan L, et al: Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 51:181-189, 2014 24556538
- Rodríguez-Sosa JT, Suárez-Lovelle A, Navarrete-Betancort E, et al: Electroconvulsive therapy in dementia. *Actas Esp Psiquiatr* 41(3):204-207, 2013 23803804
- Rosa MA, Gattaz WF, Pascual-Leone A, et al: Comparison of repetitive transcranial magnetic stimulation and

- electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmacol* 9(6):667-676, 2006 16923322
- Rosebush PI, Mazurek MF: Catatonia and its treatment. *Schizophr Bull* 36(2):239-242, 2010 19969591
- Rossini PM, Burke D, Chen R, et al: Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 126(6):1071-1107, 2015 25797650
- Rush AJ, Thase ME: Strategies and tactics in the treatment of chronic depression. *J Clin Psychiatry* 58 (suppl 13):14-22, 1997 9402915
- Rush AJ, George MS, Sackeim HA, et al: Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry* 47(4):276-286, 2000 10686262
- Rush AJ, Marangell LB, Sackeim HA, et al: Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry* 58(5):347-354, 2005a 16139580
- Rush AJ, Sackeim HA, Marangell LB, et al: Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry* 58(5):355-363, 2005b 16139581
- Rush AJ, Warden D, Wisniewski SR, et al: STAR\*D: revising conventional wisdom. *CNS Drugs* 23(8):627-647, 2009 19594193
- Saatcioglu O, Tomruk NB: The use of electroconvulsive therapy in pregnancy: a review. *Isr J Psychiatry Relat Sci* 48(1):6-11, 2011 21572236
- Sackeim HA: Central issues regarding the mechanisms of action of electroconvulsive therapy: directions for future

research. *Psychopharmacol Bull* 30(3):281-308, 1994  
7878177

Sackeim HA: The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. *J ECT* 15(1):5-26, 1999 10189616

Sackeim HA, Prudic J, Devanand DP, et al: The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol* 10(2):96-104, 1990 2341598

Sackeim HA, Devanand DP, Prudic J: Stimulus intensity, seizure threshold, and seizure duration: impact on the efficacy and safety of electroconvulsive therapy. *Psychiatr Clin North Am* 14(4):803-843, 1991 1771150

Sackeim HA, Prudic J, Devanand DP, et al: Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med* 328(12):839-846, 1993 8441428

Sackeim HA, Lubner B, Moeller JR, et al: Electrophysiological correlates of the adverse cognitive effects of electroconvulsive therapy. *J ECT* 16(2):110-120, 2000 10868321

Sackeim HA, Haskett RF, Mulsant BH, et al: Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA* 285(10):1299-1307, 2001a 11255384

Sackeim HA, Rush AJ, George MS, et al: Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 25(5):713-728, 2001b 11682255

Sackeim HA, Prudic J, Fuller R, et al: The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 32(1):244-254, 2007 16936712

- Sackeim HA, Prudic J, Nobler MS, et al: Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulat* 1(2):71-83, 2008 19756236
- Sackeim HA, Dillingham EM, Prudic J, et al: Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry* 66(7):729-737, 2009 19581564
- Sadananda SK, Narayanaswamy JC, Srinivasaraju R, Math SB: Delirium during the course of electroconvulsive therapy in a patient on lithium carbonate treatment. *Gen Hosp Psychiatry* 35(6):678.e1-678.e2, 2013 23517818
- Saito S: Anesthesia management for electroconvulsive therapy: hemodynamic and respiratory management. *J Anesth* 19(2): 142-149, 2005 15875132
- Saleh C, Fontaine D: Deep brain stimulation for psychiatric diseases: what are the risks? *Curr Psychiatry Rep* 17(5):33, 2015 25795265
- Sanacora G, Mason GF, Rothman DL, et al: Increased cortical GABA concentrations in depressed patients receiving ECT. *Am J Psychiatry* 160(3):577-579, 2003 12611844
- Santarelli L, Saxe M, Gross C, et al: Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301(5634):805-809, 2003 12907793
- Sartorius A, Wolf J, Henn FA: Lithium and ECT—concurrent use still demands attention: three case reports. *World J Biol Psychiatry* 6(2):121-124, 2005 16156485
- Scalia J, Lisanby SH, Dwork AJ, et al: Neuropathologic examination after 91 ECT treatments in a 92-year-old woman with late-onset depression. *J ECT* 23(2):96-98, 2007 17548979
- Schlaepfer TE, Bewernick BH, Kayser S, et al: Rapid effects of deep brain stimulation for treatment-resistant major



- depression. *Biol Psychiatry* 73(12):1204-1212, 2013 23562618
- Schloss P, Henn FA: New insights into the mechanisms of antidepressant therapy. *Pharmacol Ther* 102(1):47-60, 2004 15056498
- Scott A: Is the use of electroconvulsive therapy falling because of fewer referrals of patients with severe depression? *J ECT* 28(3):162-164, 2012 22513512
- Scott BW, Wojtowicz JM, Burnham WM: Neurogenesis in the dentate gyrus of the rat following electroconvulsive shock seizures. *Exp Neurol* 165(2):231-236, 2000 10993683
- Seminowicz DA, Mayberg HS, McIntosh AR, et al: Limbic-frontal circuitry in major depression: a path modeling meta-analysis. *Neuroimage* 22(1):409-418, 2004 15110034
- Semkovska M, McLoughlin DM: Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry* 68(6):568-577, 2010 20673880
- Shapira B, Gorfine M, Lerer B: A prospective study of lithium continuation therapy in depressed patients who have responded to electroconvulsive therapy. *Convuls Ther* 11(2):80-85, 1995 7552058
- Shapira B, Tubi N, Lerer B: Balancing speed of response to ECT in major depression and adverse cognitive effects: role of treatment schedule. *J ECT* 16(2):97-109, 2000 10868320
- Shin HW, O'Donovan CA, Boggs JG, et al: Successful ECT treatment for medically refractory nonconvulsive status epilepticus in pediatric patient. *Seizure* 20(5):433-436, 2011 21333551
- Shiozawa P, Fregni F, Benseñor IM, et al: Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *Int J*

Neuropsychopharmacol 17(9):1443–1452, 2014  
24713139

Shrestha S, Shrestha BR, Thapa C, et al: Comparative study of esmolol and labetalol to attenuate haemodynamic responses after electroconvulsive therapy (KUMJ). Kathmandu Univ Med J (KUMJ) 5(3):318–323, 2007  
18604047

Sienaert P, Vansteelandt K, Demyttenaere K, et al: Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: cognitive side-effects. J Affect Disord 122(1–2):60–67, 2010 19577808

Small JG, Klapper MH, Kellams JJ, et al: Electroconvulsive treatment compared with lithium in the management of manic states. Arch Gen Psychiatry 45(8):727–732, 1988  
2899425

Sobin C, Sackeim HA, Prudic J, et al: Predictors of retrograde amnesia following ECT. Am J Psychiatry 152(7):995–1001, 1995 7793470

Song HJ, Stevens CF, Gage FH: Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. Nat Neurosci 5(5):438–445, 2002  
11953752

Spaans HP, Kho KH, Verwijk E, et al: Efficacy of ultrabrief pulse electroconvulsive therapy for depression: a systematic review. J Affect Disord 150(3):720–726, 2013a 23790557

Spaans HP, Verwijk E, Comijs HC, et al: Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. J Clin Psychiatry 74(11):e1029–e1036, 2013b 24330903

Spodniakova B, Halmo M, Nosalova P: Electroconvulsive therapy in pregnancy—a review. J Obstet Gynaecol 35(7):659–662, 2014 25526509

- Stadtland C, Erfurth A, Ruta U, et al: A switch from propofol to etomidate during an ECT course increases EEG and motor seizure duration. *J ECT* 18(1):22-25, 2002 11925517
- Steffens DC, Conway CR, Dombeck CB, et al: Severity of subcortical gray matter hyperintensity predicts ECT response in geriatric depression. *J ECT* 17(1):45-49, 2001 11281515
- Stryjer R, Ophir D, Bar F, et al: Rivastigmine treatment for the prevention of electroconvulsive therapy-induced memory deficits in patients with schizophrenia. *Clin Neuropharmacol* 35(4):161-164, 2012 22751086
- Sundsted KK, Burton MC, Shah R, et al: Preanesthesia medical evaluation for electroconvulsive therapy: a review of the literature. *J ECT* 30(1):35-42, 2014 24091900
- Swaim JC, Mansour M, Wydo SM, et al: A retrospective comparison of anesthetic agents in electroconvulsive therapy. *J ECT* 22(4):243-246, 2006 17143154
- Swartz CM: Physiological response to ECT stimulus dose. *Psychiatry Res* 97(2-3): 229-235, 2000 11166093
- Swartz CM, Saheba NC: Comparison of Atropine with Glycopyrrolate for Use in ECT. *Convuls Ther* 5(1):56-60, 1989 11940995
- Tan LP, Tan LE: Electroconvulsive therapy for severe neuropsychiatric lupus with psychosis. *J ECT* 29(3):243-246, 2013 23535497
- Tang Y, Hermida AP, Khanh H, et al: Efficacy and safety of ECT for behavioral and psychological symptoms of dementia (BPSD): a retrospective chart review. *Am J Geriatr Psychiatry* 22 (3 suppl):S114-S115, 2014
- Taylor MA, Fink M: Catatonia in psychiatric classification: a home of its own. *Am J Psychiatry* 160(7):1233-1241, 2003 12832234
- Tharyan P, Adams CE: Electroconvulsive therapy for schizophrenia. *Cochrane Database Syst Rev*

(2):CD000076, 2005 15846598

- Thirthalli J, Harish T, Gangadhar BN: A prospective comparative study of interaction between lithium and modified electroconvulsive therapy. *World J Biol Psychiatry* 12(2):149-155, 2011 20645670
- Thomas SG, Kellner CH: Remission of major depression and obsessive-compulsive disorder after a single unilateral ECT. *J ECT* 19(1):50-51, 2003 12621279
- Thompson JW, Weiner RD, Myers CP: Use of ECT in the United States in 1975, 1980, and 1986. *Am J Psychiatry* 151(11):1657-1661, 1994 7943457
- Tiller JW, Ingram N: Seizure threshold determination for electroconvulsive therapy: stimulus dose titration versus age-based estimations. *Aust N Z J Psychiatry* 40(2): 188-192, 2006 16476138
- Tor PC, Bautovich A, Wang MJ, et al: A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. *J Clin Psychiatry* 76(9):e1092-e1098, 2015 26213985
- Tsuchiyama K, Nagayama H, Yamada K, et al: Predicting efficacy of electroconvulsive therapy in major depressive disorder. *Psychiatry Clin Neurosci* 59(5):546-550, 2005 16194256
- Tzabazis A, Schmitt HJ, Ihmsen H, et al: Postictal agitation after electroconvulsive therapy: incidence, severity, and propofol as a treatment option. *J ECT* 29(3):189-195, 2013 23792779
- Ujkaj M, Davidoff DA, Seiner SJ, et al: Safety and efficacy of electroconvulsive therapy for the treatment of agitation and aggression in patients with dementia. *Am J Geriatr Psychiatry* 20(1):61-72, 2012 22143072
- UK ECT Review Group: Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 361(9360):799-808, 2003 12642045

- Unterrainer M, Oduncu FS: The ethics of deep brain stimulation (DBS). *Med Health Care Philos* 18(4):475-485, 2015 25597042
- Usui C, Doi N, Nishioka M, et al: Electroconvulsive therapy improves severe pain associated with fibromyalgia. *Pain* 121(3): 276-280, 2006 16495009
- Valentí M, Benabarre A, García-Amador M, et al: Electroconvulsive therapy in the treatment of mixed states in bipolar disorder. *Eur Psychiatry* 23(1):53-56, 2008 18191551
- van Waarde JA, Stolker JJ, van der Mast RC: ECT in mental retardation: a review. *J ECT* 17(4):236-243, 2001 11731724
- van Waarde JA, Tuerlings JH, Verwey B, van der Mast RC: Electroconvulsive therapy for catatonia: treatment characteristics and outcomes in 27 patients. *J ECT* 26(4): 248-252, 2010 19935090
- van Waarde JA, van Oudheusden LJ, Tonino BA, et al: MRI characteristics predicting seizure threshold in patients undergoing electroconvulsive therapy: a prospective study. *Brain Stimulat* 6(4):607-614, 2013 23318096
- Verwijk E, Comijs HC, Kok RM, et al: Neurocognitive effects after brief pulse and ultrabrief pulse unilateral electroconvulsive therapy for major depression: a review. *J Affect Disord* 140(3):233-243, 2012 22595374
- Vieta E: Bipolar mixed states and their treatment. *Expert Rev Neurother* 5(1):63-68, 2005 15853475
- Vishne T, Aronov S, Amiaz R, et al: Remifentanyl supplementation of propofol during electroconvulsive therapy: effect on seizure duration and cardiovascular stability. *J ECT* 21(4):235-238, 2005 16301884
- Wachtel LE, Schuldt S, Ghaziuddin N, et al: The potential role of electroconvulsive therapy in the 'Iron Triangle' of pediatric catatonia, autism, and psychosis. *Acta Psychiatr Scand* 128(5):408-409, 2013 23773168

- Wang HN, Wang L, Zhang RG, et al: Anti-depressive mechanism of repetitive transcranial magnetic stimulation in rat: the role of the endocannabinoid system. *J Psychiatr Res* 51:79-87, 2014 24479995
- Watts BV, Groft A: Retrospective evaluation of the dexamethasone suppression test as a predictor of response to electroconvulsive therapy in patients with comorbid major depressive disorder and posttraumatic stress disorder. *J ECT* 26(3):213-217, 2010 20386115
- Watts BV, Groft A, Bagian JP, et al: An examination of mortality and other adverse events related to electroconvulsive therapy using a national adverse event report system. *J ECT* 27(2):105-108, 2011 20966769
- Weiner RD: ECT and seizure threshold: effects of stimulus wave form and electrode placement. *Biol Psychiatry* 15(2):225-241, 1980 7417613
- Weiner RD: Does electroconvulsive therapy cause brain damage? *Behavioral and Brain Sciences* 7:1-53, 1984
- Weiner RD, Rogers HJ, Davidson JR, et al: Effects of electroconvulsive therapy upon brain electrical activity. *Ann N Y Acad Sci* 462:270-281, 1986a 3458408
- Weiner RD, Rogers HJ, Davidson JR, et al: Effects of stimulus parameters on cognitive side effects. *Ann N Y Acad Sci* 462:315-325, 1986b 3458412
- Wengel SP, Burke WJ, Pfeiffer RF, et al: Maintenance electroconvulsive therapy for intractable Parkinson's disease. *Am J Geriatr Psychiatry* 6(3):263-269, 1998 9659959
- Yonkers KA, Wisner KL, Stewart DE, et al: The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry* 31(5):403-413, 2009 19703633
- Yuuki N, Ida I, Oshima A, et al: HPA axis normalization, estimated by DEX/CRH test, but less alteration on cerebral glucose metabolism in depressed patients

receiving ECT after medication treatment failures. *Acta Psychiatr Scand* 112(4):257-265, 2005 16156832

Zachrisson OC, Balldin J, Ekman R, et al: No evident neuronal damage after electroconvulsive therapy. *Psychiatry Res* 96(2): 157-165, 2000 11063788

Zhang Y, White PF, Thornton L, et al: The use of nicardipine for electroconvulsive therapy: a dose-ranging study. *Anesth Analg* 100(2):378-381, 2005 15673861

## **PART III**

# Psychopharmacological Treatment



# CHAPTER 46

## Treatment of Depression

William V. Bobo, M.D., M.P.H.

Richard C. Shelton, M.D.

Major depressive disorder (MDD) affects more than 350 million people worldwide ([World Health Organization 2012](#)), making it one of the most prevalent illnesses in all of medicine. MDD is characterized by pronounced changes in mood (persisting depressed mood or anhedonia) coupled with distinct psychological (feelings of worthlessness or excessive guilt, difficulties maintaining concentration) and neurovegetative (sleep and/or appetite disturbance, fatigue or loss of energy and drive) changes and, all too often, suicidal thinking and behavior ([American Psychiatric Association 2013](#)). For many patients with MDD, the illness course is episodic, whereas others may experience more prolonged episodes that persist for years ([Coryell et al. 1994](#); [Eaton et al. 2008](#); [Stegenga et al. 2012](#)).

The adverse effects of MDD on quality of life and functioning are staggering. Pooled estimates of global disease burden ranked MDD as the second leading cause of years of life lived with a disability in 2010, accounting for 8.2% of global years of life lived with a disability ([Ferrari et al. 2013](#)). Even milder but more chronic and persisting forms of unipolar depression, such as persistent depressive disorder (dysthymia) (formerly known as dysthymic disorder), are among the leading causes of disability in the United States ([Murray et al. 2013](#)). The goal of treatment of all forms of

depression is to return patients to an asymptomatic state (remission), restore “normal” psychosocial functioning, prevent relapses of depression once patients are well, and minimize adverse effects of treatment ([Davidson 2010](#)). Thus, the treatment of patients with MDD and other depressive disorders requires aggressive and varied therapies that may need to continue for years, if not indefinitely.

---

## Epidemiology

---

### Prevalence of Depressive Disorders

MDD is one of the most common medical disorders affecting adults worldwide ([Lopez and Murray 1998](#); [World Health Organization 2012](#)). In the United States, the lifetime prevalence of MDD is 9% for men and 17% for women ([Hasin et al. 2005](#)), whereas the lifetime prevalence of dysthymia is 4% for men and 8% for women ([Kessler et al. 1994](#)). The lifetime prevalence of minor depression, a type of depression with milder symptoms than MDD, is 10% for individuals between the ages of 15 and 54 years ([Kessler et al. 1997](#)). For persons 65 years and older, the 1-month point prevalence of minor depression is 13%, which is twice the prevalence of MDD for this age group ([Judd and Akiskal 2002](#); [McCusker et al. 2005](#)). The lifetime prevalence of subsyndromal depression is 11.8% for the general population ([Goldney et al. 2004](#); [Judd et al. 1994](#)).

### Risk Factors for Depressive Disorders

Risk factors for MDD and other depressive disorders are numerous and include demographic, biological (genetic), and psychosocial (environmental) factors. Risk factors with the strongest body of evidence include female sex, age, a family history of a mood disorder, a history of psychological trauma or childhood adversity, and comorbid medical and psychiatric conditions.

A significant body of evidence indicates that sex is an important risk factor for the development of MDD. Prior to puberty, the prevalence of depression is equal in boys and girls. However, beginning with puberty, women demonstrate a twofold increase in the prevalence of MDD ([Burt and Stein 2002](#); [Hasin et al. 2005](#); [Kessler et al. 1994](#); [Weissman and Klerman 1977](#)). This trend is seen across countries and ethnic groups ([Joyce et al. 1990](#); [Lee et al. 1990, 2009](#); [Slone et al. 2006](#); [Weissman et al. 1996](#)). However, sex does not appear to affect rates of illness recurrence among people with MDD ([Kessler et al. 1993](#)). The lifetime prevalence rate of persistent depressive disorder (dysthymia) is also higher in women than in men ([Alonso et al. 2004](#); [Chiu 2004](#); [Falk et al. 2008](#); [Lee et al. 1990](#); [Weissman et al. 1988](#)).

Age is another risk factor in the development of depressive disorders; the onset of MDD can occur at any age, but onset appears to increase dramatically beginning in adolescence (12–16 years) and continuing through the age of about 44 years ([Hasin et al. 2005](#)). Whereas the mean age at onset has been reported to be 30 years, the mean age at the start of treatment is 33.5 years, a 3-year span reflecting the amount of time that depression remains undiagnosed or untreated. Early age at MDD onset (i.e., onset during childhood or adolescence) appears to be associated with more severe and recurrent forms of illness, more lifetime suicide attempts, and a greater illness burden ([Zisook et al. 2007](#)). In elderly individuals, risk factors for depression include female sex, low socioeconomic status, recent bereavement, prior depression, medical comorbidity, disability, cognitive deterioration, and vascular disease ([Helmer et al. 2004](#)).

A family history of psychiatric illness, particularly MDD, is among the most profound risk factors for the development of a major depressive episode ([Reinherz et al. 2003](#); [Sullivan et al. 2000](#)). Compared with the general population, first-degree relatives of patients with MDD have two to four times the risk of developing MDD ([Gershon et al. 1982](#); [Weissman et al. 1984](#)). Estimated heritability rates of up to 46% for MDD based on data from twin studies strengthen the notion of a strong genetic basis for MDD risk ([Kendler et al. 1993](#)).

Prolonged exposure to severe traumatic events in childhood and adolescence has also been linked to the development of depressive episodes later in life ([Alloy et al. 2006](#); [Hammen 2005](#); [Hosang et al. 2010](#)). Trauma such as sexual abuse or the loss of a parent that occurs at a critical developmental period can result in permanent alteration of stress-related neuroendocrine systems (especially the hypothalamic-pituitary-adrenal [HPA] axis) and immune/inflammatory markers ([Ehlert 2013](#)). It is recognized that individuals with depression, particularly those exposed to early trauma, have altered stress and pro-inflammatory responses ([Danese et al. 2008](#); [Gillespie and Nemeroff 2005](#); [Heim et al. 2000, 2008](#); [Nemeroff and Vale 2005](#)).

Other clinical and demographic variables have been linked to an increased risk of developing depressive disorders. These include stressful life events such as the death of a loved one, divorce, or job loss ([Kendler et al. 1999](#)). Certain personality characteristics may also predispose an individual to developing a mood disorder. Individuals who score higher on measures of neuroticism, interpersonal dependency, or external locus of control may be vulnerable to stressful life events precipitating a major depressive episode ([Hirschfeld et al. 1983](#); [Paykel et al. 1996](#)). Investigations suggesting that some cultural groups may be at increased risk of mood disorders (Native Americans) or may have greater inherent resilience (Asian and Hispanic groups) are an area of continued interest ([Hasin et al. 2005](#)), as are potential epigenetic mediators of the effect of stressful life events (including childhood trauma) on the risk of MDD across generations ([Franklin et al. 2010](#); [Sun et al. 2013](#)).

Many medical illnesses are comorbid with MDD ([Table 46-1](#)). Cancer, AIDS, respiratory disease, cardiovascular disease, Parkinson's disease, and stroke are associated with an increased risk for depression ([Katon 2003](#)). MDD is associated with poorer outcomes in medically ill persons. For example, in patients with coronary heart disease and heart failure, depression is associated with a higher risk of rehospitalization and mortality ([Rutledge et al. 2006](#); [van Melle et al. 2004](#)). The clinical course and level of functioning are poorer in patients with MDD and co-occurring medical conditions ([Katon and Schulberg 1992](#); [Keitner et al. 1991](#)).

**TABLE 46-1. Medical conditions often comorbid with major depressive disorder**

<b>Infectious conditions</b>	<b>Metabolic conditions</b>	<b>Neurological conditions</b>	<b>General medical conditions</b>
Encephalitis	Addison's disease	Brain tumor	Alcohol or sedative withdrawal
Hepatitis	Cushing's disease	Dementia, cortical	Arthritis
HIV/AIDS	Diabetes	Dementia, subcortical	Cancer
Influenza	Hyponatremia	Huntington's disease	Cardiovascular disease
Meningitis	Nutritional deficiencies	Migraine headaches	Chronic pain syndromes
Mononucleosis	Pituitary dysfunction	Multiple sclerosis	Cocaine or stimulant withdrawal
Pneumonia	Renal disease	Parkinson's disease	Connective tissue diseases
Postviral syndrome	Thyroid disease	Poststroke syndrome	Fibromyalgia
Syphilis		Seizure disorders	Heavy metal poisoning
Tuberculosis		Traumatic brain injury	Irritable bowel syndrome
Urinary tract infection			Liver failure
			Menopause
			Myocardial infarction
			Premenstrual dysphoric disorder
			Pulmonary disease

*Note.* AIDS=acquired immunodeficiency syndrome; HIV=human immunodeficiency virus.

<b>Infectious conditions</b>	<b>Metabolic conditions</b>	<b>Neurological conditions</b>	<b>General medical conditions</b>
			Selenium toxicity
			Sleep disturbance

*Note.* AIDS=acquired immunodeficiency syndrome; HIV=human immunodeficiency virus.

MDD is also highly comorbid with other psychiatric disorders. In primary care settings, more than 75% of patients with diagnosed depression also have an anxiety disorder (Olfson et al. 1997). Patients with depression and anxiety have more chronic and severe illness, greater occupational and psychosocial impairment, and (when the comorbidity is unrecognized) higher rates of psychiatric hospitalization and suicide attempt (Hirschfeld 2001; Sareen et al. 2005). In acknowledgment of the high comorbidity of anxiety disorders with MDD, DSM-5 includes a specifier—“with anxious distress”—that can be added to a major depressive episode diagnosis if at least two of the following symptoms are present during the majority of the episode: feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful may happen, and feeling that one might lose control of oneself (American Psychiatric Association 2013). High anxiety in the context of MDD is associated with lower rates of response to initial treatment with an antidepressant (Fava et al. 2008).

Substance use disorders are also highly comorbid with depressive disorders. The reported prevalence of depressive disorders in patients with alcohol use disorder is 15%–67%; for patients with cocaine use disorder, the prevalence is 33%–53%, and for patients with opioid use disorder, the lifetime rate of mood disorders ranges from 16% to 75% (Davis et al. 2005; Rapaport et al. 1993; Zimmerman et al. 2002). As is the case with comorbid anxiety, co-occurring substance use disorders are associated with worse long-term outcomes and illness course in individuals with MDD (Davis et al. 2005), including higher rates of suicide (Sher et al. 2005).

Remission from substance use has been shown to reduce the risk of depression ([Agosti and Levin 2006](#)).

In summary, there are several biological and nonbiological factors that can increase the risk of developing a depressive disorder.

## Disability and Costs Associated With Depressive Disorders

MDD is associated with significant disease burden, exceeding that of cerebrovascular disease, cancer, and numerous other chronic medical illnesses ([Wells et al. 1989](#); [World Health Organization 2004](#)). It is the leading cause of years lived with disability worldwide for young adults ([Lopez et al. 2006](#)) and is predicted to become the second leading cause of disability (behind HIV/AIDS) worldwide by the year 2030 ([Mathers and Loncar 2006](#)). It is estimated that the economic burden of adults with MDD in the U.S. is \$210.5 billion, 45% of which is attributable to direct costs, 50% to workplace costs, and 5% to suicide-related costs ([Greenberg et al. 2015](#)).

The most severe outcome for persons with depressive disorders is death by suicide. Suicide is the tenth leading cause of death in the United States across all age groups (~37,000 known suicides were identified in the 2009 census), the second leading cause of death for individuals between the ages of 25 and 34 years, and the third leading cause of death for young people between the ages of 15 and 24 years ([Kochanek et al. 2012](#)). Data from the 2013 National Survey on Drug Use and Health showed that among an estimated 15.7 million adults with a major depressive episode in 2013, 4.4 million (28%) had serious thoughts of suicide ([Substance Abuse and Mental Health Services Administration 2014](#)). Individuals with unipolar depressive illnesses including MDD have 20 times the risk of dying by suicide compared with the general population ([American Association of Suicidology 2009](#); [Harris and Barraclough 1997](#)). Among depressed individuals, suicide risk is highest among males and among persons with past suicide attempts, with more severe depression, with hopelessness, and with comorbid substance use, anxiety, and personality disorders ([Hawton et al. 2013](#)).

In summary, depressive disorders in general and MDD in particular are costly and are associated with adverse effects on functioning, including disability that is as severe as—or more severe than—disability associated with most chronic medical illnesses. Depressive disorders are the diagnoses most commonly associated with suicide. Suicidal ideation with intent and a plan is a medical emergency that merits the same type of acute response that a physician would give to a myocardial infarction or stroke.

---

## Neurobiology of Depression

---

Current evidence suggests that there is no single, unifying etiopathophysiology for MDD ([Kupfer et al. 2012](#)). However, certain neurobiological alterations have been consistently observed in animal models of MDD and in human patients, many of which are modifiable through antidepressant or other biological treatments for MDD. These neurobiological markers of MDD are discussed below.

### Dysregulation of Neurotransmitter Functioning

For several decades, drug development and biological treatment models for MDD were based primarily on the hypothesis that abnormalities in monoamine neurotransmitter signaling caused the psychological and neurovegetative signs and symptoms of the disorder ([Owens 2004](#)). Indeed, all known orally administered antidepressant medications interact with monoamine transporters or receptors or with enzymes responsible for their degradation ([Li et al. 2012](#)). Although this hypothesis has added profoundly to our understanding of the pathophysiology of MDD and the mechanisms of antidepressive treatment response, it alone cannot explain the wide variation in phenotypic presentation across large numbers of affected patients, nor can it explain the tremendous interindividual variability in clinical response to antidepressants ([Hindmarch 2001](#)).



As our understanding of the mechanism of action of antidepressant therapies has grown, more attention has been given to other neurotransmitter systems. Converging evidence from postmortem genetic in vivo neuroimaging studies has implicated glutamate abnormalities in the pathophysiology of mood disorders, including MDD ([Duman 2014](#); [Sanacora et al. 2012](#)). Moreover, pharmacotherapies that target glutamatergic *N*-methyl-D-aspartate (NMDA) receptors have shown considerable promise as putative antidepressants. For example, subanesthetic doses of ketamine, an NMDA receptor antagonist, have been shown to induce rapid (within hours) antidepressant activity that may persist over several days to weeks in patients with pharmacotherapy-resistant MDD and bipolar depression ([Newport et al. 2015](#)). However, rates of antidepressant response to ketamine therapy vary widely, and not all glutamatergic compounds—or even all NMDA receptor antagonists—produce antidepressant effects.

## Neuroendocrine Dysfunction and Maladaptive Responses to Stress

Not surprisingly, depression is marked by dysregulation of important biological systems other than those involved in neurotransmitter signaling. Depressed individuals are often characterized as having altered biological responses to stress, likely due to dysregulation and overstimulation of the HPA axis ([Gold 2015](#)). Early studies showed that administration of dexamethasone to unmedicated depressed persons failed to suppress the secretion of cortisol ([Brown and Shuey 1980](#); [Carroll 1982](#); [Coppen et al. 1983](#)), a condition known as *dexamethasone nonsuppression*. This impairment of HPA axis regulation has been traced to dysregulated corticotropin-releasing hormone (CRH) secretion from the hypothalamus ([Holsboer 2000](#)). Depressed individuals have higher CRH neuronal activity ([Raadsheer et al. 1994](#)) and display a blunted adrenocorticotrophic hormone and cortisol response to infusion of synthetic CRH ([Gispens-de Wied et al. 1993](#); [Gold et al. 1986](#)). Remission of depressive symptoms induces a normalization of responses to dexamethasone

or CRH challenge along with normalization of plasma cortisol levels ([Amsterdam et al. 1988](#); [Arana et al. 1985](#); [Sachar et al. 1970](#)). As noted earlier, dysregulation of HPA axis activity and higher rates of depression are more common in individuals exposed to childhood trauma or abuse ([Ehlert 2013](#); [Heim et al. 2008](#)), suggesting that hyperactivity of the HPA axis during critical periods of brain development leads to higher rates of depression later in life.

This cascade of alterations in the HPA axis, and subsequent increase in glucocorticoids, is thought to be responsible for the structural and functional changes seen in certain limbic structures that are crucial for regulating emotion, motivation, reward, cognitive functioning, and reactivity to stress ([Hamon and Blier 2013](#)). Postmortem and neuroimaging studies have reported significant reductions in gray matter volume and glial density in frontolimbic brain regions, including the hippocampus and prefrontal cortex, in depressed patients ([Arnone et al. 2012](#); [Kempton et al. 2011](#); [Rajkowska 2003](#)). Successful antidepressant therapy has been shown to increase cellular proliferation in these brain regions ([Duman 2004](#); [Warner-Schmidt and Duman 2006](#)), whereas chronically elevated levels of stress and glucocorticoid hormones interfere with normal hippocampal neurogenesis ([Anacker et al. 2013](#)). Dysregulation of the HPA axis, however, has not been observed uniformly across samples of depressed individuals and therefore cannot be considered a sole cause of MDD or other depressive states.

## Neuroimmune Mechanisms

Psychosocial stressors are known to activate not only the HPA axis but also pro-inflammatory responses, which may represent another link between the effects of stress and the onset of MDD ([Haroon et al. 2012](#)). Compared with healthy subjects, depressed patients have been found to have higher levels of inflammatory biomarkers, including higher circulating pro-inflammatory cytokines, such as interleukin 6 (IL-6), IL-1, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) ([Dantzer et al. 2008](#); [Hiles et al. 2012](#)). Exposure to interferon- $\alpha$  (INF- $\alpha$ ), an inflammatory cytokine used to treat chronic hepatitis C

and neoplastic diseases, can induce depressive symptoms that overlap with MDD ([Capuron et al. 2009](#)) and that can be reduced or prevented by antidepressants ([Baraldi et al. 2012](#); [Udina et al. 2014](#)). Pro-inflammatory cytokines have been shown to activate the HPA axis and to alter the metabolism of monoamine neurotransmitters and glutamate ([Haroon et al. 2012](#)). Antidepressant treatment of depressed patients has been shown to reduce plasma levels of cytokines (IL-1 $\beta$  and possibly IL-6) in some studies but not others ([Hannestad et al. 2011](#); [Hiles et al. 2012](#)), and decreases in pro-inflammatory cytokine levels over time have not always correlated with improvement in depressive symptoms ([Brunoni et al. 2014b](#)). For this reason, a neuroimmune mechanism cannot account for all cases of clinically significant depression or serve as a unified explanation of antidepressant activity.

## Dysfunctional Neurotrophic Responses and Neuroplasticity

Deficiencies in a host of growth factors (neurotrophins) that regulate plasticity in the human brain have also been implicated in the pathophysiology of MDD and of other disease states. More specifically, several types of psychosocial stress have been linked with reduced brain-derived neurotrophic factor (BDNF) signaling in the hippocampus ([Duman and Monteggia 2006](#)). Expression of BDNF and BDNF-related genes is reduced or altered in postmortem brain samples and circulating lymphocytes from depressed persons, and serum BDNF levels are decreased in patients with MDD ([Krishnan and Nestler 2008](#)). Antidepressant treatment and electroconvulsive therapy (ECT) have both been found to produce upregulation of BDNF expression in clinical and preclinical studies ([Brunoni et al. 2014a](#); [Cattaneo et al. 2013](#); [Polyakova et al. 2015](#)). Additionally, preclinical studies have shown that BDNF infused directly into the hippocampus produces antidepressant-like effects that are blocked in animals lacking the BDNF gene ([Krishnan and Nestler 2008](#)). However, infusion of BDNF into other brain regions produces increases in depression-like behaviors ([Krishnan and](#)

[Nestler 2008](#)). Enthusiasm for a “neurotrophic hypothesis” for MDD has been further tempered by negative findings from studies that failed to replicate stress- or antidepressant-induced changes in BDNF expression, by the lack of a satisfactory mechanism through which neurotrophic factors might improve mood in depressed patients, and by findings indicating that decreased neurogenesis is not a sole cause of depression ([Groves 2007](#); [Krishnan and Nestler 2008](#)).

## Genetics and Epigenetics

A variety of susceptibility genes have been investigated in hopes of identifying a genetic profile that will help us to better understand the pathophysiology of MDD and provide novel neurobiological targets for treatment interventions. Candidate gene studies have identified several potential risk genes for MDD, including *BDNF*, *SLC6A4*, *ACE*, *P2RX7*, *TPH2*, *PDE9A*, *PDE11A*, *DISC1*, *NR3C1*, *GRIK3*, and genes for monoamine oxidase A and glycogen synthase kinase-3 $\beta$  ([Fan et al. 2010](#); [Levinson 2006](#); [van Rossum et al. 2006](#); [Yoon and Kim 2010](#)). No single gene has been clearly identified as a cause of MDD ([López-León et al. 2008](#)), and it may be concluded that depressive disorders are likely polygenetic in nature ([Uher 2009](#)). Interactions between genes and environmental factors (including childhood trauma and other adverse life events) may contribute more strongly than either alone to the development of depression ([Caspi et al. 2010](#); [Cohen-Woods et al. 2013](#); [Kendler et al. 1995](#)).

Gene expression is influenced by more than simple variations in DNA sequence. The field of epigenetics investigates changes in gene expression caused by biological processes (such as DNA methylation/demethylation and histone acetylation) that do not change the underlying DNA sequence but instead either activate or deactivate the expression of specific genes. Epigenetic alterations in chromatin structure have been associated with depression-like behaviors in animal models and have been found in postmortem brains of depressed persons ([Nestler et al. 2016](#)). Epigenetic changes can occur in response to environmental insults and stress, resulting in long-lasting effects on gene expression ([Qureshi and](#)

[Mehler 2014](#)). Therefore, epigenetic modifications are candidate mechanisms for stress-induced effects on gene expression, neuronal functioning, and the risk of MDD and other depressive states ([Nestler et al. 2016](#)). Interestingly, treatment with antidepressants has been shown to result in epigenetic changes in genes associated with the risk of MDD, including *BDNF* and *SLC6A4* ([Domschke et al. 2014](#); [Duclot and Kabbaj 2015](#)). Epigenetic (dys)regulation of gene expression may therefore represent not only an important pathophysiological mechanism linking environmental or life stress and the risk of MDD but also an important neurobiological mechanism of antidepressant treatment response.

---

## Treatment Options

---

### Antidepressant Medications

Pharmacotherapy with antidepressants is an important component of a comprehensive biopsychosocial treatment plan for managing MDD. The pharmacological profiles of individual antidepressants are extensively reviewed in [Chapters 8–23](#) of this volume. Our focus in this chapter is the practical aspects of antidepressant use and the broader range of treatments for MDD and other depressive disorders.

#### Choosing the Initial Antidepressant

With regard to initial antidepressant choice, there is little evidence that one antidepressant is clearly superior to other agents under most routine treatment conditions, although there may be some evidence of modest efficacy advantages for venlafaxine or other serotonin-norepinephrine reuptake inhibitors (SNRIs) over selective serotonin reuptake inhibitors (SSRIs) ([Nemeroff et al. 2008](#); [Papakostas et al. 2007b](#); [Schueler et al. 2011](#)) and for sertraline, escitalopram, or mirtazapine over selected other antidepressants ([Cipriani et al. 2008, 2009](#); [Gartlehner et al. 2011](#); [Kennedy et al. 2009](#); [Montgomery et al. 2007](#)). However, there is limited research

supporting differential benefit. Therefore, in most cases, initial antidepressant choice is made on the basis of differential side-effect and tolerability profiles. For example, SSRIs are generally preferred for initial antidepressant treatment in patients with MDD because they are associated with fewer side effects than SNRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) (Anderson 2000; Nemeroff et al. 2008; Schueler et al. 2011) and are regarded as being relatively safe in overdose (Barbey and Roose 1998). However, sexual side effects can be treatment limiting with the SSRIs (and with SNRIs, TCAs, MAOIs, vilazodone, and vortioxetine), whereas bupropion and mirtazapine have lower rates of treatment-emergent sexual dysfunction and therefore may be preferred by some patients (Montejo et al. 2015).

Additional factors that may be considered when choosing among antidepressants for treating patients with depressive disorders are summarized in Table 46-2. Drug-drug interactions may increase blood levels of concomitantly administered medications, and at times those interactions can be unpleasant or even life-threatening (Spina et al. 2012). When comorbid psychiatric or medical conditions are present, it may be particularly advantageous to select an antidepressant that effectively addresses both the depression and the comorbid disorder and to avoid antidepressants that may aggravate the comorbid condition. Persons with MDD *with atypical features*—a DSM-5 (American Psychiatric Association 2013) specifier defined as depression with intact mood reactivity and at least two associated symptoms (significant weight gain/increase in appetite, hypersomnia, “lead-like” heaviness in the limbs, sensitivity to perceived rejection)—may respond preferentially to an oral MAOI or to SSRIs (Henkel et al. 2006). For most patients with MDD *with psychotic features* (defined as the presence of hallucinations or delusions), the use of an antidepressant in combination with an antipsychotic drug is more efficacious than antidepressant monotherapy, although the side-effect burden may be greater with combination therapy than with monotherapy (Farahani and Correll 2012).

---

**TABLE 46-2. Factors to consider when selecting an antidepressant for treatment of major depressive disorder**

---

Efficacy profile (no evidence of large differences between agents for routine use)

Side-effect (tolerability) profile

Safety in overdose

Concomitant medications and the potential for drug–drug interactions

Comorbid psychiatric illness(es)

Comorbid general medical illness(es)

Prior treatment response to the medication (efficacy, tolerability)

Family history of treatment response to the medication (efficacy, tolerability)

Patient preference

Medication cost/insurance coverage

---

*Source.* [Cleare et al. 2015](#); [Lam et al. 2009](#); [Malhi et al. 2013](#); [Mann 2005](#).

Compared with the extensive literature on antidepressants in MDD, far fewer studies have focused on antidepressant efficacy in patients with persistent depressive disorder (dysthymia); however, SSRIs and TCAs appear to be effective in this disorder ([Kriston et al. 2014](#)).

## **Assessing and Optimizing Treatment Response**

The initial goals of treatment are to achieve symptom remission (absence of clinically significant depressive symptoms) and to restore normal functioning. Once a patient is well, the primary goals are to prevent relapses and minimize adverse effects.

In general, 2–6 weeks of treatment are required for most antidepressants to show positive clinical benefit, and some patients require an even longer period of time. However, lack of significant clinical benefit by 4 weeks predicts lower odds of an eventual positive treatment response, and a change in treatment may be needed ([Szegedi et al. 2003](#)). Lack of discernible positive treatment response to an antidepressant may reflect inefficacy of the medication for that patient; however, this conclusion can be reached



only after practical reasons for poor response to antidepressant pharmacotherapy have been ruled out ([Table 46-3](#)).

---

**TABLE 46-3. Reasons for poor response to antidepressant pharmacotherapy**

---

Poor adherence to medication (consider therapeutic drug monitoring, where appropriate)
Inadequate dosage (or serum value in the case of certain TCAs)
Inadequate duration of treatment
Inaccurate diagnosis (e.g., secondary depression, bipolar I or II depression)
Undiagnosed psychiatric symptoms (e.g., psychotic or atypical features) or comorbidity (e.g., substance use disorder, personality disorder, anxiety disorder)
New or worsening medical comorbidities
Drug-drug interactions (particularly concomitant medications that may worsen depressive symptoms, aggravate antidepressant side effects, or lead to excessively rapid metabolism of the antidepressant)
Undiagnosed psychosocial factors that are prolonging depressive symptoms

---

*Note.* TCAs=tricyclic antidepressants.

*Source.* [Cleare et al. 2015](#); [Culpepper et al. 2015](#).

Positive antidepressant responses that fall short of remission are clinically meaningful but are also associated with higher rates of relapse and residual functional impairment ([Culpepper et al. 2015](#)). Strategies for managing partial response to antidepressants include incrementally increasing the dosage of antidepressant (assuming good tolerability), adding another medication and/or psychotherapy to the antidepressant (if the dosage of the antidepressant cannot be increased and switching to a new drug carries the risk of a full symptom relapse), or switching to a new antidepressant (if combination pharmacotherapy is infeasible or if side effects are intolerable).



With regard to combination pharmacotherapy to improve efficacy, there is evidence supporting the adjunctive use of lithium with TCAs or possibly SSRIs ([Crossley and Bauer 2007](#); [Zhou et al. 2015](#)); the adjunctive use of selected atypical antipsychotic drugs primarily with SSRIs ([Papakostas et al. 2007a, 2015](#)); and the adjunctive use of thyroid hormone (T<sub>3</sub>, liothyronine) with SSRIs and TCAs ([Zhou et al. 2015](#)). There is also evidence supporting the use of mirtazapine or TCAs in combination with SSRIs in improving remission rates, as compared with SSRIs alone ([Rocha et al. 2012](#)). Other commonly used strategies in clinical practice include augmentation of antidepressants with a second antidepressant (e.g., bupropion, mirtazapine), with buspirone, with modafinil or armodafinil, or with a traditional psychostimulant such as methylphenidate; however, there is less evidence supporting most of these strategies ([Lam et al. 2009](#); [Zhou et al. 2015](#)).

There is some evidence supporting combination pharmacotherapy to manage adverse effects of antidepressants, including bupropion or selected phosphodiesterase inhibitors (sildenafil, tadalafil) for reducing antidepressant-associated sexual side effects ([Taylor et al. 2013](#)), with the best evidence supporting sildenafil for both men and women ([Fava et al. 2006](#); [Nurnberg et al. 2008](#)). Use of adjunctive pharmacotherapy to manage antidepressant-associated side effects may be appropriate if lowering the antidepressant dosage or switching to a new antidepressant is not feasible, provided that adding the second agent does not introduce unacceptable medical risk or drug interactions.

There is controlled evidence supporting the benefit of switching from one SSRI to another after insufficient response to an initial SSRI trial, especially if the first SSRI was poorly tolerated ([Ruhé et al. 2006](#)). Clinical guidelines and controlled evidence also support the benefit of switching to a non-SSRI antidepressant if there is either a lack of clinical benefit from the initial SSRI trial or a lack of response to two SSRI trials ([Cleare et al. 2015](#); [Lam et al. 2009](#); [Malhi et al. 2013](#); [Ruhé et al. 2006](#)). Treatment-resistant depression—defined as depression that has not responded to at least two therapeutic trials of antidepressants from different pharmacological classes (e.g., an SSRI followed by an SNRI, an SSRI followed by

bupropion)—is discussed in the following subsection, “Managing Treatment-Resistant Major Depressive Disorder.”

In general, patients who respond well to an antidepressant at a given dosage should continue at that same dosage for at least 6–9 months. However, there is no broad consensus as to how long antidepressants should be continued in patients whose depressive symptoms remit before a medication-free trial is undertaken. A longer duration of antidepressant treatment may be beneficial for patients who are at higher risk of relapse, including those with a history of multiple depressive episodes. Adjunctive psychotherapy may be useful as an added relapse-preventive measure (see section “Psychotherapies” later in this chapter).

## **Managing Treatment-Resistant Major Depressive Disorder**

Unfortunately, up to one-third of patients with MDD do not respond to at least two therapeutic trials of antidepressants from different pharmacological classes and are considered to have treatment-resistant depression (TRD). Compared with treatment-responsive depression, TRD is associated with more severe and chronic depressive symptoms, greater psychiatric and medical comorbidity, higher health care costs, and higher risks of death from medical illness and suicide ([Greden 2001](#)).

For patients whose depression has not responded to serial therapeutic trials of antidepressants and whose nonresponse cannot be better explained by practical factors (see [Table 46-3](#)), management options include switching antidepressants, using combination pharmacotherapy, augmenting antidepressants with psychotherapy, or initiating a course of ECT. There is support in the literature for switching to a different antidepressant after nonresponse to the current antidepressant at virtually any stage of treatment. For patients with TRD, there is also support for initiating a therapeutic trial of mirtazapine or TCAs (in the case of poor response to other antidepressants), for initiating combination pharmacotherapy with an augmenting agent (e.g., adding an atypical antipsychotic, lithium, or thyroid hormone to the antidepressant), and for switching to an alternative TCA or to an oral

MAOI (in the case of poor response to an initial TCA trial) ([Carvalho et al. 2014](#); [Culpepper et al. 2015](#); [McIntyre et al. 2014](#); [Zhou et al. 2015](#)). Psychotherapy and somatic therapies such as ECT are also treatment options and are reviewed in the following subsections.

There has been recent excitement about the therapeutic potential of ketamine and related glutamatergic NMDA receptor-targeting agents in treatment-resistant unipolar and bipolar depression. When provided at subanesthetic doses, ketamine has shown a rapid onset (within hours) of transient (1–4 weeks) antidepressive effects with very large effect sizes in patients with severely refractive depression ([Newport et al. 2015](#)). However, ketamine therapy for depression is still considered investigational at this time.

## Somatic Therapies

ECT is the best studied of the somatic interventions. It is a clearly one of the treatments of choice for individuals with TRD, and it is effective for MDD with psychotic or catatonic features and for other situations in which a rapid antidepressive effect is needed and lag times to therapeutic benefit with conventional antidepressants are unacceptable (e.g., persons with MDD who are at high suicide risk or those who are nutritionally compromised because of food refusal). Although the mechanism of action of ECT is still not well understood, it is a safe and effective treatment. In repeated studies, ECT has been found to be more effective than placebo (sham ECT) and pharmacotherapy in patients with TRD ([UK ECT Review Group 2003](#)). Adverse cognitive effects and relapses following a successful course (even with ongoing pharmacotherapy) are the main limitations of ECT ([Jelovac et al. 2013](#); [UK ECT Review Group 2003](#)). Relapse rates can be reduced with maintenance ECT. Cognitive side effects may be limited by the use of alternative electrode placements (unilateral instead of bitemporal) and by the use of ultrabrief-pulse (instead of brief-pulse) ECT ([Tor et al. 2015](#)). For a review of recent advances in ECT and other somatic therapies, see [Chapter 45](#) in this volume, “Electroconvulsive Therapy and Other Neuromodulation Therapies,” by McDonald et al.

Vagus nerve stimulation (VNS) was initially developed for the treatment of epilepsy. In 2005 it was approved by the U.S. Food and Drug Administration (FDA) for use in TRD. One of the key findings to emerge from studies of VNS is that its effects may be cumulative, with the full benefits usually not evident until 9–12 months after treatment initiation ([Sackeim et al. 2007](#); [Schlaepfer et al. 2008](#)). VNS is generally available only in specialized settings with adequate surgical capabilities.

Transcranial magnetic stimulation (TMS) was first identified as a treatment for depression in 1995 by a group of National Institute of Mental Health researchers ([George et al. 1995](#)). Since that time, several smaller studies have supported the efficacy of TMS for the treatment of MDD ([Allan et al. 2011](#)). At present, TMS is FDA approved for the treatment of MDD in individuals whose depressive episode has been unresponsive to one adequate medication trial. A number of related neurostimulation treatments are in development, including magnetic seizure therapy, transcranial direct current stimulation, low-field magnetic stimulation, and cranial electrical stimulation ([Rosa and Lisanby 2012](#)).

Deep brain stimulation (DBS) is an FDA-approved treatment for severe, intractable Parkinson's disease, essential tremor, dystonia, and obsessive-compulsive disorder (under a humanitarian device exemption). In a large multisite study of DBS therapy in 20 individuals with TRD, the initial 6-month response and remission rates were 60% and 30%, respectively ([Lozano et al. 2008](#)). Significant reductions in depressive symptoms and high remission rates have subsequently been demonstrated in small open studies of DBS therapy for severely treatment-resistant depression ([Anderson et al. 2012](#)). Despite these encouraging results, there is still an inadequate understanding of the precise mechanisms underlying the therapeutic effects of DBS for TRD, and its use in the treatment of MDD is still considered to be investigational. Furthermore, larger trials of DBS in TRD have not confirmed its efficacy ([Dougherty et al. 2015](#)). As with VNS, longer periods of exposure to DBS may yield better effects ([Holtzheimer et al. 2012](#)).

Bright light therapy appears to be an effective augmentation therapy for certain types of depressive disorders ([Oldham and Ciraulo 2014](#)). Light has been best studied in patients with seasonal

affective disorder (i.e., DSM-5 major depressive episode with seasonal pattern), although it also appears to be effective for some patients with nonseasonal depression (Even et al. 2008). Light therapy for up to 90 minutes per day has been shown to effectively treat—and also to prevent the development of—depressive disorders (Even et al. 2008; Westrin and Lam 2007), especially those with a seasonal pattern. Light therapy has also been shown to improve depressive symptoms in pregnant and postpartum women (Corral et al. 2007; Wirz-Justice et al. 2011).

In summary, ECT is clearly effective for TRD and severe forms of depression, including MDD with psychotic features. VNS and TMS are also approved for the treatment of MDD that has not responded to at least one antidepressant trial. Additional neuromodulatory treatments such as DBS are under clinical development and show considerable promise but are likely to be available only in highly specialized treatment settings. It is clear that more work needs to be done in investigating somatic options for patients with TRD.

## Psychotherapies

### Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) is a time-limited psychotherapy that aims to help patients systematically assess and modify distorted (depression promoting) automatic thoughts and assumptions about themselves, their current situation, and their future. These cognitive techniques are coupled with behavioral interventions designed to combat passive disengagement from life activities, including social withdrawal. CBT has been shown to be effective in reducing active symptoms of depression and preventing depressive relapses (Lynch et al. 2010). Although practice guidelines have preferentially recommended antidepressant pharmacotherapy over psychotherapy for severe episodes of MDD, recent evidence has suggested that for patients with nonpsychotic MDD, baseline depression severity may not moderate differences in antidepressive efficacy between CBT and antidepressant pharmacotherapy (Weitz et al. 2015). The combination of CBT with antidepressant pharmacotherapy may be

more effective than medication alone in reducing depressive symptoms and improving recovery rates and adherence to treatment ([Hollon et al. 2014](#)). CBT also appears to be just as effective as continuation medication in preventing relapse after recovery from a depressive episode ([Hollon et al. 2005](#)).

## **Interpersonal Therapy**

Interpersonal psychotherapy (IPT) is a time-limited individual psychotherapy that focuses on four problem areas—grief, role transitions, role disputes, and interpersonal deficits—during acute treatment of depression. IPT has been demonstrated to be an efficacious acute treatment for patients with MDD, both alone and in combination with antidepressant pharmacotherapy ([Cuijpers et al. 2011](#)).

Both IPT and CBT are recommended as first-line psychotherapies for treating patients with MDD, and there is no clear evidence that one is more efficacious than the other ([Jakobsen et al. 2012](#)). However, IPT appears to be effective in reducing relapse only while it is continued ([Frank et al. 2007](#)).

## **Mindfulness-Based Cognitive Therapy**

Mindfulness-based cognitive therapy (MBCT) is a next-generation psychotherapy based in part on cognitive therapy principles, supplemented by techniques that teach depressed patients to adopt a nonjudgmental awareness of the present moment in an effort to disengage from negative thought patterns that maintain depressive episodes and lead to depressive relapses ([van der Velden et al. 2015](#)). MBCT has been shown to be effective in preventing relapse in patients with recurrent MDD, particularly those with three or more lifetime mood episodes ([Piet and Hougaard 2011](#)). The effectiveness of MBCT in treating acute depressive episodes, including acute episodes in patients with severe MDD, has not been established.

## **Other Psychotherapies for Depression**

Other forms of psychotherapy that have been studied in patients with MDD and other forms of depressive illness include behavioral activation, short-term psychodynamic psychotherapy, acceptance



and commitment therapy, motivational interviewing, cognitive-behavioral analysis system of psychotherapy, and self-guided treatments such as bibliotherapy and computer-based delivery platforms for psychotherapy ([Lampe et al. 2013](#); [Parikh et al. 2009](#)). In general, there is much less empirical support for these approaches than for either CBT or IPT; therefore, more high-quality studies are needed.

In conclusion, both CBT and IPT are efficacious in the treatment of MDD. Evidence to date suggests that CBT is also effective in the maintenance treatment of depressive disorders. However, there is still uncertainty about how best to select the most appropriate form of psychotherapy for an individual patient. To a significant degree, the success of IPT and CBT appears to depend on therapist training and competence in delivering the specific form of psychotherapy ([Hollon and Ponniah 2010](#)).

## Other Adjunctive Treatments

### Complementary and Alternative Medicine Approaches

There are a host of complementary and alternative medicine approaches that have been studied for treating patients with MDD and other types of unipolar depression. There is evidence from controlled studies to support the use of *Hypericum perforatum* (St. John's wort) for mild to moderate depression ([Linde et al. 2008](#)), although this agent should not be combined with serotonin-potentiating antidepressants (such as SSRIs, SNRIs, TCAs, or MAOIs) to avoid risk of serotonin syndrome.

There is also some controlled evidence supporting the use of S-adenosylmethionine (SAM-e) alone and omega-3 fatty acid supplementation alone or in combination with antidepressants for mainly mild to moderate depression ([Grosso et al. 2014](#); [Papakostas et al. 2010](#)). Other approaches that have also shown promise include partial wake therapy (sleep deprivation) and supplementation with L-methylfolate, dehydroepiandrosterone (DHEA), tryptophan, or other nutraceuticals. Further controlled research is warranted.

## Lifestyle Interventions

A variety of lifestyle interventions have been systematically evaluated, mainly as adjuncts to core depression treatments. Beneficial effects have been observed for increasing physical activity and exercise; making dietary modifications; maintaining adequate relaxation and sleep practices; practicing mindfulness-based meditation; and reducing or eliminating recreational substance use, including nicotine, drugs, and alcohol ([Sarris et al. 2014](#)). In general, nearly all of these interventions can be recommended for improving general health and well-being in most patients with little risk of harm.

---

## Conclusion

---

Over the past decade, there have been remarkable advances in our knowledge about the neurobiology, course and prognosis, and treatment of MDD and other unipolar depressive illnesses. Some patients with MDD have an episodic course with relatively normal functioning between discrete mood episodes. The majority of patients, however, have a more chronic and persisting course.

Fortunately, there are a large number of first-line treatments for MDD, including a wide variety of antidepressants. Although many patients benefit from treatment with antidepressants, a significant percentage of patients do not respond to a degree that leads to symptomatic remission and full functional recovery. Furthermore, a substantial number of patients do not benefit even after multiple therapeutic trials of antidepressants. For those who respond but do not achieve remission, options for management include implementing dosage increases as tolerated, initiating pharmacological augmentation regimens (combination pharmacotherapy), integrating pharmacotherapy with psychosocial treatments (including CBT or IPT), and switching treatments. For patients with TRD, the same general approaches can be used, although older antidepressants (such as TCAs and MAOIs) and ECT are higher-priority treatment options. Most patients with MDD with psychotic features will require combination pharmacotherapy with



an antidepressant and an antipsychotic drug. Seasonal forms of depression may respond well to light therapy. Adoption of healthy lifestyle habits can be recommended for nearly all patients.

Although the field has made significant progress with regard to depression treatment, many challenges remain, particularly for patients with TRD, for which treatment options are the most limited. However, advances in basic biological investigations of depression are greatly expanding our knowledge, and new psychotherapies and biological treatments continue to be developed. Future research will be focused on integrating findings across multiple neuroscientific disciplines to better elucidate the roles of and interactions between the variety of neurotransmitter-, neuroendocrine-, immune-, neurohormonal-, neurotrophic-, and circuitry-based systems implicated in the pathogenesis of depression. Advances in translational research will identify novel biological targets for depression treatment and will allow us to develop better and more personalized approaches for our patients.

---

## References

---

- Agosti V, Levin FR: The effects of alcohol and drug dependence on the course of depression. *Am J Addict* 15(1):71-75, 2006 16449095
- Allan CL, Herrmann LL, Ebmeier KP: Transcranial magnetic stimulation in the management of mood disorders. *Neuropsychobiology* 64(3):163-169, 2011 21811086
- Alloy LB, Abramson LY, Smith JM, et al: Role of parenting and maltreatment histories in unipolar and bipolar mood disorders: mediation by cognitive vulnerability to depression. *Clin Child Fam Psychol Rev* 9(1):23-64, 2006 16718583
- Alonso J, Angermeyer MC, Bernert S, et al; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project: Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 109(420):21-27, 2004 15128384
- American Association of Suicidology: Some Facts About Suicide and Depression. Washington, DC: American Association for

- Suicidology, 2009. Available at: <https://www.cga.ct.gov/asaferconnecticut/tmy/0129/Some%20Facts%20About%20Suicide%20and%20Depression%20-%20Article.pdf>. Accessed March 17, 2016.
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Amsterdam JD, Maislin G, Winokur A, et al: The oCRH stimulation test before and after clinical recovery from depression. *J Affect Disord* 14(3):213-222, 1988 2838538
- Anacker C, Cattaneo A, Musaelyan K, et al: Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis. *Proc Natl Acad Sci U S A* 110(21):8708-8713, 2013 23650397
- Anderson IM: Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord* 58(1):19-36, 2000 10760555
- Anderson RJ, Frye MA, Abulseoud OA, et al: Deep brain stimulation for treatment-resistant depression: efficacy, safety and mechanisms of action. *Neurosci Biobehav Rev* 36(8):1920-1933, 2012 22721950
- Arana GW, Baldessarini RJ, Ornstein M: The dexamethasone suppression test for diagnosis and prognosis in psychiatry: commentary and review. *Arch Gen Psychiatry* 42(12):1193-1204, 1985 3000317
- Arnone D, McIntosh AM, Ebmeier KP, et al: Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *Eur Neuropsychopharmacol* 22(1):1-16, 2012 21723712
- Baraldi S, Hepgul N, Mondelli V, et al: Symptomatic treatment of interferon- $\alpha$ -induced depression in hepatitis C: a systematic review. *J Clin Psychopharmacol* 32(4):531-543, 2012 22722514
- Barbey JT, Roose SP: SSRI safety in overdose. *J Clin Psychiatry* 59 (suppl 15):42-48, 1998 9786310
- Brown WA, Shuey I: Response to dexamethasone and subtype of depression. *Arch Gen Psychiatry* 37(7):747-751, 1980 7190379
- Brunoni AR, Baeken C, Machado-Vieira R, et al: BDNF blood levels after electroconvulsive therapy in patients with mood disorders: a systematic review and meta-analysis. *World J Biol Psychiatry* 15(5):411-418, 2014a 24628093

- Brunoni AR, Machado-Vieira R, Zarate CA, et al: Cytokines plasma levels during antidepressant treatment with sertraline and transcranial direct current stimulation (tDCS): results from a factorial, randomized, controlled trial. *Psychopharmacology (Berl)* 231(7):1315-1323, 2014b 24150249
- Burt VK, Stein K: Epidemiology of depression throughout the female life cycle. *J Clin Psychiatry* 63 (suppl 7):9-15, 2002 11995779
- Capuron L, Fornwalt FB, Knight BT, et al: Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? *J Affect Disord* 119(1-3):181-185, 2009 19269036
- Carroll BJ: The dexamethasone suppression test for melancholia. *Br J Psychiatry* 140:292-304, 1982 7093598
- Carvalho AF, Berk M, Hyphantis TN, et al: The integrative management of treatment-resistant depression: a comprehensive review and perspectives. *Psychother Psychosom* 83(2):70-88, 2014 24458008
- Caspi A, Hariri AR, Holmes A, et al: Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry* 167(5):509-527, 2010 20231323
- Cattaneo A, Gennarelli M, Uher R, et al: Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology* 38(3):377-385, 2013 22990943
- Chiu E: Epidemiology of depression in the Asia Pacific region. *Australas Psychiatry* 12 (suppl):S4-S10, 2004 15715830
- Cipriani A, Furukawa TA, Geddes JR, et al; MANGA Study Group: Does randomized evidence support sertraline as first-line antidepressant for adults with acute major depression? A systematic review and meta-analysis. *J Clin Psychiatry* 69(11):1732-1742, 2008 19026250
- Cipriani A, Furukawa TA, Salanti G, et al: Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 373(9665):746-758, 2009 19185342
- Cleare A, Pariante CM, Young AH, et al; Members of the Consensus Meeting: Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British

- Association for Psychopharmacology guidelines. *J Psychopharmacol* 29(5):459-525, 2015 25969470
- Cohen-Woods S, Craig IW, McGuffin P: The current state of play on the molecular genetics of depression. *Psychol Med* 43(4):673-687, 2013 22687339
- Coppen A, Abou-Saleh M, Milln P, et al: Dexamethasone suppression test in depression and other psychiatric illness. *Br J Psychiatry* 142:498-504, 1983 6409195
- Corral M, Wardrop AA, Zhang H, et al: Morning light therapy for postpartum depression. *Arch Women Ment Health* 10(5):221-224, 2007 17701271
- Coryell W, Akiskal HS, Leon AC, et al: The time course of nonchronic major depressive disorder. Uniformity across episodes and samples. National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies. *Arch Gen Psychiatry* 51(5):405-410, 1994 8179464
- Crossley NA, Bauer M: Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry* 68(6):935-940, 2007 17592920
- Cuijpers P, Geraedts AS, van Oppen P, et al: Interpersonal psychotherapy for depression: a meta-analysis. *Am J Psychiatry* 168(6):581-592, 2011 21362740
- Culpepper L, Muskin PR, Stahl SM, et al: Major depressive disorder: understanding the significance of residual symptoms and balancing efficacy with tolerability. *Am J Med* 128 (9 suppl):S1-S15, 2015 26337210
- Danese A, Moffitt TE, Pariante CM, et al: Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry* 65(4): 409-415, 2008 18391129
- Dantzer R, O'Connor JC, Freund GG, et al: From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9(1):46-56, 2008 18073775
- Davidson JR: Major depressive disorder treatment guidelines in America and Europe. *J Clin Psychiatry* 71 (suppl E1): e04, 2010
- Davis LL, Rush JA, Wisniewski SR, et al: Substance use disorder comorbidity in major depressive disorder: an exploratory analysis of the Sequenced Treatment Alternatives to Relieve Depression cohort. *Compr Psychiatry* 46(2):81-89, 2005 15723023

- Domschke K, Tidow N, Schwarte K, et al: Serotonin transporter gene hypomethylation predicts impaired antidepressant treatment response. *Int J Neuropsychopharmacol* 17(8):1167-1176, 2014 24679990
- Dougherty DD, Rezai AR, Carpenter LL, et al: A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression. *Biol Psychiatry* 78(4):240-248, 2015 25726497
- Duclot F, Kabbaj M: Epigenetic mechanisms underlying the role of brain-derived neurotrophic factor in depression and response to antidepressants. *J Exp Biol* 218(pt 1):21-31, 2015 25568448
- Duman RS: Depression: a case of neuronal life and death? *Biol Psychiatry* 56(3):140-145, 2004 15271581
- Duman RS: Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues Clin Neurosci* 16(1):11-27, 2014 24733968
- Duman RS, Monteggia LM: A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 59(12):1116-1127, 2006 16631126
- Eaton WW, Shao H, Nestadt G, et al: Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry* 65(5):513-520, 2008 18458203
- Ehlert U: Enduring psychobiological effects of childhood adversity. *Psychoneuroendocrinology* 38(9):1850-1857, 2013 23850228
- Even C, Schröder CM, Friedman S, et al: Efficacy of light therapy in nonseasonal depression: a systematic review. *J Affect Disord* 108(1-2):11-23, 2008 17950467
- Falk DE, Yi HY, Hilton ME: Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. *Drug Alcohol Depend* 94(1-3):234-245, 2008 18215474
- Fan M, Liu B, Jiang T, et al: Meta-analysis of the association between the monoamine oxidase-A gene and mood disorders. *Psychiatr Genet* 20(1):1-7, 2010 20010318
- Farahani A, Correll CU: Are antipsychotics or antidepressants needed for psychotic depression? A systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. *J Clin Psychiatry* 73(4):486-496, 2012 22579147
- Fava M, Nurnberg HG, Seidman SN, et al: Efficacy and safety of sildenafil in men with serotonergic antidepressant-associated

erectile dysfunction: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 67(2):240-246, 2006 16566619

Fava M, Rush AJ, Alpert JE, et al: Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR\*D report. *Am J Psychiatry* 165(3):342-351, 2008 18172020

Ferrari AJ, Charlson FJ, Norman RE, et al: Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 10(11):e1001547, 2013 24223526

Frank E, Kupfer DJ, Buysse DJ, et al: Randomized trial of weekly, twice-monthly, and monthly interpersonal psychotherapy as maintenance treatment for women with recurrent depression. *Am J Psychiatry* 164(5):761-767, 2007 17475735

Franklin TB, Russig H, Weiss IC, et al: Epigenetic transmission of the impact of early stress across generations. *Biol Psychiatry* 68(5):408-415, 2010 20673872

Gartlehner G, Hansen RA, Morgan LC, et al: Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med* 155(11):772-785, 2011 22147715

George MS, Wassermann EM, Williams WA, et al: Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 6(14):1853-1856, 1995 8547583

Gershon ES, Hamovit J, Guroff JJ, et al: A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry* 39(10):1157-1167, 1982 7125846

Gillespie CF, Nemeroff CB: Hypercortisolemia and depression. *Psychosom Med* 67 (suppl 1):S26-S28, 2005 15953796

Gispen-de Wied CC, Kok FW, Koppeschaar HP, et al: Stimulation of the pituitary-adrenal system with graded doses of CRH and low dose vasopressin infusion in depressed patients and healthy subjects: a pilot study. *Eur Neuropsychopharmacol* 3(4):533-541, 1993 8111227

Gold PW: The organization of the stress system and its dysregulation in depressive illness. *Mol Psychiatry* 20(1):32-47, 2015 25486982

Gold PW, Loriaux DL, Roy A, et al: Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease: pathophysiologic and diagnostic implications. *N Engl J Med* 314(21):1329-1335, 1986 3010108

- Goldney RD, Fisher LJ, Dal Grande E, et al: Subsyndromal depression: prevalence, use of health services and quality of life in an Australian population. *Soc Psychiatry Psychiatr Epidemiol* 39(4):293-298, 2004 15085331
- Greden JF: The burden of disease for treatment-resistant depression. *J Clin Psychiatry* 62 (suppl 16):26-31, 2001 11480881
- Greenberg PE, Fournier AA, Sisitsky T, et al: The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 76(2):155-162, 2015 25742202
- Grosso G, Pajak A, Marventano S, et al: Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One* 9(5):e96905, 2014 24805797
- Groves JO: Is it time to reassess the BDNF hypothesis of depression? *Mol Psychiatry* 12(12):1079-1088, 2007 17700574
- Hammen C: Stress and depression. *Annu Rev Clin Psychol* 1:293-319, 2005 17716090
- Hamon M, Blier P: Monoamine neurocircuitry in depression and strategies for new treatments. *Prog Neuropsychopharmacol Biol Psychiatry* 45:54-63, 2013 23602950
- Hannestad J, DellaGioia N, Bloch M: The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* 36(12):2452-2459, 2011 21796103
- Haroon E, Raison CL, Miller AH: Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology* 37(1):137-162, 2012 21918508
- Harris EC, Barraclough B: Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry* 170:205-228, 1997 9229027
- Hasin DS, Goodwin RD, Stinson FS, et al: Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry* 62(10): 1097-1106, 2005 16203955
- Hawton K, Casañas I, Comabella C, Haw C, et al: Risk factors for suicide in individuals with depression: a systematic review. *J Affect Disord* 147(1-3):17-28, 2013 23411024
- Heim C, Newport DJ, Heit S, et al: Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 284(5):592-597, 2000 10918705

- Heim C, Mletzko T, Purstelle D, et al: The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry* 63(4):398-405, 2008 17825799
- Helmer C, Montagnier D, Pérès K: Descriptive epidemiology and risk factors of depression in the elderly [in French]. *Psychol Neuropsychiatr Vieil* 2 (suppl 1):S7-S12, 2004 15899639
- Henkel V, Mergl R, Allgaier AK, et al: Treatment of depression with atypical features: a meta-analytic approach. *Psychiatry Res* 141(1):89-101, 2006 16321446
- Hiles SA, Baker AL, de Malmanche T, et al: A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. *Brain Behav Immun* 26(7): 1180-1188, 2012 22687336
- Hindmarch I: Expanding the horizons of depression: beyond the monoamine hypothesis. *Hum Psychopharmacol* 16(3): 203-218, 2001 12404573
- Hirschfeld RM: The comorbidity of major depression and anxiety disorders: recognition and management in primary care. *Prim Care Companion J Clin Psychiatry* 3(6):244-254, 2001 15014592
- Hirschfeld RM, Klerman GL, Clayton PJ, et al: Personality and depression. Empirical findings. *Arch Gen Psychiatry* 40(9):993-998, 1983 6615162
- Hollon SD, Ponniah K: A review of empirically supported psychological therapies for mood disorders in adults. *Depress Anxiety* 27(10):891-932, 2010 20830696
- Hollon SD, DeRubeis RJ, Shelton RC, et al: Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Arch Gen Psychiatry* 62(4):417-422, 2005 15809409
- Hollon SD, DeRubeis RJ, Fawcett J, et al: Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 71(10):1157-1164, 2014 25142196
- Holsboer F: The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23(5):477-501, 2000 11027914
- Holtzheimer PE, Kelley ME, Gross RE, et al: Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* 69(2):150-158, 2012 22213770
- Hosang GM, Korszun A, Jones L, et al: Adverse life event reporting and worst illness episodes in unipolar and bipolar affective



- disorders: measuring environmental risk for genetic research. *Psychol Med* 40(11):1829-1837, 2010 20132580
- Jakobsen JC, Hansen JL, Simonsen S, et al: Effects of cognitive therapy versus interpersonal psychotherapy in patients with major depressive disorder: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. *Psychol Med* 42(7):1343-1357, 2012 22051174
- Jelovac A, Kolshus E, McLoughlin DM: Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. *Neuropsychopharmacology* 38(12):2467-2474, 2013 23774532
- Joyce PR, Oakley-Browne MA, Wells JE, et al: Birth cohort trends in major depression: increasing rates and earlier onset in New Zealand. *J Affect Disord* 18(2):83-89, 1990 2137473
- Judd LL, Akiskal HS: The clinical and public health relevance of current research on subthreshold depressive symptoms to elderly patients. *Am J Geriatr Psychiatry* 10(3):233-238, 2002 11994210
- Judd LL, Rapaport MH, Paulus MP, et al: Subsyndromal symptomatic depression: a new mood disorder? *J Clin Psychiatry* 55 (suppl):18-28, 1994 8077164
- Katon WJ: Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 54(3):216-226, 2003 12893098
- Katon W, Schulberg H: Epidemiology of depression in primary care. *Gen Hosp Psychiatry* 14(4):237-247, 1992 1505745
- Keitner GI, Ryan CE, Miller IW, et al: 12-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). *Am J Psychiatry* 148(3):345-350, 1991 1992837
- Kempton MJ, Salvador Z, Munafò MR, et al: Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry* 68(7):675-690, 2011 21727252
- Kendler KS, Neale MC, Kessler RC, et al: The lifetime history of major depression in women. Reliability of diagnosis and heritability. *Arch Gen Psychiatry* 50(11):863-870, 1993 8215812
- Kendler KS, Kessler RC, Walters EE, et al: Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry* 152(6):833-842, 1995 7755111
- Kendler KS, Karkowski LM, Prescott CA: Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* 156(6):837-841, 1999 10360120

- Kennedy SH, Andersen HF, Thase ME: Escitalopram in the treatment of major depressive disorder: a meta-analysis. *Curr Med Res Opin* 25(1):161-175, 2009 19210149
- Kessler RC, McGonagle KA, Swartz M, et al: Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 29(2-3):85-96, 1993 8300981
- Kessler RC, McGonagle KA, Zhao S, et al: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 51(1):8-19, 1994 8279933
- Kessler RC, Zhao S, Blazer DG, et al: Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J Affect Disord* 45(1-2):19-30, 1997 9268772
- Kochanek KD, Xu J, Murphy SL, et al: Deaths: Final Data for 2009. *National Vital Statistics Reports Vol 60 No 3*. Hyattsville, MD, National Center for Health Statistics, 2012. Available at: [http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60\\_03.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_03.pdf). Accessed March 17, 2016.
- Krishnan V, Nestler EJ: The molecular neurobiology of depression. *Nature* 455(7215): 894-902, 2008 18923511
- Kriston L, von Wolff A, Westphal A, et al: Efficacy and acceptability of acute treatments for persistent depressive disorder: a network meta-analysis. *Depress Anxiety* 31(8):621-630, 2014 24448972
- Kupfer DJ, Frank E, Phillips ML: Major depressive disorder: new clinical, neurobiological, and treatment perspectives. *Lancet* 379(9820):1045-1055, 2012 22189047
- Lam RW, Kennedy SH, Grigoriadis S, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT): Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affect Disord* 117 (suppl 1):S26-S43, 2009 19674794
- Lampe L, Coulston CM, Berk L: Psychological management of unipolar depression. *Acta Psychiatr Scand Suppl* (443):24-37, 2013 23586874
- Lee CK, Kwak YS, Yamamoto J, et al: Psychiatric epidemiology in Korea. Part I: Gender and age differences in Seoul. *J Nerv Ment Dis* 178(4):242-246, 1990 2319232
- Lee S, Tsang A, Huang YQ, et al: The epidemiology of depression in metropolitan China. *Psychol Med* 39(5):735-747, 2009 18713484

- Levinson DF: The genetics of depression: a review. *Biol Psychiatry* 60(2):84-92, 2006 16300747
- Li X, Frye MA, Shelton RC: Review of pharmacological treatment in mood disorders and future directions for drug development. *Neuropsychopharmacology* 37(1):77-101, 2012 21900884
- Linde K, Berner MM, Kriston L: St John's wort for major depression. *Cochrane Database Syst Rev* (4):CD000448, 2008 18843608
- Lopez AD, Murray CC: The global burden of disease, 1990-2020. *Nat Med* 4(11):1241-1243, 1998 9809543
- Lopez AD, Mathers CD, Ezzati M, et al: Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 367(9524):1747-1757, 2006 16731270
- López-León S, Janssens AC, González-Zuloeta Ladd AM, et al: Meta-analyses of genetic studies on major depressive disorder. *Mol Psychiatry* 13(8):772-785, 2008 17938638
- Lozano AM, Mayberg HS, Giacobbe P, et al: Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 64(6):461-467, 2008 18639234
- Lynch D, Laws KR, McKenna PJ: Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. *Psychol Med* 40(1):9-24, 2010 19476688
- Malhi GS, Hitching R, Berk M, et al: Pharmacological management of unipolar depression. *Acta Psychiatr Scand Suppl* (443):6-23, 2013 23586873
- Mann JJ: The medical management of depression. *N Engl J Med* 353(17):1819-1834, 2005 16251538
- Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 3(11):e442, 2006 17132052
- McCusker J, Cole M, Dufouil C, et al: The prevalence and correlates of major and minor depression in older medical inpatients. *J Am Geriatr Soc* 53(8):1344-1353, 2005 16078960
- McIntyre RS, Filteau M-J, Martin L, et al: Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord* 156:1-7, 2014 24314926
- Montejo AL, Montejo L, Navarro-Cremades F: Sexual side-effects of antidepressant and antipsychotic drugs. *Curr Opin Psychiatry* 28(6):418-423, 2015 26382168

- Montgomery SA, Baldwin DS, Blier P, et al: Which antidepressants have demonstrated superior efficacy? A review of the evidence. *Int Clin Psychopharmacol* 22(6):323-329, 2007 17917550
- Murray CJ, Atkinson C, Bhalla K, et al; U.S. Burden of Disease Collaborators: The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA* 310(6):591-608, 2013 23842577
- Nemeroff CB, Vale WW: The neurobiology of depression: inroads to treatment and new drug discovery. *J Clin Psychiatry* 66 (suppl 7):5-13, 2005 16124836
- Nemeroff CB, Entsuah R, Benattia I, et al: Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. *Biol Psychiatry* 63(4):424-434, 2008 17888885
- Nestler EJ, Peña CJ, Kundakovic M, et al: Epigenetic basis of mental illness. *Neuroscientist* 22(5):447-463, 2016 26450593
- Newport DJ, Carpenter LL, McDonald WM, et al; APA Council of Research Task Force on Novel Biomarkers and Treatments: Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry* 172(10):950-966, 2015 26423481
- Nurnberg HG, Hensley PL, Heiman JR, et al: Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA* 300(4):395-404, 2008 18647982
- Oldham MA, Ciraulo DA: Bright light therapy for depression: a review of its effects on chronobiology and the autonomic nervous system. *Chronobiol Int* 31(3): 305-319, 2014 24397276
- Olfson M, Fireman B, Weissman MM, et al: Mental disorders and disability among patients in a primary care group practice. *Am J Psychiatry* 154(12):1734-1740, 1997 9396954
- Owens MJ: Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond. *J Clin Psychiatry* 65 (suppl 4):5-10, 2004 15046536
- Papakostas GI, Shelton RC, Smith J, et al: Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry* 68(6):826-831, 2007a 17592905
- Papakostas GI, Thase ME, Fava M, et al: Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis

of studies of newer agents. *Biol Psychiatry* 62(11):1217-1227, 2007b 17588546

Papakostas GI, Mischoulon D, Shyu I, et al: S-adenosyl methionine (S-AMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *Am J Psychiatry* 167(8):942-948, 2010 20595412

Papakostas GI, Fava M, Baer L, et al: Ziprasidone Augmentation of Escitalopram for Major Depressive Disorder: Efficacy Results From a Randomized, Double-Blind, Placebo-Controlled Study. *Am J Psychiatry* 172(12):1251-1258, 2015 26085041

Parikh SV, Segal ZV, Grigoriadis S, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT): Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults, II: psychotherapy alone or in combination with antidepressant medication. *J Affect Disord* 117 (suppl 1):S15-S25, 2009 19682749

Paykel ES, Cooper Z, Ramana R, et al: Life events, social support and marital relationships in the outcome of severe depression. *Psychol Med* 26(1):121-133, 1996 8643751

Piet J, Hougaard E: The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clin Psychol Rev* 31(6):1032-1040, 2011 21802618

Polyakova M, Stuke K, Schuemberg K, et al: BDNF as a biomarker for successful treatment of mood disorders: a systematic and quantitative meta-analysis. *J Affect Disord* 174:432-440, 2015 25553404

Qureshi IA, Mehler MF: An evolving view of epigenetic complexity in the brain. *Philos Trans R Soc Lond B Biol Sci* 369(1652):20130506, 2014 25135967

Raadsheer FC, Hoogendijk WJ, Stam FC, et al: Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology* 60(4):436-444, 1994 7824085

Rajkowska G: Depression: what we can learn from postmortem studies. *Neuroscientist* 9(4):273-284, 2003 12934710

Rapaport MH, Tipp JE, Schuckit MA: A comparison of ICD-10 and DSM-III-R criteria for substance abuse and dependence. *Am J Drug Alcohol Abuse* 19(2):143-151, 1993 8387239

- Reinherz HZ, Paradis AD, Giaconia RM, et al: Childhood and adolescent predictors of major depression in the transition to adulthood. *Am J Psychiatry* 160(12):2141-2147, 2003 14638584
- Rocha FL, Fuzikawa C, Riera R, et al: Combination of antidepressants in the treatment of major depressive disorder: a systematic review and meta-analysis. *J Clin Psychopharmacol* 32(2):278-281, 2012 22367652
- Rosa MA, Lisanby SH: Somatic treatments for mood disorders. *Neuropsychopharmacology* 37(1):102-116, 2012 21976043
- Ruhé HG, Huyser J, Swinkels JA, et al: Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. *J Clin Psychiatry* 67(12):1836-1855, 2006 17194261
- Rutledge T, Reis VA, Linke SE, et al: Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 48(8):1527-1537, 2006 17045884
- Sachar EJ, Hellman L, Fukushima DK, et al: Cortisol production in depressive illness. A clinical and biochemical clarification. *Arch Gen Psychiatry* 23(4):289-298, 1970 4918519
- Sackeim HA, Brannan SK, Rush AJ, et al: Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol* 10(6):817-826, 2007 17288644
- Sanacora G, Treccani G, Popoli M: Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* 62(1):63-77, 2012 21827775
- Sareen J, Cox BJ, Afifi TO, et al: Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. *Arch Gen Psychiatry* 62(11):1249-1257, 2005 16275812
- Sarris J, O'Neil A, Coulson CE, et al: Lifestyle medicine for depression. *BMC Psychiatry* 14:107, 2014 24721040
- Schlaepfer TE, Frick C, Zobel A, et al: Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med* 38(5):651-661, 2008 18177525
- Schueler YB, Koesters M, Wieseler B, et al: A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. *Acta Psychiatr Scand* 123(4):247-265, 2011 20831742

- Sher L, Oquendo MA, Galfalvy HC, et al: The relationship of aggression to suicidal behavior in depressed patients with a history of alcoholism. *Addict Behav* 30(6): 1144-1153, 2005 15925124
- Slone LB, Norris FH, Murphy AD, et al: Epidemiology of major depression in four cities in Mexico. *Depress Anxiety* 23(3):158-167, 2006 16453336
- Spina E, Trifirò G, Caraci F: Clinically significant drug interactions with newer antidepressants. *CNS Drugs* 26(1):39-67, 2012 22171584
- Stegenga BT, Kamphuis MH, King M, et al: The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL study. *Soc Psychiatry Psychiatr Epidemiol* 47(1):87-95, 2012 21057769
- Substance Abuse and Mental Health Services Administration: Results from the 2013 National Survey on Drug Use and Health: Mental Health Findings. Rockville, MD, Substance Abuse and Mental Health Services Administration, 2014
- Sullivan PF, Neale MC, Kendler KS: Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* 157(10):1552-1562, 2000 11007705
- Sun H, Kennedy PJ, Nestler EJ: Epigenetics of the depressed brain: role of histone acetylation and methylation. *Neuropsychopharmacology* 38(1):124-137, 2013 22692567
- Szegedi A, Müller MJ, Anghelescu I, et al: Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. *J Clin Psychiatry* 64(4):413-420, 2003 12716243
- Taylor MJ, Rudkin L, Bullemor-Day P, et al: Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database Syst Rev* 5: CD003382, 2013 23728643
- Tor PC, Bautovich A, Wang MJ, et al: A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. *J Clin Psychiatry* 76(9):e1092-e1098, 2015 26213985
- Udina M, Hidalgo D, Navinés R, et al: Prophylactic antidepressant treatment of interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *J Clin Psychiatry* 75(10):e1113-e1121, 2014 25373120
- Uher R: The role of genetic variation in the causation of mental illness: an evolution-informed framework. *Mol Psychiatry*

14(12):1072-1082, 2009 19704409

UK ECT Review Group: Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 361(9360):799-808, 2003 12642045

van der Velden AM, Kuyken W, Wattar U, et al: A systematic review of mechanisms of change in mindfulness-based cognitive therapy in the treatment of recurrent major depressive disorder. *Clin Psychol Rev* 37:26-39, 2015 25748559

van Melle JP, de Jonge P, Spijkerman TA, et al: Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 66(6):814-822, 2004 15564344

van Rossum EF, Binder EB, Majer M, et al: Polymorphisms of the glucocorticoid receptor gene and major depression. *Biol Psychiatry* 59(8):681-688, 2006 16580345

Warner-Schmidt JL, Duman RS: Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 16(3):239-249, 2006 16425236

Weissman MM, Klerman GL: Sex differences and the epidemiology of depression. *Arch Gen Psychiatry* 34(1):98-111, 1977 319772

Weissman MM, Gershon ES, Kidd KK, et al: Psychiatric disorders in the relatives of probands with affective disorders. The Yale University—National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry* 41(1):13-21, 1984 6691780

Weissman MM, Leaf PJ, Tischler GL, et al: Affective disorders in five United States communities. *Psychol Med* 18(1):141-153, 1988 3363034

Weissman MM, Bland RC, Canino GJ, et al: Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 276(4):293-299, 1996 8656541

Weitz ES, Hollon SD, Twisk J, et al: Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy: an individual patient data meta-analysis. *JAMA Psychiatry* 72(11):1002-1109, 2015 26397232

Wells KB, Stewart A, Hays RD, et al: The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA* 262(7):914-919, 1989 2754791

Westrin A, Lam RW: Long-term and preventative treatment for seasonal affective disorder. *CNS Drugs* 21(11):901-909, 2007 17927295



- Wirz-Justice A, Bader A, Frisch U, et al: A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *J Clin Psychiatry* 72(7):986-993, 2011 21535997
- World Health Organization: Promoting mental health: concepts, emerging evidence, practice (summary report). 2004. Available at: [www.who.int/mental\\_health/evidence/en/promoting\\_mhh.pdf](http://www.who.int/mental_health/evidence/en/promoting_mhh.pdf). Accessed March 18, 2016.
- World Health Organization: Depression. Fact sheet No. 369, October 2012. Available at: [www.who.int/mediacentre/factsheets/fs369/en/](http://www.who.int/mediacentre/factsheets/fs369/en/). Accessed March 18, 2016.
- Yoon HK, Kim YK: Association between glycogen synthase kinase-3 $\beta$  gene polymorphisms and major depression and suicidal behavior in a Korean population. *Prog Neuropsychopharmacol Biol Psychiatry* 34(2):331-334, 2010 20015462
- Zhou X, Ravindran AV, Qin B, et al: Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *J Clin Psychiatry* 76(4):e487-e498, 2015 25919841
- Zimmerman M, Chelminski I, McDermut W: Major depressive disorder and axis I diagnostic comorbidity. *J Clin Psychiatry* 63(3):187-193, 2002 11926716
- Zisook S, Lesser I, Stewart JW, et al: Effect of age at onset on the course of major depressive disorder. *Am J Psychiatry* 164(10):1539-1546, 2007 17898345

---

This chapter is an update and revision of Shaywitz J, Rapaport MH: "Treatment of Depression," in *Essentials of Clinical Psychopharmacology*, Third Edition. Edited by Schatzberg AF, Nemeroff CB. Arlington, VA, American Psychiatric Publishing, 2013, pp 577-589.

## CHAPTER 47

# Treatment of Bipolar Disorder

Paul E. Keck Jr., M.D.

Susan L. McElroy, M.D.

In this chapter, we review strategies for treating bipolar disorder, drawing primarily on data from randomized controlled trials. Where such data are lacking, strategies based on data from open trials, naturalistic studies, and expert consensus guidelines are included. The treatment of bipolar disorder in children and adolescents is covered elsewhere in this book (see [Chapter 55](#) in this volume, “Treatment of Child and Adolescent Disorders,” by Wagner and Pliszka).

---

## Treatment of Acute Bipolar Manic and Mixed Episodes

---

Manic and mixed episodes are medical emergencies and frequently require treatment in a hospital to ensure the safety of patients and those around them. The primary goal of treatment of manic and mixed episodes is rapid symptom reduction, followed by full remission of symptoms and restoration of psychosocial and vocational functioning ([Hirschfeld et al. 2002](#)).

Pharmacotherapy is the cornerstone of treatment of acute manic and mixed episodes and of bipolar disorder in general. We review medications that have shown efficacy in the treatment of acute manic and mixed episodes. Although these agents typically produce rates of response (defined as  $\geq 50\%$  reduction in manic symptoms from baseline to endpoint) of approximately 50% in short-term (3- to 4-week) trials, relatively few patients ( $<25\%$ ) actually achieve remission of symptoms within these time intervals while receiving monotherapy with any of these agents. Thus, use of combination therapy is common in clinical practice to improve response and remission rates ([Suppes et al. 2005](#)).

## Lithium

Lithium has been a mainstay of treatment for acute mania for more than 50 years, with superior efficacy compared with placebo (reviewed in [Goodwin and Jamison 2007](#)) and equivalent efficacy compared with divalproex ([Bowden et al. 1994](#)), carbamazepine ([Lerer et al. 1987](#); [Small et al. 1991](#)), risperidone ([Segal et al. 1998](#)), olanzapine ([Berk et al. 1999](#)), quetiapine ([Bowden et al. 2005](#)), aripiprazole ([Keck et al. 2003a](#)), and typical antipsychotics ([Garfinkel et al. 1980](#); [Johnson et al. 1971](#); [Platman 1970](#); [Prien et al. 1972](#); [Shopsin et al. 1975](#); [Spring et al. 1970](#); [Takahashi et](#)

[al. 1975](#)). Lithium produced improvement in psychotic as well as manic symptoms in these trials.

Lithium response for acute mania can be maximized by titrating to plasma concentrations at the upper end of the therapeutic range (1.0–1.4 mmol/L) as tolerated ([Stokes et al. 1976](#)). In randomized controlled trials, significant clinical improvement usually was reported within 7–14 days among responders ([Keck and McElroy 2001](#)). Common side effects associated with acute treatment with lithium include nausea, vomiting, tremor, somnolence, weight gain, and cognitive slowing. Lithium also may interfere with thyroid function and exacerbate renal disease; thus, monitoring of thyroid and renal function tests is an important part of lithium administration.

## Antiepileptics

### Divalproex

Divalproex and related formulations of valproic acid had superior efficacy compared with placebo ([Bowden et al. 1994, 2006](#); [Brennan et al. 1984](#); [Emrich et al. 1981](#); [Pope et al. 1991](#)) and equivalent efficacy compared with lithium ([Bowden et al. 1994](#); [Freeman et al. 1992](#)), haloperidol ([McElroy et al. 1996](#)), and olanzapine ([Zajack et al. 2002](#)) in randomized controlled treatment trials of acute bipolar manic or mixed episodes. Olanzapine was superior to divalproex as measured by mean reduction of manic symptoms and proportion of patients in remission at study completion in a second head-to-head comparison trial ([Tohen et al. 2002a](#)). [Müller-Oerlinghausen et al. \(2000\)](#) found that valproate augmentation of typical antipsychotics led to significantly lower mean antipsychotic dosages and

higher response rates compared with placebo added to typical antipsychotics in patients with acute mania.

Acute antimanic response is correlated with divalproex plasma concentrations between 50 and 125 mg/L, with some evidence of greater response at the upper end of the therapeutic range ([Allen et al. 2006](#); [Zajacka et al. 2002](#)). Some patients may require plasma concentrations greater than 125 mg/L, but side effects become progressively more prevalent above this level. Divalproex administered at a therapeutic starting dosage of 20–30 mg/kg/day has shown good tolerability in inpatients, and some evidence indicates a more rapid response than with gradual titration from a lower (e.g., 750 mg/day) starting dosage ([Hirschfeld et al. 1999](#); [Keck et al. 1993](#)).

Divalproex is generally well tolerated during treatment of acute manic or mixed episodes. Common side effects include somnolence, nausea, vomiting, tremor, weight gain, and cognitive slowing. Enteric-coated and extended-release formulations (the latter requiring a 20% dosage increase to yield plasma concentrations equivalent to those with immediate-release formulations) have improved tolerability compared with valproic acid formulations. Rare serious adverse events include pancreatitis, thrombocytopenia, significant hepatic transaminase elevation, hyperammonemic encephalopathy in patients with urea cycle disorders, and hepatic failure.

## **Carbamazepine and Oxcarbazepine**

An extended-release formulation of carbamazepine was superior to placebo in two large randomized, placebo-controlled multicenter trials ([Weisler et al. 2004b, 2005](#)). These findings replicated earlier results from a placebo-controlled crossover trial ([Ballenger and Post 1978](#)).

Common side effects of carbamazepine include diplopia, blurred vision, ataxia, somnolence, fatigue, and nausea. Less common side effects include rash, mild leukopenia and thrombocytopenia, and hyponatremia. Rare serious adverse events include agranulocytosis, aplastic anemia, hepatic failure, pancreatitis, and exfoliative dermatitis.

In the only large randomized, placebo-controlled multicenter trial of oxcarbazepine in acute mania to date, a 7-week study in children and adolescents, oxcarbazepine was not superior to placebo in reduction of manic symptoms ([Wagner et al. 2006](#)). Thus, the use of oxcarbazepine in acute bipolar mania is not supported by evidence from clinical studies but rather is based on the drug's putative similarities to carbamazepine in mechanism of action and improved tolerability.

## Antipsychotics

### Typical (First-Generation) Antipsychotics

Chlorpromazine ([Klein 1967](#)) and haloperidol ([McIntyre et al. 2005](#)) were superior to placebo in randomized controlled trials. Typical antipsychotics bear the burden of neurological and neuroendocrinological side effects and may carry an increased risk of postmanic depressive episodes ([Kukopulos et al. 1980](#)).

---

## Atypical (Second-Generation) Antipsychotics

---

The atypical antipsychotics olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, and cariprazine have all shown efficacy in the treatment of acute bipolar mania in at least two randomized, placebo-controlled trials.

Olanzapine was found to be superior to placebo ([Tohen et al. 1999, 2000](#)), superior or equal in efficacy to divalproex ([Tohen et al. 2002a](#); [Zajecka et al. 2002](#)), and comparable in efficacy to lithium ([Berk et al. 1999](#); [Niufan et al. 2008](#)), risperidone ([Perlis et al. 2006](#)), and haloperidol ([Tohen et al. 2003a](#)) in mean reduction of manic and mixed symptoms in 3- to 4-week monotherapy trials. Adjunctive treatment with olanzapine was superior to placebo in patients whose symptoms were inadequately responsive to lithium or divalproex monotherapy ([Tohen et al. 2002b](#)). In short-term studies, the most common side effects associated with olanzapine were somnolence, constipation, dry mouth, increased appetite, weight gain, and orthostatic hypotension.

Risperidone was superior to placebo ([Hirschfeld et al. 2004](#); [Khanna et al. 2005](#)) and comparable to olanzapine ([Perlis et al. 2006](#)), haloperidol ([Smulevich et al. 2005](#)), and lithium ([Segal et al. 1998](#)) in mean reduction of manic and mixed symptoms as monotherapy in 3- to 4-week trials. Risperidone was superior to placebo as an adjunctive therapy with lithium or divalproex in one placebo-controlled trial ([Sachs et al. 2002](#)), but not in a second placebo-controlled trial in combination with lithium, divalproex, or carbamazepine ([Yatham et al. 2003](#)). The rate of extrapyramidal side effects (EPS) associated with risperidone was low when the drug was administered at average dosages up to 4 mg/day ([Hirschfeld et al. 2004](#); [Sachs et al. 2002](#); [Yatham et al. 2003](#)), but not when

administered at average dosages of 6 mg/day or greater ([Khanna et al. 2005](#); [Segal et al. 1998](#)). In short-term trials, other commonly occurring side effects included prolactin elevation, akathisia, somnolence, dyspepsia, and nausea.

Quetiapine was superior to placebo as monotherapy in two 12-week studies in adult patients ([Bowden et al. 2005](#); [McIntyre et al. 2005](#)) and was comparable to lithium in a 4-week study in adult patients ([Li et al. 2008](#)). Similarly, quetiapine was superior to placebo as adjunctive treatment with lithium or divalproex ([Sachs et al. 2004](#); [Yatham et al. 2004](#)). The mean modal dosage of quetiapine associated with antimanic efficacy in most studies was approximately 600 mg/day ([Vieta et al. 2005b](#)). Quetiapine was also superior to placebo in the reduction of hypomanic or mild manic symptoms among outpatients in an 8-week trial ([McElroy et al. 2010a](#)). The most common side effects from quetiapine in monotherapy trials were headache, dry mouth, constipation, weight gain, somnolence, and dizziness.

Ziprasidone was superior to placebo (mean dosage=120–130 mg/day) in two 3-week monotherapy trials in adult patients ([Keck et al. 2003b](#); [Potkin et al. 2005](#)) and comparable to haloperidol in a 12-week trial ([Ramey et al. 2003](#)). Ziprasidone was not superior to placebo as an adjunctive treatment with lithium in a study designed to prove superior onset of action by 2 weeks of treatment ([Weisler et al. 2004a](#)). Ziprasidone-related side effects in monotherapy trials included headache, somnolence, EPS, akathisia, and dizziness.

Aripiprazole had significantly greater efficacy in the reduction of manic symptoms compared with placebo in three 3-week trials ([Keck et al. 2003a, 2007](#); [Sachs et al. 2006](#)) and equivalent efficacy compared with haloperidol



([Vieta et al. 2005a](#)) and lithium ([Keck et al. 2009](#)) in adequately powered 12-week comparison trials. Aripiprazole was initiated at 15 or 30 mg/day. Common side effects associated with aripiprazole in the placebo-controlled trials were headache, nausea, vomiting, constipation, insomnia, and akathisia.

Asenapine was superior to placebo in mean reduction of manic symptoms in two 3-week trials ([McIntyre et al. 2009, 2010](#)). Common side effects attributed to asenapine were EPS and mild weight gain.

Cariprazine, a dopamine D<sub>3</sub> and D<sub>2</sub> receptor partial agonist, was superior to placebo in reduction of manic symptoms in three randomized controlled trials ([Calabrese et al. 2015](#); [Durgam et al. 2015](#); [Sachs et al. 2015](#)). The most common side effects associated with cariprazine (occurring in  $\geq 10\%$  of subjects and at twice the rate with placebo) were akathisia, EPS, tremor, dyspepsia, and vomiting.

In the studies of atypical antipsychotics reviewed in this section, no significant differences in response were seen between patients with and patients without psychotic features or between patients with manic episodes and patients with mixed episodes among all agents, with the exception of trials of quetiapine, many of which excluded patients with mixed episodes. The prototypical atypical agent clozapine was reported to have substantial efficacy in several large case series of patients with treatment-refractory mania ([Calabrese et al. 1996](#); [Green et al. 2000](#)) but has not been studied in placebo-controlled trials in mania.

## Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is an important treatment option for manic patients with severe, psychotic, or catatonic symptoms. ECT was superior in efficacy both to lithium ([Small et al. 1988](#)) and to the combination of lithium and haloperidol ([Mukherjee et al. 1994](#)) in prospective comparison studies. In addition, ECT in combination with chlorpromazine was superior to sham ECT and chlorpromazine ([Sikdar et al. 1994](#)). Although these were small studies, their findings are consistent with those of other naturalistic studies of ECT in the treatment of acute mania ([Black et al. 1987](#); [Thomas and Reddy 1982](#)). There is a risk of neurotoxicity in patients receiving ECT while also receiving lithium; thus, lithium should be discontinued when ECT is administered ([Hirschfeld et al. 2002](#)).

## Novel Treatments

In two short-term monotherapy pilot trials ([Yildiz et al. 2008](#); [Zarate et al. 2007](#)) and one adjunctive therapy trial ([Amrollahi et al. 2011](#)), the protein kinase C inhibitor tamoxifen was superior to placebo in reduction of manic symptoms.

Placebo-controlled trials of the extended-release formulation of the atypical antipsychotic paliperidone in acute mania have thus far yielded mixed findings ([Berwaerts et al. 2011, 2012b](#); [Vieta et al. 2010](#)).

---

## Treatment of Acute Bipolar Depressive Episodes

---

The goal of treatment of bipolar depression is full remission of symptoms ([Hirschfeld et al. 2002](#)). This straightforward goal is complicated by the limited efficacy of many mood stabilizers in bipolar depression ([Zornberg and Pope 1993](#)), often requiring the adjunctive use of unimodal antidepressants with the attendant risk of cycle acceleration or switching.

## Lithium

Eight of nine placebo-controlled trials conducted in the 1960s and 1970s in patients with bipolar I and II disorders found lithium superior to placebo in acute bipolar depression (reviewed in [Zornberg and Pope 1993](#)). In an analysis of five studies in which it was possible to distinguish “unequivocal” lithium responders from patients who had partial but incomplete improvement in depression, [Zornberg and Pope \(1993\)](#) reported that 36% had an unequivocal response, compared with 79% who had partial but incomplete benefit.

## Atypical Antipsychotics

### Quetiapine

Quetiapine (300 mg/day and 600 mg/day) was superior to placebo in reduction of depressive symptoms in four large 8-week multicenter trials involving outpatients with bipolar I and II depression ([Calabrese et al. 2005a](#); [McElroy et al. 2010b](#); [Thase et al. 2006](#); [Young et al. 2010](#)). No significant difference in efficacy was found between the two quetiapine dosage groups. However, the rate of side effects was lower

in the 300 mg/day groups compared with the 600 mg/day groups. Switch rates were low across all treatment groups and were not significantly different among the quetiapine and placebo groups.

## **Olanzapine and Olanzapine-Fluoxetine Combination**

Olanzapine and the combination of olanzapine and fluoxetine (OFC) were superior to placebo in reducing depressive symptoms in an 8-week trial of 833 patients with bipolar I depression ([Tohen et al. 2003c](#)). However, the OFC was superior not only to placebo throughout the trial but also to olanzapine for weeks 4 through 8. No significant differences in switch rates (6%–7%) were found among the three groups. [Brown et al. \(2006\)](#) compared OFC with lamotrigine (titrated to 200 mg/day) in a 7-week comparison trial in outpatients with bipolar I depression. Patients receiving OFC had greater reductions in depressive symptoms compared with patients receiving lamotrigine, although the lamotrigine group may have had a greater response with a longer trial, given the need for gradual lamotrigine titration. Switch rates were not significantly different between the two groups.

## **Lurasidone**

Findings from two placebo-controlled trials indicate that lurasidone is efficacious in the treatment of bipolar I depressive episodes (reviewed by [Franklin et al. 2015](#)). Notably, the onset of therapeutic effect occurred within the first 2–3 weeks of treatment among responders. Safety data from these trials also suggest that lurasidone is significantly

less likely than other atypical agents to produce metabolic side effects.

## Antiepileptics

### Lamotrigine

In an initial large 7-week randomized, placebo-controlled trial, lamotrigine (at 50 mg/day and 200 mg/day) was superior to placebo in patients with bipolar I depression ([Calabrese et al. 1999](#)). Switch rates (3%–8%) were not significantly different among the three groups. A second large placebo-controlled, parallel-group, flexible-dose trial involving patients with bipolar I and II depression did not find a significant advantage for lamotrigine over placebo ([Bowden 2001](#)). In a double-blind crossover trial, [Frye et al. \(2000\)](#) found lamotrigine superior to placebo in improving depression in patients with treatment-refractory rapid-cycling bipolar I or II disorder. Lamotrigine was superior to placebo when added to lithium treatment in an 8-week trial in patients with breakthrough depressive episodes ([van der Loos et al. 2009](#)). Common side effects of lamotrigine in these studies included headache, nausea, infection, and xerostomia. The risk of serious rash from lamotrigine can be reduced by carefully adhering to recommended titration schedules ([GlaxoSmithKline 2016](#)), but patients should be warned of the risk of rash and of the need to report any such symptoms immediately.

### Carbamazepine

In two small controlled trials in patients with treatment-refractory bipolar depression, response to carbamazepine

was superior to that seen with placebo (Post et al. 1986) or lithium ([Small 1990](#)). The results of these initial intriguing findings have not been followed by large placebo-controlled, parallel-group studies.

## **Divalproex**

Two small randomized, placebo-controlled trials of divalproex in the treatment of acute bipolar depression yielded opposite findings. [Sachs and Collins \(2001\)](#) did not find divalproex to be superior to placebo in one pilot trial, whereas [Davis et al. \(2005\)](#) found divalproex superior to placebo in reduction of depressive and anxiety symptoms in a later pilot study.

## **Antidepressants**

Because of the meager evidence base, current recommendations regarding the use of antidepressants in conjunction with mood stabilizers for acute bipolar I depression tend toward the conservative (i.e., avoid antidepressants if possible). However, some general impressions can be gleaned from the available clinical trials. First, switch rates associated with newer antidepressants in short-term trials, in general, appear to be lower than those associated with tricyclic antidepressants (TCAs) in older studies ([Thase and Sachs 2000](#)). Second, among all of the antidepressants studied, the most substantial evidence for efficacy rests with the monoamine oxidase inhibitor (MAOI) tranylcypromine ([Himmelhoch et al. 1991](#)), but safety concerns often eliminate this agent from first-line therapy choices ([Hirschfeld et al. 2002](#)). Bupropion ([Sachs et al. 1994](#)) and

selective serotonin reuptake inhibitors (SSRIs) ([Nemeroff et al. 2001](#)) are common first-line agents administered in conjunction with mood stabilizers.

## Electroconvulsive Therapy

ECT had significantly greater efficacy than MAOIs, TCAs, or placebo in several randomized controlled trials in patients with bipolar depression (reviewed in [Zornberg and Pope 1993](#)). ECT may be particularly indicated for patients with severe, psychotic, or catatonic symptoms.

## Psychotherapy

Very few randomized controlled trials of any form of psychotherapy for patients with acute bipolar depression have been conducted. Cognitive-behavioral and interpersonal therapy have demonstrated efficacy in the treatment of unipolar major depression, but these modalities have been examined only in very small preliminary studies in patients with bipolar depression, thus far without conclusive findings ([Cole et al. 2002](#); [Zaretsky et al. 1999](#)).

## Novel Treatments

Two preliminary placebo-controlled trials found the dopamine D<sub>2</sub> and D<sub>3</sub> receptor agonist pramipexole superior to placebo in the adjunctive treatment of depression in patients with bipolar I or bipolar II disorder ([Goldberg et al.](#)

2004; Zarate et al. 2004). Switch rates with pramipexole did not differ significantly from those with placebo.

In a 1-week placebo-controlled trial, Watson et al. (2012) examined the efficacy of mifepristone in improvement in spatial working memory in 60 patients with bipolar depression. They found that mifepristone (600 mg/day) treatment was associated with sustained improvement in spatial working memory as an independent variable apart from improvement in depressive symptoms.

---

## Maintenance Treatment

---

Bipolar disorder is a recurrent lifelong illness in more than 90% of the patients who experience a manic episode (Goodwin and Jamison 2007). Because of the high risk of recurrence and morbidity associated with mood episodes and interepisode symptoms, maintenance treatment is usually recommended after a single manic episode (Hirschfeld et al. 2002). The goals of maintenance treatment include prevention of syndromal relapse and subsyndromal symptoms, optimization of functioning, and prevention of suicide.

### Lithium

Lithium is the most extensively studied medication in the maintenance treatment of bipolar disorder. Data from randomized, placebo-controlled trials conducted in the 1960s and 1970s indicated that lithium protected against relapse, with a fourfold lower risk compared with placebo at 6-month and 1-year follow-up (Keck et al. 2000). Lithium



was superior to placebo in preventing relapse into mania in two randomized controlled parallel-group trials lasting 18 months ([Bowden et al. 2003](#); [Calabrese et al. 2003](#)).

The optimal maintenance lithium serum concentration is an important consideration in successful maintenance treatment. Maintenance lithium serum concentrations usually are lower than those required to produce acute antimanic efficacy. However, studies by [Gelenberg et al. \(1989\)](#) and [Keller et al. \(1992\)](#) found a serum level-response relationship, with levels of 0.4–0.6 mEq/L being associated with 2.6 times the relapse rate and a significantly greater likelihood of experiencing subsyndromal symptoms compared with levels of 0.8 mEq/L or higher. There was also a serum level-side effect relationship, with patients at higher levels experiencing significantly higher rates of side effects, often leading to discontinuation. [Perlis et al. \(2002\)](#), in yet another reanalysis of the [Gelenberg et al. \(1989\)](#) data, reported that an abrupt drop in serum lithium levels, whether due to random reassignment or to nonadherence, was the most powerful predictor of relapse. The optimal lithium level for many patients will be the level that balances relapse prevention and suppression of subsyndromal symptoms against minimization of bothersome day-to-day side effects.

## Antiepileptics

Two large 18-month placebo-controlled maintenance trials comparing lamotrigine (200–400 mg/day) with lithium (0.8–1.1 mEq/L) found lamotrigine, but not lithium, superior to placebo in preventing depressive episodes ([Bowden et al. 2003](#); [Calabrese et al. 2003](#)). In contrast, lithium, but not

lamotrigine, was superior to placebo in preventing manic episodes. Of the nearly 1,200 patients who received lamotrigine in these trials, 9% developed a benign rash (morbilliform or exanthematous eruptions), compared with 8% of the 1,056 patients receiving placebo. When patients who received lamotrigine during the open-label run-in phase of the studies were included in the analysis, the total incidence of rash was 13%, with two cases of serious rash requiring hospitalization ([Calabrese 2002](#)).

[Calabrese et al. \(2000\)](#) conducted a 6-month placebo-controlled relapse prevention study of lamotrigine (mean dosage=288 mg/day) in 182 patients with rapid-cycling bipolar I or II disorder. There was no significant difference between the lamotrigine and the placebo treatment groups in time to need for additional medications for recurrent mood symptoms.

The only randomized, placebo-controlled maintenance study of divalproex in bipolar I disorder found no significant difference in time to development of any mood episode among patients receiving divalproex, lithium, or placebo ([Bowden et al. 2000](#)). A number of unforeseen methodological limitations in this trial complicated interpretation of its results. Among patients who received divalproex for treatment of the index manic episode in an open treatment period prior to randomization, divalproex was superior to placebo on rates of early termination due to any mood episode (29% vs. 50%) during the subsequent year. Divalproex was also compared with olanzapine in a 47-week blinded maintenance trial ([Tohen et al. 2003b](#)). [Calabrese et al. \(2005b\)](#) compared divalproex with lithium in a 20-month study of patients with rapid-cycling bipolar disorder and found comparable relapse rates in both treatment groups.

There are no data regarding the optimal maintenance valproic acid concentration in bipolar disorder. Current practice usually consists of titrating to therapeutic serum concentrations (50–125 µg/mL) and, as with lithium, balancing relapse and subsyndromal symptom prevention against minimization of side effects ([Hirschfeld et al. 2002](#)). Treatment with valproate appears to pose an increased risk of polycystic ovarian syndrome (PCOS), although the relationship between PCOS and weight gain as a possible mechanism is unclear ([Hirschfeld et al. 2002](#)).

Although a number of studies have examined the efficacy of carbamazepine in the maintenance treatment of bipolar disorder, most of these studies yielded results that were difficult to reliably interpret on methodological grounds ([Dardennes et al. 1995](#)).

## Atypical Antipsychotics

Olanzapine was comparable to divalproex in a 47-week comparison trial ([Tohen et al. 2003b](#)) and to lithium in a 1-year comparison trial ([Tohen et al. 2005](#)). Olanzapine received an indication for maintenance treatment in bipolar disorder based on superiority over placebo in prevention of manic and depressive episodes over 48 weeks ([Tohen et al. 2006](#)). The combination of olanzapine and lithium or divalproex was superior to placebo and lithium or divalproex in relapse prevention over 18 months in patients who had initially responded to the active combination acutely ([Tohen et al. 2002b](#)) and then were re-randomized ([Tohen et al. 2004](#)). However, patients in the combination therapy group had twice the weight gain of patients in the monotherapy group.

Aripiprazole was superior to placebo in preventing manic relapse over a 6-month follow-up period in patients with bipolar disorder who were initially stabilized on aripiprazole monotherapy for an acute manic or mixed episode ([Keck et al. 2006, 2007](#)). By contrast, no significant difference between aripiprazole and placebo was found for rates of depressive relapse. However, the overall low rate of depressive relapse in this trial may have been due to the inclusion of patients whose index episodes were manic or mixed rather than depressive.

Two 104-week adjunctive placebo-controlled trials found quetiapine in combination with lithium or divalproex to be superior to placebo with lithium or divalproex in prolonging time to recurrence of a mood episode ([Suppes et al. 2009](#); [Vieta et al. 2008](#)). The quetiapine combination groups also had lower proportions of patients experiencing a mood event.

In a 6-month maintenance trial, ziprasidone was superior to placebo in combination with lithium or divalproex in prolonging time to intervention for a mood episode and in proportion of patients requiring an intervention during the length of the trial ([Bowden et al. 2010](#)).

In two randomized controlled trials, risperidone (long-acting injectable formulation) was found to be superior to placebo in prevention of relapse, both as monotherapy and as adjunctive therapy ([Quiroz et al. 2010](#); [Vieta et al. 2012](#)).

Evidence from one placebo-controlled trial suggests that paliperidone extended release may be efficacious as a maintenance treatment in patients with bipolar disorder ([Berwaerts et al. 2012a](#)).

## Electroconvulsive Therapy

The use of ECT in the maintenance treatment of bipolar disorder has never been studied systematically in a randomized controlled trial. However, several naturalistic studies suggest that maintenance ECT may be a useful treatment alternative for patients whose symptoms are inadequately responsive to pharmacotherapy ([Schwarz et al. 1995](#); [Vanelle et al. 1994](#)).

## Psychotherapy

Most patients with bipolar disorder experience a common cluster of psychological problems stemming directly from the illness. A number of specific psychosocial interventions as adjuncts to mood stabilizer therapy have been shown to improve the long-term outcome of bipolar disorder (reviewed in [Rizvi and Zaretsky 2007](#)). The best-studied interventions include educational, interpersonal, family, and cognitive-behavioral therapies. Randomized controlled trials conducted over 1- to 2-year follow-up periods support the efficacy of cognitive-behavioral therapy ([Lam et al. 2005](#)), family-focused and related forms of therapy ([Clarkin et al. 1990, 1998](#); [Miklowitz et al. 2003](#); [Rea et al. 2003](#)), interpersonal and social rhythm therapies ([Frank et al. 2005](#)), and group psychoeducation ([Colom et al. 2003](#)) in reducing or delaying mood episode recurrence, increasing treatment adherence, and improving functioning. Family-focused, interpersonal, and social rhythm therapies were all associated with delaying time to depressive episode relapse compared with brief treatment ([Miklowitz et al. 2007](#)).

---

## Conclusion

---

There have been substantial advances in the pharmacological treatment of bipolar disorder in the past two decades. A number of medications have demonstrated efficacy in the treatment of acute mania in placebo-controlled trials, either as monotherapy or as an adjunct to mood stabilizers. In addition, available data indicate that combination therapy with an antipsychotic and a mood stabilizer is more rapidly effective, with better overall response rates in acute mania, than either mood stabilizers or antipsychotics alone.

The treatment of bipolar depression remains one of the least-studied aspects of the illness. The “mood stabilizer first” strategy and the combined use of mood stabilizers and antidepressants in moderate to severe bipolar depression are common approaches.

Most patients with bipolar disorder require treatment with more than one medication during the course of their illness. The efficacy of combination strategies is only now receiving close scrutiny. Recent studies suggest that for some patients, the use of combinations of antidepressants and mood stabilizers as maintenance treatment may be important to prevent depressive relapse.

The role and efficacy of different types of psychotherapy at different phases of illness management in bipolar disorder are now becoming clearly established. These components of treatment are important in educating patients and families, improving insight and treatment adherence, enhancing coping skills, and dealing with the sequelae of mood symptoms and episodes—and, it is hoped, improving functioning and outcome. Treatment advances in bipolar disorder are finally occurring rapidly. Bringing these treatments to patients with bipolar disorder is both

the challenge and the reward of helping people manage this illness.

---

## References

---

- Allen MH, Hirschfeld RM, Wozniak PJ, et al: Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *Am J Psychiatry* 163(2):272-275, 2006 16449481
- Amrollahi Z, Rezaei F, Salehi B, et al: Double-blind, randomized, placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania. *J Affect Disord* 129(1-3):327-331, 2011 20843556
- Ballenger JC, Post RM: Therapeutic effects of carbamazepine in affective illness: a preliminary report. *Commun Psychopharmacol* 2(2):159-175, 1978 352607
- Berk M, Ichim L, Brook S: Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int Clin Psychopharmacol* 14(6):339-343, 1999 10565800
- Berwaerts J, Lane R, Nuamah IF, et al: Paliperidone extended-release as adjunctive therapy to lithium or valproate in the treatment of acute mania: a randomized, placebo-controlled study. *J Affect Disord* 129(1-3):252-260, 2011 20947174
- Berwaerts J, Melkote R, Nuamah I, et al: A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. *J Affect Disord* 138(3):247-258, 2012a 22377512
- Berwaerts J, Xu H, Nuamah I, et al: Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-

blind, dose-response study. *J Affect Disord* 136(1-2):e51-e60, 2012b 20624657

Black DW, Winokur G, Nasrallah A: Treatment of mania: a naturalistic study of electroconvulsive therapy versus lithium in 438 patients. *J Clin Psychiatry* 48(4):132-139, 1987 3104316

Bowden CL: Novel treatments for bipolar disorder. *Expert Opin Investig Drugs* 10(4):661-671, 2001 11281816

Bowden CL, Brugger AM, Swann AC, et al; The Depakote Mania Study Group: Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA* 271(12):918-924, 1994 8120960

Bowden CL, Calabrese JR, McElroy SL, et al; Divalproex Maintenance Study Group: A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry* 57:481-489, 2000 10807488

Bowden CL, Calabrese JR, Sachs G, et al; Lamictal 606 Study Group: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 60(4):392-400, 2003 12695317

Bowden CL, Grunze H, Mullen J, et al: A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 66(1):111-121, 2005 15669897

Bowden CL, Swann AC, Calabrese JR, et al; Depakote ER Mania Study Group: A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry* 67(10):1501-1510, 2006 17107240

Bowden CL, Vieta E, Ice KS, et al: Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month,



- randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 71(2):130-137, 2010 20122373
- Brennan MJ, Sandyk R, Borsook D: Use of sodium valproate in the management of affective disorders: basic and clinical aspects, in *Anticonvulsants in Affective Disorders*. Edited by Emrich HM, Okuma T, Muller AA. Amsterdam, Excerpta Medica, 1984, pp 56-65
- Brown EB, McElroy SL, Keck PE Jr, et al: A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry* 67(7): 1025-1033, 2006 16889444
- Calabrese JR: *Clinical Relevance and Management of Bipolar Disorders: Weighing Benefits Versus Risks (Presentations in Focus)*. New York, Medical Education Network, 2002
- Calabrese JR, Kimmel SE, Woyshville MJ, et al: Clozapine for treatment-refractory mania. *Am J Psychiatry* 153(6):759-764, 1996 8633686
- Calabrese JR, Bowden CL, Sachs GS, et al: A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 60:79-88, 1999 10084633
- Calabrese JR, Suppes T, Bowden CL, et al: A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry* 61(11): 841-850, 2000 11105737
- Calabrese JR, Bowden CL, Sachs G, et al; Lamictal 605 Study Group: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 64(9):1013-1024, 2003 14628976
- Calabrese JR, Keck PE Jr, Macfadden W, et al: A randomized, double-blind, placebo-controlled trial of

- quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 162(7):1351-1360, 2005a 15994719
- Calabrese JR, Shelton MD, Rapport DJ, et al: A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 162(11):2152-2161, 2005b 16263857
- Calabrese JR, Keck PE Jr, Starace A, et al: Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry* 76(3):284-292, 2015 25562205
- Clarkin JF, Glick ID, Haas GL, et al: A randomized clinical trial of inpatient family intervention, V: results for affective disorders. *J Affect Disord* 18(1):17-28, 1990 2136866
- Clarkin JF, Carpenter D, Hull J, et al: Effects of psychoeducational intervention for married patients with bipolar disorder and their spouses. *Psychiatr Serv* 49(4):531-533, 1998 9550248
- Cole DP, Thase ME, Mallinger AG, et al: Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. *Am J Psychiatry* 159(1):116-121, 2002 11772699
- Colom F, Vieta E, Martinez-Aran A, et al: A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry* 60(4):402-407, 2003 12695318
- Dardennes R, Even C, Bange F, et al: Comparison of carbamazepine and lithium in the prophylaxis of bipolar disorders: a meta-analysis. *Br J Psychiatry* 166(3):378-381, 1995 7788131
- Davis LL, Bartolucci A, Petty F: Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord* 85(3):259-266, 2005 15780695

- Durgam S, Starace A, Li D, et al: The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *Bipolar Disord* 17(1):63-75, 2015 25056368
- Emrich HM, von Zerssen D, Kissling W: On a possible role of GABA in mania: therapeutic efficacy of sodium valproate, in *GABA and Benzodiazepine Receptors*. Edited by Costa E, Dicharia G, Gessa GL. New York, Raven, 1981, pp 287-296
- Frank E, Kupfer DJ, Thase ME, et al: Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch Gen Psychiatry* 62(9):996-1004, 2005 16143731
- Franklin R, Zorowitz S, Corse AK, et al: Lurasidone for the treatment of bipolar depression: an evidence-based review. *Neuropsychiatr Dis Treat* 11:2143-2152, 2015 26316760
- Freeman TW, Clothier JL, Pazzaglia P, et al: A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry* 149(1):108-111, 1992 1728157
- Frye MA, Ketter TA, Kimbrell TA, et al: A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 20(6):607-614, 2000 11106131
- Garfinkel PE, Stancer HC, Persad E: A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. *J Affect Disord* 2(4):279-288, 1980 6450787
- Gelenberg AJ, Kane JM, Keller MB, et al: Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. *N Engl J Med* 321(22):1489-1493, 1989 2811970
- GlaxoSmithKline: Lamictal (lamotrigine) full prescribing information. Research Triangle Park, NC, GlaxoSmithKline, March 4, 2016. Available at:

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d7e3572d-56fe-4727-2bb4-013ccca22678>.

Accessed May 4, 2016.

- Goldberg JF, Burdick KE, Endick CJ: Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 161(3):564-566, 2004 14992985
- Goodwin FK, Jamison KR: *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. New York, Oxford University Press, 2007
- Green AI, Tohen M, Patel JK, et al: Clozapine in the treatment of refractory psychotic mania. *Am J Psychiatry* 157(6):982-986, 2000 10831480
- Himmelhoch JM, Thase ME, Mallinger AG, et al: Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry* 148(7):910-916, 1991 2053632
- Hirschfeld RM, Allen MH, McEvoy JP, et al: Safety and tolerability of oral loading divalproex sodium in acutely manic bipolar patients. *J Clin Psychiatry* 60(12):815-818, 1999 10665626
- Hirschfeld RM, Bowden CL, Gitlin MJ, et al; American Psychiatric Association: Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 159 (4 suppl):1-50, 2002 11958165
- Hirschfeld RM, Keck PE Jr, Kramer M, et al: Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry* 161(6):1057-1065, 2004 15169694
- Johnson G, Gershon S, Burdock EI, et al: Comparative effects of lithium and chlorpromazine in the treatment of acute manic states. *Br J Psychiatry* 119(550):267-276, 1971 4936131
- Keck PE Jr, McElroy SL: Definition, evaluation, and management of treatment refractory mania.

- Psychopharmacol Bull 35(4):130-148, 2001 12397862
- Keck PE Jr, McElroy SL, Tugrul KC, et al: Valproate oral loading in the treatment of acute mania. J Clin Psychiatry 54(8):305-308, 1993 8253698
- Keck PE Jr, Welge JA, Strakowski SM, et al: Placebo effect in randomized, controlled maintenance studies of patients with bipolar disorder. Biol Psychiatry 47(8):756-761, 2000 10773185
- Keck PE Jr, Marcus R, Tourkodimitris S, et al; Aripiprazole Study Group: A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 160(9):1651-1658, 2003a 12944341
- Keck PE Jr, Versiani M, Potkin S, et al; Ziprasidone in Mania Study Group: Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. Am J Psychiatry 160(4):741-748, 2003b 12668364
- Keck PE Jr, Calabrese JR, McQuade RD, et al; Aripiprazole Study Group: A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry 67(4):626-637, 2006 16669728
- Keck PE Jr, Calabrese JR, McIntyre RS, et al; Aripiprazole Study Group: Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 68(10):1480-1491, 2007 17960961
- Keck PE Jr, Orsulak PJ, Cutler AJ, et al; CN138-135 Study Group: Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. J Affect Disord 112(1-3):36-49, 2009 18835043
- Keller MB, Lavori PW, Kane JM, et al: Subsyndromal symptoms in bipolar disorder: a comparison of standard

- and low serum levels of lithium. *Arch Gen Psychiatry* 49(5):371-376, 1992 1586272
- Khanna S, Vieta E, Lyons B, et al: Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry* 187:229-234, 2005 16135859
- Klein DF: Importance of psychiatric diagnosis in prediction of clinical drug effects. *Arch Gen Psychiatry* 16(1):118-126, 1967 5333776
- Kukopulos A, Reginaldi D, Laddomada P, et al: Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr Neuropsychopharmakol* 13(4):156-167, 1980 6108577
- Lam DH, Hayward P, Watkins ER, et al: Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. *Am J Psychiatry* 162(2):324-329, 2005 15677598
- Lerer B, Moore N, Meyendorff E, et al: Carbamazepine versus lithium in mania: a double-blind study. *J Clin Psychiatry* 48(3):89-93, 1987 3546274
- Li H, Ma C, Wang G, et al: Response and remission rates in Chinese patients with bipolar mania treated for 4 weeks with either quetiapine or lithium: a randomized and double-blind study. *Curr Med Res Opin* 24(1):1-10, 2008 18028587
- McElroy SL, Keck PE Jr, Stanton SP, et al: A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. *J Clin Psychiatry* 57(4):142-146, 1996 8601548
- McElroy SL, Martens BE, Winstanley EL, et al: Placebo-controlled study of quetiapine monotherapy in ambulatory bipolar spectrum disorder with moderate-to-severe hypomania or mild mania. *J Affect Disord* 124(1-2):157-163, 2010a 19963274
- McElroy SL, Weisler RH, Chang W, et al; EMBOLDEN II (Trial D1447C00134) Investigators: A double-blind,

placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry* 71(2):163–174, 2010b 20122366

McIntyre RS, Brecher M, Paulsson B, et al: Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol* 15(5):573–585, 2005 16139175

McIntyre RS, Cohen M, Zhao J, et al: A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord* 11(7):673–686, 2009 19839993

McIntyre RS, Cohen M, Zhao J, et al: Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 122(1–2):27–38, 2010 20096936

Miklowitz DJ, George EL, Richards JA, et al: A randomized study of family focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Arch Gen Psychiatry* 60(9):904–912, 2003 12963672

Miklowitz DJ, Otto MW, Frank E, et al: Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *Arch Gen Psychiatry* 64(4):419–426, 2007 17404119

Mukherjee S, Sackeim HA, Schnur DB: Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. *Am J Psychiatry* 151(2):169–176, 1994 8296883

Müller-Oerlinghausen B, Retzow A, Henn FA, et al; European Valproate Mania Study Group: Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized,

- double-blind, placebo-controlled, multicenter study. *J Clin Psychopharmacol* 20(2):195-203, 2000 10770458
- Nemeroff CB, Evans DL, Gyulai L, et al: Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry* 158(6):906-912, 2001 11384898
- Niufan F, Tohen M, Qiuqing A, et al: Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. *J Affect Disord* 23: 105(1-3):101-108, 2008 17531327
- Perlis RH, Sachs GS, Lafer B, et al: Effect of abrupt change from standard to low serum levels of lithium: a reanalysis of double-blind lithium maintenance data. *Am J Psychiatry* 159(7):1155-1159, 2002 12091193
- Perlis RH, Baker RW, Zarate CA Jr, et al: Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry* 67(11):1747-1753, 2006 17196055
- Platman SR: A comparison of lithium carbonate and chlorpromazine in mania. *Am J Psychiatry* 127(3):351-353, 1970 4917856
- Pope HG Jr, McElroy SL, Keck PE Jr, et al: Valproate in the treatment of acute mania. A placebo-controlled study. *Arch Gen Psychiatry* 48(1):62-68, 1991 1984763
- Post RM, Uhde TW, Roy-Byrne PP, et al: Antidepressant effects of carbamazepine. *Am J Psychiatry* 143(1):29-34, 1986 3510572
- Potkin SG, Keck PE Jr, Segal S, et al: Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol* 25(4):301-310, 2005 16012271
- Prien RF, Caffey EM Jr, Klett CJ: Comparison of lithium carbonate and chlorpromazine in the treatment of mania. Report of the Veterans Administration and National Institute of Mental Health Collaborative Study



- Group. Arch Gen Psychiatry 26(2):146-153, 1972 4551257
- Quiroz JA, Yatham LN, Palumbo JM, et al: Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry 68(2):156-162, 2010 20227682
- Ramey TS, Giller EL, English EP: Ziprasidone efficacy and safety in acute bipolar mania: a 12-week study. Abstracts of the 6th International Conference on Bipolar Disorders, Pittsburgh, PA, June 16, 2003
- Rea MM, Tompson MC, Miklowitz DJ, et al: Family focused treatment versus individual treatment for bipolar disorder: results of a randomized clinical trial. J Consult Clin Psychol 71(3):482-492, 2003 12795572
- Rizvi S, Zaretsky AE: Psychotherapy through the phases of bipolar disorder: evidence for general efficacy and differential effects. J Clin Psychol 63(5):491-506, 2007 17417815
- Sachs GS, Collins MC: A placebo-controlled trial of divalproex sodium in acute bipolar depression. Presented at the American College of Neuropsychopharmacology Annual Meeting, San Juan, PR, December 2001
- Sachs GS, Lafer B, Stoll AL, et al: A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 55(9):391-393, 1994 7929019
- Sachs GS, Grossman F, Ghaemi SN, et al: Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 159(7):1146-1154, 2002 12091192
- Sachs G, Chengappa KN, Suppes T, et al: Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord 6(3):213-223, 2004 15117400

- Sachs G, Sanchez R, Marcus R, et al; Aripiprazole Study Group: Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol* 20(4):536-546, 2006 16401666
- Sachs GS, Greenberg WM, Starace A, et al: Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord* 174:296-302, 2015 25532076
- Schwarz T, Loewenstein J, Isenberg KE: Maintenance ECT: indications and outcome. *Convuls Ther* 11(1):14-23, 1995 7796063
- Segal J, Berk M, Brook S: Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clin Neuropharmacol* 21(3):176-180, 1998 9617509
- Shopsin B, Gershon S, Thompson H, et al: Psychoactive drugs in mania. A controlled comparison of lithium carbonate, chlorpromazine, and haloperidol. *Arch Gen Psychiatry* 32(1):34-42, 1975 1089401
- Sikdar S, Kulhara P, Avasthi A, et al: Combined chlorpromazine and electroconvulsive therapy in mania. *Br J Psychiatry* 164(6):806-810, 1994 7952988
- Small JG: Anticonvulsants in affective disorders. *Psychopharmacol Bull* 26(1):25-36, 1990 2196624
- Small JG, Klapper MH, Kellams JJ, et al: Electroconvulsive treatment compared with lithium in the management of manic states. *Arch Gen Psychiatry* 45(8):727-732, 1988 2899425
- Small JG, Klapper MH, Milstein V, et al: Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry* 48(10):915-921, 1991 1929761
- Smulevich AB, Khanna S, Eerdekens M, et al: Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week

- double-blind trial of risperidone and haloperidol. *Eur Neuropsychopharmacol* 15(1):75-84, 2005 15572276
- Spring G, Schweid D, Gray C, et al: A double-blind comparison of lithium and chlorpromazine in the treatment of manic states. *Am J Psychiatry* 126(9):1306-1310, 1970 4905019
- Stokes PE, Kocsis JH, Arcuni OJ: Relationship of lithium chloride dose to treatment response in acute mania. *Arch Gen Psychiatry* 33(9):1080-1084, 1976 17642108
- Suppes T, Dennehy EB, Hirschfeld RM, et al; Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder: The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry* 66(7):870-886, 2005 16013903
- Suppes T, Vieta E, Liu S, et al; Trial 127 Investigators: Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). *Am J Psychiatry* 166(4):476-488, 2009 19289454
- Takahashi R, Sakuma A, Itoh K, et al: Comparison of efficacy of lithium carbonate and chlorpromazine in mania. Report of collaborative study group on treatment of mania in Japan. *Arch Gen Psychiatry* 32(10):1310-1318, 1975 1101844
- Thase ME, Sachs GS: Bipolar depression: pharmacotherapy and related therapeutic strategies. *Biol Psychiatry* 48(6):558-572, 2000 11018227
- Thase ME, Macfadden W, Weisler RH, et al; BOLDER II Study Group: Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 26(6):600-609, 2006 17110817
- Thomas J, Reddy B: The treatment of mania. A retrospective evaluation of the effects of ECT, chlorpromazine, and

- lithium. *J Affect Disord* 4(2):85-92, 1982 6213694
- Tohen M, Sanger TM, McElroy SL, et al; Olanzapine HGEH Study Group: Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry* 156(5):702-709, 1999 10327902
- Tohen M, Jacobs TG, Grundy SL, et al; The Olanzapine HGGW Study Group: Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 57(9):841-849, 2000 10986547
- Tohen M, Baker RW, Altshuler LL, et al: Olanzapine versus divalproex in the treatment of acute mania. *Am J Psychiatry* 159(6):1011-1017, 2002a 12042191
- Tohen M, Chengappa KNR, Suppes T, et al: Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry* 59(1):62-69, 2002b 11779284
- Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al: A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Arch Gen Psychiatry* 60(12):1218-1226, 2003a 14662554
- Tohen M, Ketter TA, Zarate CA Jr, et al: Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry* 160(7):1263-1271, 2003b 12832240
- Tohen M, Vieta E, Calabrese J, et al: Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 60(11):1079-1088, 2003c 14609883
- Tohen M, Chengappa KN, Suppes T, et al: Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry* 184:337-345, 2004 15056579
- Tohen M, Greil W, Calabrese JR, et al: Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind,

- controlled clinical trial. *Am J Psychiatry* 162(7):1281-1290, 2005 15994710
- Tohen M, Calabrese JR, Sachs GS, et al: Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry* 163(2):247-256, 2006 16449478
- van der Loos ML, Mulder PG, Hartong EG, et al; LamLit Study Group: Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 70(2):223-231, 2009 19200421
- Vanelle JM, Loo H, Galinowski A, et al: Maintenance ECT in intractable manic-depressive disorders. *Convuls Ther* 10(3):195-205, 1994 7834256
- Vieta E, Bourin M, Sanchez R, et al; Aripiprazole Study Group: Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry* 187:235-242, 2005a 16135860
- Vieta E, Mullen J, Brecher M, et al: Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. *Curr Med Res Opin* 21(6):923-934, 2005b 15969892
- Vieta E, Suppes T, Eggers I, et al: Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord* 109(3):251-263, 2008 18579216
- Vieta E, Nuamah IF, Lim P, et al: A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord* 12(3):230-243, 2010 20565430

- Vieta E, Montgomery S, Sulaiman AH, et al: A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol* 22(11):825-835, 2012 22503488
- Wagner KD, Kowatch RA, Emslie GJ, et al: A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry* 163(7):1179-1186, 2006 16816222
- Watson S, Gallagher P, Porter RJ, et al; North-East Mood Disorders Clinical Research Group: A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. *Biol Psychiatry* 72(11):943-949, 2012 22770649
- Weisler RH, Dunn J, English P: Ziprasidone adjunctive treatment of acute bipolar mania: a randomized, double-blind placebo-controlled trial. Abstracts of the 16th Annual Meeting of the European College of Neuropsychopharmacology, Prague, Czech Republic, September 24, 2004a
- Weisler RH, Kalali AH, Ketter TA; SPD417 Study Group: A multicenter, randomized, double-blind, placebo-controlled trial of extended release carbamazepine capsules as monotherapy for bipolar patients with manic or mixed episodes. *J Clin Psychiatry* 65:478-484, 2004b 15119909
- Weisler RH, Keck PE Jr, Swann AC, et al; SPD417 Study Group: Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 66(3):323-330, 2005 15766298

- Yatham LN, Grossman F, Augustyns I, et al: Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. *Br J Psychiatry* 182:141-147, 2003 12562742
- Yatham LN, Paulsson B, Mullen J, et al: Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol* 24(6):599-606, 2004 15538120
- Yildiz A, Guleryuz S, Ankerst DP, et al: Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. *Arch Gen Psychiatry* 65(3):255-263, 2008 18316672
- Young AH, McElroy SL, Bauer M, et al; EMBOLDEN I (Trial 001) Investigators: A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 71(2):150-162, 2010 20122369
- Zajecka JM, Weisler R, Sachs G, et al: A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *J Clin Psychiatry* 63(12):1148-1155, 2002 12523875
- Zarate CA Jr, Payne JL, Singh J, et al: Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry* 56(1):54-60, 2004 15219473
- Zarate CA Jr, Singh JB, Carlson PJ, et al: Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar Disord* 9(6):561-570, 2007 17845270
- Zaretsky AE, Segal ZV, Gamar M: Cognitive therapy for bipolar depression: a pilot study. *Can J Psychiatry* 44(5):491-494, 1999 10389612
- Zornberg GL, Pope HG Jr: Treatment of depression in bipolar disorder: new directions for research. *J Clin Psychopharmacol* 13(6):397-408, 1993 8120153

## CHAPTER 48

# Treatment of Anxiety and Related Disorders

Daniella David, M.D.

Jonathan R.T. Davidson, M.D.

Over the past two decades, there has been substantial progress in the treatment of anxiety and related disorders. In this chapter, we review the main findings from double-blind and some open-label trials in each disorder.

---

## Panic Disorder

---

Treatment outcome in panic disorder can be measured with the Panic Disorder Severity Scale (PDSS), which can be administered both as a clinician-rated and as a self-rated scale ([Shear et al. 1997](#)). Other widely used measures include the Sheehan Panic and Anticipatory Anxiety Scale (PAAS; [Sheehan 1986](#)) and the self-rated Marks-Mathews



Fear Questionnaire (FQ; [Marks and Mathews 1979](#)). Although not always attainable, the desired endpoint is full remission. Effective treatment results in reduced emergency department and laboratory resource utilization ([Roy-Byrne et al. 2001](#)).

## First-Line Drug Treatments

### Selective Serotonin Reuptake Inhibitors

In 1995, [Boyer](#) reported that selective serotonin reuptake inhibitor (SSRI) drugs were more effective than imipramine and alprazolam in treating panic disorder, although a meta-analysis by [Otto et al. \(2001\)](#) failed to confirm these findings. Evidence is now available in support of citalopram ([Wade et al. 1997](#)), escitalopram ([Stahl et al. 2003](#)), fluoxetine ([Michelson et al. 1998, 2001](#)), fluvoxamine ([Asnis et al. 2001](#); [Black et al. 1993](#)), paroxetine ([Ballenger et al. 1998](#); [Oehrberg et al. 1995](#); [Sheehan et al. 2005](#)), and sertraline ([Londborg et al. 1998](#)), and also the nonselective serotonin reuptake inhibitor clomipramine ([Lecrubier and Judge 1997](#)). Fluoxetine, paroxetine, and sertraline have been approved by the U.S. Food and Drug Administration (FDA) for treatment of panic disorder.

Patients with panic disorder are often extremely sensitive to activating effects of antidepressants; have poor tolerance of symptoms such as palpitations, sweating, and tremor; and frequently discontinue treatment or drop out. This problem can almost always be prevented by coprescribing a benzodiazepine ([Goddard et al. 2001](#); [Pollack et al. 2003](#)) or by starting with low dosages of an SSRI and increasing them gradually as tolerated. Physician availability and thorough preparation and education of patients are crucial.

Other common side effects of SSRIs include weight gain, sexual dysfunction, impairment of sleep, and potential drug-drug interactions.

Discontinuation of treatment can lead to relapse, which mimics panic symptoms and is quite distressing. Gradual dosage reduction is recommended, as are patient education, physician availability, and coping strategies, including behavior therapy ([Otto et al. 1993](#)). Switching to a long-acting SSRI such as fluoxetine may be considered. Serotonin 2 (5-HT<sub>2</sub>) or serotonin 3 (5-HT<sub>3</sub>) receptor antagonists, such as mirtazapine, nefazodone, and ondansetron, may be used to limit some of the symptoms that are mediated through these pathways (e.g., insomnia, agitation, gastrointestinal distress).

## **Benzodiazepines**

The [Cross-National Collaborative Panic Study \(1992\)](#) showed that alprazolam, along with imipramine, was more effective than placebo in panic disorder; [Lydiard et al. \(1992\)](#) showed that alprazolam 2 mg/day was more effective than placebo. Efficacy for clonazepam was also demonstrated in panic disorder ([Davidson and Moroz 1998](#); [Rosenbaum et al. 1997](#); [Tesar et al. 1991](#)), and its use for this indication is now FDA approved.

Alprazolam is now regarded as a second-line treatment. Problems include sedation at higher dosages, abuse liability, and discontinuation-related distress. Comparable efficacy and tolerability have been demonstrated for the sustained-release formulation of alprazolam ([Pecknold et al. 1994](#); [Schweizer et al. 1993](#)), with decreased likelihood of adverse discontinuation effects.

Clonazepam has an advantage over alprazolam due to its longer half-life; however, it can also produce sedation, depression, and discontinuation symptoms. [Bandelow et al. \(1995\)](#) showed that reduction of panic attacks is an unsatisfactory marker of treatment benefits and therefore should not be relied on as the principal outcome measure. Substantial improvement of quality of life and work productivity were demonstrated in the clonazepam trials compared to placebo ([Jacobs et al. 1997](#)). A recent review supports a role for clonazepam alone or in combination with SSRIs and/or cognitive-behavioral therapy (CBT) in the management of panic disorder ([Nardi et al. 2013](#)).

A particular concern with benzodiazepines is their use in the elderly, who are more prone to sedation and falls that can result in fractures and potential head injury, and who are also more likely to experience discontinuation problems.

## Other Pharmacological Approaches

### Tricyclic Antidepressants

Although tricyclic antidepressants (TCAs) are effective ([Andersch et al. 1991](#); [Cross-National Collaborative Panic Study 1992](#); [Fahy et al. 1992](#); [Lecrubier et al. 1997](#); [Lydiard et al. 1993](#); [Mavissakalian and Perel 1989](#); [Modigh et al. 1992](#)), they are considered second-line treatments for panic disorder because of their side effects. [Mavissakalian and Perel \(1995\)](#) found that phobic symptoms responded best if the plasma level of imipramine and desmethyylimipramine was in the range of 110–140 ng/mL, whereas control of panic attacks tended to occur at lower plasma levels. As with SSRIs, low starting dosages in the range of 10–25

mg/day are in order, with gradual titration thereafter as per patient tolerance.

## **Monoamine Oxidase Inhibitors**

[Sheehan et al. \(1980\)](#) found that phenelzine, along with imipramine, was more effective than placebo in the treatment of panic disorder with agoraphobia, and [Lydiard and Ballenger \(1987\)](#) noted that monoamine oxidase inhibitors (MAOIs) may be superior to TCAs. Although MAOIs may still be the best treatment for some patients, the overall role of MAOIs in managing anxiety disorders is now fairly small because of their potential side effects and drug-drug interactions. The role of the safer reversible inhibitors of monoamine oxidase A (RIMAs) in panic disorder is unclear.

## **Other Drugs**

The extended-release (XR) formulation of venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), demonstrated greater efficacy than placebo in patients with panic disorder in a 10-week trial ([Bradwejn et al. 2005](#)), was as effective as paroxetine in a 12-week placebo-controlled trial ([Pollack et al. 2007](#)), and has received FDA approval for the treatment of panic disorder. The drug is well tolerated, with an adverse-effect profile comparable to that of the drug in depression and other anxiety disorders.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, demonstrated possible benefit in panic disorder in open trials ([Boshuisen et al. 2001](#); [Sarchiapone et al. 2003](#)) and in a double-blind comparison with fluoxetine ([Ribeiro et al. 2001](#)); however, double-blind, placebo-controlled trials have yet to be conducted. It is

noteworthy that mirtazapine has been associated with the induction of panic attacks in depressed patients undergoing dosage escalation and discontinuation ([Berigan 2003](#); [Klesmer et al. 2000](#)).

Reboxetine, a selective noradrenergic reuptake inhibitor, has been found to produce greater improvement than placebo in patients with panic disorder ([Versiani et al. 2002](#)), and in general to be well tolerated. In a more recent randomized, single-blind study comparing reboxetine with paroxetine, paroxetine was more effective for panic attacks, but no differences between the treatments were noted for anticipatory anxiety and avoidance ([Bertani et al. 2004](#)). These findings suggest perhaps different roles of norepinephrine and serotonin in the treatment of panic disorder. However, the selective noradrenergic reuptake inhibitor maprotiline appears to be ineffective in panic disorder ([Den Boer and Westenberg 1988](#)), whereas the data for bupropion are inconclusive ([Sheehan et al. 1983](#); [Simon et al. 2003](#)).

Trazodone was less effective than imipramine and alprazolam in the treatment of panic disorder ([Charney et al. 1986](#)). The 5-HT<sub>1A</sub> partial agonist buspirone and the anticonvulsant gabapentin were generally ineffective in panic disorder ([Pande et al. 2000](#); [Sheehan et al. 1990](#)). Possible benefit has been reported in open-label trials for other anticonvulsant drugs, including levetiracetam, tiagabine, and valproic acid ([Keck et al. 1993](#); [Papp 2006](#); [Zwanzger et al. 2001](#)). A small double-blind, placebo-controlled trial with tiagabine did not show clinical benefits, although cholecystokinin-tetrapeptide (CCK-4)-induced sensitivity to panic attacks decreased ([Zwanzger et al. 2009](#)).

Preliminary data suggest improvement in refractory panic disorder when atypical antipsychotics are used as augmentation of SSRI treatment (olanzapine: [Sepede et al. 2006](#); risperidone: [Simon et al. 2006](#)) or in higher dosages as monotherapy (olanzapine: [Hollifield et al. 2005](#)). A single-blind comparison trial comparing paroxetine and low-dose risperidone found the low-dose risperidone to be as effective as paroxetine in the treatment of panic attacks ([Prosser et al. 2009](#)); however, double-blind, placebo-controlled trials are needed. In a recent randomized, placebo-controlled monotherapy trial of quetiapine XR versus divalproex extended release in bipolar patients with comorbid panic disorder or generalized anxiety disorder, quetiapine XR at a dosage range of 50–300 mg/day showed rapid and sustained effects in reducing anxiety symptoms ([Sheehan et al. 2013](#)).

Metabotropic glutamate type 2 receptor agonists have shown promise in preclinical models of anxiety but have yet to demonstrate clinical efficacy in panic disorder ([Bergink and Westenberg 2005](#)). Similarly, the effect of a cholecystokinin-B receptor antagonist was no different from placebo in patients with panic disorder ([Pande et al. 1999a](#)).

## Long-Term Management

Maintenance treatment is recommended for at least 12–24 months, if not longer. In a controlled trial of paroxetine, clomipramine, and placebo, 84% of the paroxetine-treated patients eventually became panic free over the 9-month period ([Lecrubier and Judge 1997](#)). In a 4-year naturalistic follow-up study of 367 patients with panic disorder, greater

improvements in panic attacks, phobic avoidance, and daily functioning were observed in those who received continuation treatment for 4 years, compared with 1 year ([Katschnig et al. 1995](#)), suggesting that recovery continues over several years.

Long-term randomized controlled trials have reported efficacy for citalopram ([Lepola et al. 1998](#)), clomipramine ([Fahy et al. 1992](#)), fluoxetine ([Michelson et al. 1999](#)), paroxetine ([Lecrubier and Judge 1997](#); [Lydiard et al. 1998](#)), and sertraline ([Rapaport et al. 2001](#)). In a relapse prevention trial following 3 months of successful open-label treatment, [Ferguson et al. \(2007\)](#) showed that over the course of 7 months, relapse on venlafaxine XR was 22%, compared with 50% on placebo.

## Discontinuation

Even though there is some similarity between symptoms of relapse and symptoms of drug withdrawal, the existence of discontinuation symptoms is unarguable. A slow taper is recommended (for some benzodiazepines, it may be necessary to taper the drug over weeks or months). Timing of the taper may be important—it is best done when other variables in a patient's life are as stable as possible. Switching to a longer-acting benzodiazepine such as clonazepam, adding an anticonvulsant such as carbamazepine or valproate ([Pages and Ries 1998](#)), and utilizing behavior therapy ([Otto et al. 1993](#)) have all been used to ameliorate discontinuation symptoms.

Various elaborations of CBT have demonstrated consistent efficacy for panic disorder, with the common elements being education, cognitive strategies, and

exposure to feared sensations and situations ([Clum et al. 1993](#); [Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Panic Disorder and Agoraphobia 2003](#)). CBT is a first-line choice, and even when pharmacotherapy is given as the main treatment, principles of CBT should be incorporated into the management plan. It can be of benefit during the process of drug discontinuation, and perhaps in lessening the chance of relapse afterwards.

---

## **Social Anxiety Disorder (Social Phobia)**

---

Social anxiety disorder (SAD) has a lifetime prevalence of 12% ([Kessler et al. 2005b](#)). It can be grouped into generalized and nongeneralized types. Generalized SAD is more common in clinical settings, is usually more disabling, and is associated with greater levels of comorbidity and genetic loading. Most of our knowledge about pharmacotherapy for SAD derives from the generalized type, and the literature suggests that different medication approaches may be called for in treating the two subtypes.

Comprehensive treatment of SAD requires that the symptoms of fear, avoidance, and physiological distress are brought under control; comorbidity is treated; disability and impairment are improved; and quality of life is enhanced. Furthermore, evidence from maintenance and relapse prevention studies has confirmed the value of long-term therapy in treatment responders.

Instruments commonly used to measure treatment change in SAD include the clinician- and self-rated



Liebowitz Social Anxiety Scale (LSAS; [Liebowitz 1987](#)), which assesses 24 performance or interpersonal situations for fear and avoidance. A score of 30 or less is considered to equate with remission. The Social Phobia Inventory (SPIN) is a 17-item self-rating instrument that assesses fear, avoidance, and physiological distress ([Connor et al. 2000](#)) and, like the LSAS, is able to detect treatment differences.

## Pharmacotherapy

Most clinicians consider SSRIs as the first choice for generalized SAD and  $\beta$ -blockers or benzodiazepines as the first choice for nongeneralized SAD. Second-line drugs for generalized SAD comprise the benzodiazepines, venlafaxine (an SNRI), and perhaps other antidepressants, including nefazodone, mirtazapine, and MAOIs. Bupropion and TCAs have been generally disappointing.

### Serotonergic Drugs

[Van Vliet et al. \(1994\)](#) showed fluvoxamine's superiority over placebo, with response rates of 46% and 7%, respectively. [Stein et al. \(1999\)](#) confirmed the efficacy of fluvoxamine relative to placebo on all symptom domains (i.e., fear, avoidance, and physiological arousal). Controlled-released (CR) fluvoxamine was likewise found to be superior to placebo ([Davidson et al. 2004c](#); [Westenberg et al. 2004](#)), and a study in Japan also found fluvoxamine to be effective versus placebo in reducing SAD symptoms and psychosocial disability ([Asakura et al. 2007](#)).

Sertraline also has been studied ([Blomhoff et al. 2001](#); [Katzelnick et al. 1995](#); [Liebowitz et al. 2003](#); [Van Ameringen et al. 2001](#); [Walker et al. 2000](#)). In the study by

[Van Ameringen et al. \(2001\)](#), 53% of patients responded to sertraline as compared with 29% to placebo, and sertraline-treated patients showed improvement on all three symptom domains of the Brief Social Phobia Scale. In a primary care setting, [Haug et al. \(2000\)](#) showed that cognitive therapy and sertraline could be effectively delivered, although the combination did not show any superiority over treatment with drug alone.

Paroxetine's superiority relative to placebo in SAD has been shown in both short-term efficacy and relapse prevention studies. In the short-term studies by [Stein et al. \(1998\)](#), [Allgulander \(1999\)](#), and [Baldwin et al. \(1999\)](#), rates of response to paroxetine were 55%, 70%, and 66%, respectively, as compared with placebo response rates of 24%, 8%, and 32%. All subjects in the paroxetine trials fulfilled criteria for generalized SAD and showed benefit on the LSAS within 2–4 weeks. Paroxetine CR was also shown to be effective (using LSAS as the primary outcome measure) and well tolerated in a 12-week double-blind, placebo-controlled trial ([Lepola et al. 2004](#)).

Fluoxetine, while superior to placebo on primary outcomes in one study ([Davidson et al. 2004c](#)), failed to separate from placebo in another study ([Kobak et al. 2002](#)), showing a relatively high placebo response rate (30%). Another study found cognitive therapy to be superior to both fluoxetine plus exposure exercises and placebo plus exposure exercises on SAD measures, with no difference between the latter two groups ([Clark et al. 2003](#)). Another serotonergic agent, nefazodone, also failed to separate from placebo on most outcome measures ([Van Ameringen et al. 2007](#)).

Trials with escitalopram have shown it to be superior to placebo in short-term, long-term, and relapse prevention

studies of generalized SAD ([Kasper et al. 2005](#); [Lader et al. 2004](#); [Montgomery et al. 2005](#)). Venlafaxine XR has also shown superiority over placebo in two double-blind trials of generalized SAD ([Allgulander et al. 2004](#); [Liebowitz et al. 2005](#)).

A double-blind, placebo-controlled trial of mirtazapine in women showed statistically significant superiority for drug over placebo ([Muehlbacher et al. 2005](#)). However, a more recent double-blind, placebo-controlled trial in 60 outpatients with generalized SAD who received mirtazapine at dosages of 30–45 mg/day failed to find evidence of efficacy ([Schutters et al. 2010](#)).

Paroxetine, paroxetine CR, sertraline, fluvoxamine CR, and venlafaxine XR are currently FDA approved for SAD treatment.

## **Benzodiazepines**

Three major placebo-controlled trials have shown efficacy for benzodiazepines in SAD. [Gelernter et al. \(1991\)](#) showed a modest effect for alprazolam over placebo (38% vs. 20% response rate) at a mean daily dosage of 4.2 mg, although it was generally inferior to phenelzine. [Davidson et al. \(1993\)](#) found a substantial 70% clonazepam response rate compared with a 20% placebo response rate in 75 subjects. Bromazepam was also found to be more effective than placebo ([Versiani et al. 1997](#)). A recent double-blind, placebo-controlled trial of augmentation and switch strategies for refractory SAD found that clonazepam augmentation of sertraline treatment (up to 3 mg/day) was superior to placebo augmentation and also to a switch to venlafaxine, with a higher percentage of patients achieving remission ([Pollack et al. 2014](#)).

Benzodiazepines provide significant benefits yet are not considered first-line drugs because of their more limited spectrum of action and potential withdrawal difficulties. However, they work rapidly, are well tolerated, and may be particularly useful for individuals with periodic performance-related social anxiety or treatment-resistant SAD.

## **Anticonvulsants**

Gabapentin and pregabalin produce significant effects in SAD. [Pande et al. \(1999b\)](#) found a superior effect for gabapentin over placebo in a trial using flexible dosing (ranging from 900 mg/day to 3,600 mg/day, with 2,100 mg/day being the most common final gabapentin dosage), with response rates of 39% and 17%, respectively. Baseline symptom scores were comparatively high and overall response rates relatively low, suggesting a degree of treatment-resistant illness in the study population. Pregabalin also has shown benefit in generalized SAD ([Feltner et al. 2003](#); [Pande et al. 2003](#)). Although pregabalin at a dosage of 150 mg/day was no different from placebo, 600 mg/day produced greater effects than placebo, with response rates of 43% and 22%, respectively. A 26-week double-blind, placebo-controlled maintenance trial of pregabalin at a fixed dosage of 450 mg/day showed that pregabalin not only was superior to placebo in maintaining symptomatic improvement but also was relatively well tolerated ([Greist et al. 2011](#)). Levetiracetam failed to differentiate from placebo ([Stein et al. 2010](#)). Further work with anticonvulsants is needed, given that these agents are generally well tolerated, safe, and less likely to produce discontinuation symptoms compared with many SSRIs and benzodiazepines.

## Reversible Inhibitors of Monoamine Oxidase A

Moclobemide is safer than older MAOIs and was shown to be almost as effective as phenelzine and significantly better than placebo ([Versiani et al. 1992](#)). However, subsequent studies did not support these findings ([Noyes et al. 1997](#); [Schneier et al. 1998](#)). The [International Multicenter Clinical Trial Group on Moclobemide in Social Phobia \(1997\)](#) found a modestly greater response rate (47%) for moclobemide at 600 mg/day than for placebo (34%). Moclobemide is approved in some countries but is not available in the United States. Another RIMA, brofaromine, has shown promise in three trials, with response rates of 78%, 50%, and 73%, respectively, compared with placebo response rates of 23%, 19%, and 0% ([Fahlén et al. 1995](#); [Lott et al. 1997](#); [van Vliet et al. 1992](#)), but it also is not marketed in the United States.

## Irreversible Inhibitors of Monoamine Oxidase

Phenelzine showed positive benefit in four studies ([Gelernter et al. 1991](#); [Heimberg et al. 1998](#); [Liebowitz et al. 1992](#); [Versiani et al. 1992](#)). Rates of response to phenelzine were 69%, 85%, 64%, and 65%, respectively, as compared with response rates of 20%, 15%, 23%, and 33% to placebo, and phenelzine overall has been shown to have a strong effect size ([Davis et al. 2014](#)). Even though phenelzine is consistently effective, its poor tolerability and risks make it unsuitable except for patients who have been nonresponsive to other treatments and who can adhere to the necessary dietary and medication restrictions.

## Other Drugs

Olanzapine yielded greater improvement than placebo in a small ( $n=12$ ) double-blind, placebo-controlled monotherapy trial ([Barnett et al. 2002](#)), suggesting that atypical antipsychotics may deserve further investigation in SAD, although their benefits will need to be weighed against their potential metabolic effects. Ondansetron, while producing a statistically significant effect relative to placebo, seems to be of limited clinical benefit ([Bell and DeVeaugh-Geiss 1994](#); [Davidson et al. 1997b](#)), although it may be used adjunctively in some cases. Buspirone was ineffective in a double-blind trial, with a 7% response rate ([van Vliet et al. 1997](#)).

Despite their intuitive appeal,  $\beta$ -blockers have shown poor effect in treating generalized SAD. For example, atenolol failed to separate from placebo in two trials ([Liebowitz et al. 1992](#); [Turner et al. 1994](#)).  $\beta$ -Blockers do show some value in performance-related social anxiety, perhaps by virtue of their ability to reduce peripheral autonomic arousal and block negative feedback. A double-blind trial of mirtazapine failed to show benefit ([Schutters et al. 2010](#)). Nefazodone, bupropion, and selegiline have not shown impressive results in open-label reports ([Emmanuel et al. 1991](#); [Simpson et al. 1998](#); [Van Ameringen et al. 1999](#)).

A novel therapeutic approach is suggested by the findings of [Hofmann et al. \(2006\)](#), who administered a single dose of D-cycloserine or placebo to patients with social anxiety disorder treated with CBT. The drug was given prior to each CBT session and enhanced the benefit of CBT to a greater extent than did placebo. The postulated mechanism of action relates to drug-facilitated extinction of learned fear via glutamatergic pathways. However, a recent placebo-controlled multisite trial of CBT augmentation with D-cycloserine in generalized SAD by the same authors found

that although D-cycloserine augmentation was associated with approximately a 30% faster rate of improvement, there was no difference in response or remission rate compared with placebo ([Hofmann et al. 2013](#)).

A study comparing the neurokinin-1 antagonist GR205171 against citalopram and placebo in 36 social phobia patients found response rates of 41.7%, 50%, and 8.3%, respectively, as well as a significant reduction in regional cerebral blood flow (rCBF) in the rhinal cortex, amygdala, and parahippocampal-hippocampal regions during a stressful public speaking task with the active agents ([Furmark et al. 2005](#)).

[Connor et al. \(2006\)](#) reported benefit for one-time intradermal bilateral axillary injections of 50 units of botulinum toxin type A for subjects with SAD and troublesome axillary hyperhidrosis. Effects persisted over 8 weeks and were superior to those of placebo for sweating, daily function, and activities. All subjects received concomitant paroxetine for other aspects of SAD.

## Treatment in Children and Adolescents

One placebo-controlled trial of fluvoxamine in children ages 6–17 years showed that it was superior to placebo in SAD, generalized anxiety disorder (GAD), and the combination: 76% of the fluvoxamine group responded, as compared with 19% of the placebo group ([Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001](#)). Double-blind trials of immediate-release (IR) paroxetine ([Wagner et al. 2004](#)) and venlafaxine XR ([March et al. 2007](#)) have

produced positive results in children and adolescents with generalized SAD.

A multisite trial in 488 children (ages 7–17 years) with a primary diagnosis of separation anxiety disorder, GAD, or SAD compared CBT alone, sertraline alone, combination CBT and sertraline, and placebo. CBT monotherapy and sertraline monotherapy were each superior to placebo in reducing anxiety symptoms in children (59.7% and 54.9% response rate, respectively); however, the combination treatment had the best response rate (80.7%) ([Walkup et al. 2008](#)). At follow-ups at 24 and 36 weeks, the majority of acute responders maintained their response, and the combination treatment maintained its advantage over the CBT and sertraline monotherapies ([Piacentini et al. 2014](#)).

## Duration of Treatment

SAD is a chronic illness, and treatment is generally recommended for years. [Sutherland et al. \(1996\)](#) reported that at 2-year follow-up, subjects who had received an active drug rather than placebo were doing better. Relatively few relapse prevention studies have been done. In a 12-month trial with clonazepam, [Connor et al. \(1998\)](#) showed a 20% relapse rate in those switched to placebo, compared with 0% in those who continued taking clonazepam. [Stein et al. \(1996\)](#) reported that 62% of the subjects relapsed when switched double-blind from paroxetine to placebo after 12 weeks, compared with only 12% who relapsed during maintenance treatment with paroxetine.



## Other Issues

CBT is efficacious in SAD, being comparable to pharmacotherapy ([Davidson et al. 2004b](#); [Fedoroff and Taylor 2001](#)), but little is known as to whether adding CBT to medication lowers the relapse rate, and so far the limited evidence does not suggest any potentiating effects when the treatments are combined ([Davidson et al. 2004b](#)), except in children ([Walkup et al. 2008](#)). In a comparative study of drug and psychotherapy, [Heimberg et al. \(1998\)](#) showed that phenelzine and CBT were approximately similar, although phenelzine had an edge in more severely symptomatic patients. On the other hand, when subjects who had discontinued treatment were followed up, rates of relapse tended to be lower in those who had received CBT than in those who had taken phenelzine. A later study by the same group ([Blanco et al. 2010](#)) showed superior outcomes for combined phenelzine and CBT over each treatment given alone.

---

## Specific Phobia

---

Specific phobia is among the most common psychiatric disorders, with a lifetime prevalence of 8%–12.5% ([Alonso et al. 2004](#); [Kessler et al. 2005b](#)) and 12-month prevalence of 3.5%–9% ([Alonso et al. 2004](#); [Kessler et al. 2005a](#)). Although the disorder is characterized by an early onset (median age at onset is 7 years) ([Kessler et al. 2005b](#)), most individuals are unimpaired by their symptoms and rarely seek treatment ([Magee et al. 1996](#); [Stinson et al. 2007](#); [Zimmerman and Mattia 2000](#)). However, for a minority of

individuals, specific phobia causes significant disability and requires treatment. The generally accepted treatment of choice is exposure therapy, which is uniformly and rapidly effective, with techniques including virtual reality as well as in vivo exposure and muscle tension exercises (for blood-injury phobia) ([Swinson et al. 2006](#)). Few studies have evaluated the efficacy of pharmacological approaches, and no drug has yet been approved by the FDA for treating specific phobia. No standard ratings exist for this disorder, although the Marks-Mathews FQ is quite suitable for blood-injury phobia and some other fears. A modification of this scale, the Marks-Sheehan Main Phobia Severity Scale (MSMPSS; [Sheehan 1986](#)), can be recommended.

Serotonergic drugs have shown efficacy in treating symptoms of fear and avoidance in a variety of anxiety disorders and thus would seem logical choices in specific phobias. In a small ( $n=11$ ) 4-week double-blind controlled trial, subjects receiving paroxetine (up to 20 mg/day) showed a 60% response rate, compared with 17% for subjects receiving placebo ([Benjamin et al. 2000](#)). A more recent randomized double-blind pilot trial compared escitalopram versus placebo over 12 weeks in 12 adults with specific phobia ([Alamy et al. 2008](#)). No difference was observed on the primary outcome; however, 60% of escitalopram-treated subjects showed response (based on a Clinical Global Impression Scale [CGI] Improvement score of 1 or 2), compared with 29% of subjects receiving placebo (effect size=1.13). The findings from these two small trials require validation in larger controlled trials. In contrast, in a controlled trial of the serotonergic and noradrenergic TCA imipramine in 218 phobic subjects (agoraphobic, mixed phobic, or simple phobic) receiving 26 weeks of

behavior therapy, no difference was observed between imipramine and placebo ([Zitrin et al. 1983](#)).

In a long-term controlled study of clonazepam in social phobia, [Davidson et al. \(1994\)](#) observed that clonazepam was superior in reducing symptoms of anxiety related to blood-injury phobia as measured by changes in the blood-injury phobia subscale of the Marks-Mathews FQ. Intermittent use of benzodiazepines also may be helpful in the acute treatment of the somatic anxiety that accompanies specific phobia, although this usage has not been an area of active investigation.

Using a novel approach, [Ressler et al. \(2004\)](#) investigated the effect of a cognitive enhancer, D-cycloserine, as an adjunct to psychotherapy. D-Cycloserine is an *N*-methyl-D-aspartate (NMDA) receptor partial agonist that has demonstrated improvement in extinction in rodents. Subjects with acrophobia ( $n=28$ ) were randomly assigned to receive a single dose of D-cycloserine or placebo prior to each of two virtual reality exposure therapy sessions. The combination of D-cycloserine and exposure therapy was associated with greater improvement in the virtual reality setting, as well as on a variety of anxiety domains. These changes were noted early in treatment and were maintained at 3-month follow-up. A recent small ( $n=35$ ) double-blind, placebo-controlled randomized trial of D-cycloserine enhancement of prolonged exposure therapy in dog- or spider-phobic children showed that D-cycloserine helped children to better retain their fear extinction learning ([Byrne et al. 2015](#)).

Specific phobia tends to be a chronic condition. Although psychotherapeutic approaches can be beneficial in the short term, evidence suggests that the initial gains noted

with treatment may not be sustained over the long term ([Lipsitz et al. 1999](#)). Pharmacological augmentation may help to extend the benefits of exposure therapy over time.

---

## Generalized Anxiety Disorder

---

GAD is a common disorder, with a lifetime prevalence of 5%–6% ([Wittchen and Hoyer 2001](#)), and is the most prevalent anxiety disorder in primary care, with rates that exceed 8% (Goldberg and Lecrubier [1995](#)). GAD tends to be a chronic and disabling condition with lifetime rates of comorbidity as high as 90% ([Blanco et al. 2014](#)), particularly depression (prevalence rate greater than 60%), which can increase the severity and burden of the disorder. Unlike prevalences of other anxiety disorders, GAD prevalence tends to increase with age, with a lifetime prevalence of 11% in individuals older than 65 years and late-life onset occurring in at least 25% of cases ([Zhang et al. 2014](#)).

Assessment of response in almost all GAD pharmacotherapy trials has been with the clinician-administered Hamilton Anxiety Scale (Ham-A; [Hamilton 1959](#)), which measures psychic and somatic symptoms of anxiety; remission is usually defined as a Ham-A score of 7 or less. The self-rated Hospital Anxiety and Depression Scale (HADS; [Zigmond and Snaith 1983](#)) is also widely used and is capable of detecting differences in treatment efficacy.

## Anxiolytics

## Benzodiazepines

Benzodiazepines have been widely used to treat acute and chronic anxiety since their introduction in the 1960s. Their activity is mediated through potentiation of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) at the GABA<sub>A</sub> receptor. The efficacy and relative safety of benzodiazepines in short-term use (i.e., several weeks or months) are well established ([Rickels et al. 1983](#); [Shader and Greenblatt 1993](#)). However, the longer-term use of these drugs is more controversial and can be associated with the development of tolerance, physiological dependence, and withdrawal (if abruptly discontinued), as well as troublesome side effects, including ataxia, sedation, motor dysfunction, and cognitive impairment. Furthermore, these drugs should be avoided in patients with a history of substance use disorders, and long-term use may infrequently lead to the development of major depression ([Lydiard et al. 1987](#)).

Benzodiazepines have been shown to be effective in GAD, as reported by [Rickels et al. \(1993\)](#). The appeal of these drugs lies in their rapid onset of action, ease of use, tolerability, and relative safety. Findings from several 6- to 8-month trials of maintenance treatment for chronic anxiety have indicated continued efficacy of benzodiazepines over time ([Rickels et al. 1983, 1988a, 1988b](#); [Schweizer et al. 1993](#)). Because GAD tends to be a chronic disorder, many patients may need to continue pharmacotherapy with benzodiazepines (or other drugs) for many years, and long-term use of benzodiazepines may lead to the complications listed above.

Approximately 70% of patients with GAD will respond to an adequate trial of a benzodiazepine ([Greenblatt et al.](#)

1983), which corresponds to the equivalent of a 3- to 4-week treatment course of up to 40 mg/day of diazepam or 4 mg/day of alprazolam (Schweizer and Rickels 1996). Discontinuation should be managed by slow taper to minimize withdrawal symptoms, rebound anxiety, and relapse potential. Some evidence suggests that benzodiazepines may be more effective in treating the autonomic arousal and somatic symptoms of GAD but less effective for the psychic symptoms of worry and irritability (Rickels et al. 1982; Rosenbaum et al. 1984).

As our understanding of the phenomenology of GAD has grown, there has been a greater emphasis on the psychic component of the disorder (DSM-5; American Psychiatric Association 2013). Given these changes, along with the high rates of comorbid depression in GAD and the anxiolytic activity of many of the newer classes of antidepressants, the use of benzodiazepines as a primary treatment for GAD is less recommended.

## Azapirones

The azapirones are believed to exert their anxiolytic effect through partial agonism of 5-HT<sub>1A</sub> receptors. Several trials have indicated that buspirone is superior to placebo and comparable to benzodiazepines in treating GAD, with fewer side effects and without concerns for abuse, dependence, and withdrawal (Cohn et al. 1986; Enkelmann 1991; Petracca et al. 1990; Rickels et al. 1988b; Strand et al. 1990), although other studies have reported conflicting results (Fontaine et al. 1987; Olajide and Lader 1987; Ross and Matas 1987). Buspirone appears to be more effective in treating the psychic component of anxiety (Rickels et al. 1982), and possibly anxiety with mixed depressive

symptoms ([Rickels et al. 1991](#)), than in treating the somatic and autonomic symptoms of anxiety ([Schweizer and Rickels 1988](#); [Sheehan et al. 1990](#)). An adequate trial of buspirone in GAD would be 3–4 weeks of treatment at a dosage of up to 60 mg/day, in divided doses. Treatment-limiting effects of the drug include greater potential for side effects at higher dosages, slower onset of action, more variable antidepressant effects, and possibly reduced effectiveness in patients with a prior favorable response to benzodiazepines ([Schweizer et al. 1986](#)).

## Tricyclic Antidepressants

In a 6-week trial comparing imipramine and alprazolam, similar improvement was observed with both treatments by week 2; however, imipramine appeared to be more effective in treating the psychic anxiety component, whereas alprazolam was more effective in attenuating somatic symptoms ([Hoehn-Saric et al. 1988](#)). In an 8-week double-blind, placebo-controlled trial of imipramine, trazodone, and diazepam ([Rickels et al. 1993](#)), diazepam showed an early-onset effect by week 2, primarily on somatic symptoms. Over the next 6 weeks, however, psychic anxiety symptoms were more responsive to the antidepressants. Overall, imipramine was more efficacious than diazepam, trazodone was comparable to diazepam, and all treatments were superior to placebo. In a controlled trial comparing imipramine, paroxetine, and 2'-chlorodesmethyldiazepam, early onset of action was again noted with the benzodiazepine by week 2, but overall greater improvement was noted with the antidepressants by week 4, especially in psychic symptoms ([Rocca et al. 1997](#)).

# Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors

A number of SSRIs are effective in GAD. Paroxetine IR at 20–50 mg/day has been shown to be as effective as imipramine and more effective than 2'-chlordesmethyldiazepam ([Rocca et al. 1997](#)). Compared with placebo, a similar dosage range of paroxetine IR was associated with significant reduction in anxiety after 8 weeks of treatment ([Bellew et al. 2000](#); [Pollack et al. 2001](#); [Rickels et al. 2003](#)), with an improvement in Ham-A-rated psychic anxiety observed as early as 1 week after initiating treatment ([Pollack et al. 2001](#)). Paroxetine IR also improves social functioning in patients with GAD ([Bellew et al. 2000](#)).

Escitalopram was found to be superior to placebo in improving anxiety symptoms, disability, or quality of life in three 8-week trials at a dosage range of 10–20 mg/day dose range ([Davidson et al. 2004a](#); [Goodman et al. 2005](#)), and it was found to be equivalent to paroxetine IR in a 6-month trial ([Bielski et al. 2005](#)). In a larger placebo-controlled trial, escitalopram 10 mg/day was superior to paroxetine 20 mg/day, and escitalopram dosages of both 10 mg/day and 20 mg/day were superior to placebo ([Baldwin et al. 2006](#)). A relapse prevention study found that sustained treatment with escitalopram 20 mg/day up to 74 weeks reduced the relapse rate (19%) relative to placebo substitution (56%) ([Allgulander et al. 2006](#)).

Sertraline was demonstrated to be superior to placebo in GAD in a 12-week ([Allgulander et al. 2004](#)) and a 10-week ([Brawman-Mintzer et al. 2006](#)) double-blind, placebo-



controlled trial; sertraline was well tolerated and showed beneficial effects on Ham-A-rated psychic and somatic anxiety symptoms compared with placebo ([Dahl et al. 2005](#)).

Several placebo-controlled trials have confirmed the short-term efficacy of venlafaxine XR in GAD over 8 weeks on both psychic and somatic symptoms. In a trial of 365 adult outpatients treated with venlafaxine XR (75 mg/day or 150 mg/day), buspirone (30 mg/day), or placebo, the Ham-A-adjusted mean scores of the anxiety and tension items were significantly improved at both active drug dosages compared with placebo; venlafaxine XR was superior to buspirone on the HADS anxiety subscale ([Davidson et al. 1999](#)). In a second trial of 541 outpatients on either venlafaxine XR (37.5 mg/day, 75 mg/day, or 150 mg/day) or placebo ([Allgulander et al. 2001](#)), the venlafaxine 75 mg/day and 150 mg/day dosages showed superior efficacy compared with placebo on all primary outcome measures (with improvement in psychic anxiety noted earlier than somatic symptoms), whereas the 37.5 mg/day dosage was superior to placebo on only one measure (the Anxiety subscale of the HADS). In a third trial of fixed dosages (75 mg/day, 150 mg/day, and 225 mg/day) of venlafaxine XR ([Rickels et al. 2000](#)), venlafaxine XR was superior to placebo on all outcome measures, with the most robust effects observed at 225 mg/day. Venlafaxine XR significantly reduced psychic anxiety but not somatic symptoms.

Venlafaxine XR also has shown long-term efficacy in GAD. In two 6-month controlled trials of fixed (37.5 mg, 75 mg, or 150 mg/day) ([Allgulander et al. 2001](#)) and flexible (75–225 mg/day) ([Gelenberg et al. 2000](#)) dosages of venlafaxine XR, significant improvement in anxiety was observed as early as 1 week, and efficacy was sustained over the 28-week

treatment period. In the fixed-dosage study, the greatest effect was observed with the 150-mg/day dosage. Significant improvement in social functioning was noted at the two higher dosages by week 8 and was sustained over the 6 months of the trial.

Venlafaxine XR is also effective in treating GAD with comorbid depression ([Silverstone and Salinas 2001](#)). After 12 weeks of treatment with venlafaxine XR (75–225 mg/day), fluoxetine, or placebo, significant reduction was observed in both Ham-A-rated anxiety and Hamilton Rating Scale for Depression (Ham-D; [Hamilton 1960](#))-rated depression only in subjects receiving venlafaxine XR. The response was delayed somewhat in subjects with comorbid GAD and depression as compared with those with depression alone, suggesting that individuals with comorbidity may benefit from a longer course of treatment.

There is agreement that the goal of treatment is to achieve remission, (e.g., a final Ham-A score  $\leq 7$ ). Pooled analysis of data from the two long-term studies noted earlier ([Allgulander et al. 2001](#); [Gelenberg et al. 2000](#)) has determined that remission is attainable in GAD ([Meoni and Hackett 2000](#)). By 2 months, approximately 40% of those receiving venlafaxine responded to treatment, and 42% attained remission. By 6 months, the proportion of those in remission increased to almost 60%, whereas responders declined to 20%, in contrast to a remission rate of less than 40% with placebo.

Venlafaxine XR has some advantages over the benzodiazepines—notably, antidepressant activity, lack of potential for abuse and dependence, and efficacy in treating symptoms of psychic anxiety. Nonetheless, venlafaxine can be associated with some adverse effects in the long term, including sexual dysfunction and blood

pressure elevation in some patients. Abrupt discontinuation of treatment can be associated with unpleasant side effects, most commonly dizziness, light-headedness, tinnitus, nausea, vomiting, and loss of appetite, and the discontinuation syndrome is worse if one abruptly stops at higher dosage levels ([Allgulander et al. 2001](#)).

Duloxetine, another SNRI antidepressant, has shown efficacy superior to placebo in GAD ([Allgulander et al. 2007](#); [Rynn et al. 2008](#)) in the range of 60–120 mg/day and also appears to lessen the chance of relapse during maintenance therapy. A recent randomized, placebo-controlled, flexible-dose study demonstrated that duloxetine was effective and well tolerated in the treatment of GAD in children and adolescents ages 7–17 years ([Strawn et al. 2015](#)).

One interesting application of SSRIs in GAD is in combination with nonbenzodiazepine hypnotics such as eszopiclone ([Pollack et al. 2008a](#)) and zolpidem ([Fava et al. 2009](#)), which may be particularly suited where insomnia is a major problem.

## Noradrenergic and Specific Serotonergic Antidepressants (Mirtazapine, Bupropion)

The antidepressant mirtazapine also has demonstrated anxiolytic properties ([Ribeiro et al. 2001](#)). However, published reports of its effect in GAD are limited to a small open-label study in major depression and comorbid GAD ([Goodnick et al. 1999](#)) and a small open-label GAD trial in 44 outpatients ([Gambi et al. 2005](#)). Although the results

were encouraging, data from controlled trials are needed to adequately assess a possible role for mirtazapine in GAD.

A 12-week double-blind active comparison trial of bupropion extended-release at 150–300 mg/day versus escitalopram at 10–20 mg/day in 24 subjects found similar Ham-A-rated anxiolytic efficacy of bupropion extended-release and escitalopram ([Bystritsky et al. 2008](#)). Notwithstanding these intriguing findings, the current body of clinical evidence supports the use of SSRIs or SNRIs before agents that are primarily noradrenergic in action.

## Hydroxyzine

Hydroxyzine blocks histamine<sub>1</sub> (H<sub>1</sub>) and muscarinic receptors. In three controlled trials, hydroxyzine was superior to placebo ([Ferreri and Hantouche 1998](#); [Lader and Scotto 1998](#); [Llorca et al. 2002](#)). Recent reports of hydroxyzine-related ventricular arrhythmias have led to cautionary labeling in Europe in the use of this drug and restriction of the maximum dosage to 100 mg/day ([European Medicines Agency 2015](#)).

## Anticonvulsants

The  $\alpha_2\delta$  calcium channel antagonist pregabalin was superior to placebo in four studies of GAD ([Feltner et al. 2003](#); [Pande et al. 2003](#); [Pohl et al. 2005](#); [Rickels et al. 2005](#)). Efficacy was noted early in treatment, but the ability of this drug to successfully treat some of the comorbid disorders associated with GAD is unknown. A recent review of six short-term double-blind, placebo-controlled pregabalin trials in GAD showed that pregabalin treatment

significantly improved both psychic and somatic Ham-A-rated GAD symptoms, with a dose-response effect that plateaued at 300 mg/day ([Lydiard et al. 2010](#)). Pregabalin has shown efficacy and reasonably good tolerability in elderly patients with GAD ([Montgomery 2006](#)). In a long-term trial in 624 GAD patients, responders to 8 weeks of open-label pregabalin at 450 mg/day were randomly assigned to receive pregabalin or placebo for 24 weeks ([Feltner et al. 2008](#)). Relapse rates were significantly lower for pregabalin (42%) than for placebo (65%), although attrition rates for pregabalin were higher (21.4% vs. 15.3%).

The GABA reuptake inhibitor tiagabine failed to separate from placebo on key measures in three placebo-controlled multicenter trials ([Pollack et al. 2008b](#)).

## Antipsychotics

Evidence for antipsychotic monotherapy in GAD is limited for some agents and more robust for others. An open-label trial suggested benefit for ziprasidone ([Snyderman et al. 2005](#)). Flupenthixol is approved for the treatment of depression in some countries and was shown in one controlled study to be superior to amitriptyline, clonazepam, and placebo in subjects with refractory GAD ([Wurthmann et al. 1995](#)). Sulpiride is also used in similar situations ([Bruscky et al. 1974](#); [Chen et al. 1994](#)).

The strongest evidence supporting atypical antipsychotic use in GAD at present is for quetiapine XR, which was shown to be effective and superior to placebo in a multicenter trial, and at 150 mg/day was effective for both psychic and somatic anxiety symptoms, with improvement

being noted as early as 4 days ([Bandelow et al. 2010](#)). The active comparator in this trial, paroxetine 20 mg/day, showed a lesser effect on somatic anxiety and a higher prevalence of sexual side effects. Remission rates were 42.6%, 38.8%, and 27.2% for quetiapine XR, paroxetine, and placebo, respectively. A longer-term double-blind, placebo-controlled multicenter maintenance trial with quetiapine XR at 50–300 mg/day in 432 patients found it to be effective in preventing recurrence of anxiety symptoms ([Katzman et al. 2011](#)).

Long-term use of atypical antipsychotics carries some concerns about tolerability and safety, especially in regard to weight gain and metabolic adverse effects, and these concerns need to be balanced against the long-term benefits in GAD in terms of reduction of disability and improved functionality.

## Other Drugs

Riluzole, a presynaptic glutamate release inhibitor, showed promise in a small open-label study at a daily dosage of 100 mg ([Mathew et al. 2005](#)).

Agomelatine, a serotonin 5-HT<sub>2C</sub> antagonist and melatonin<sub>1/2</sub> receptor agonist, is efficacious in GAD ([Stein et al. 2008](#)).

Complementary treatments have had mixed results in GAD. Homeopathy was found to be ineffective in one trial ([Bonne et al. 2003](#)). The herbal remedy kava did not separate from placebo in one trial ([Connor and Davidson 2002](#)), although [Sarris et al. \(2009\)](#) showed some evidence supporting the benefit of a water-soluble formulation of kava in subjects with short-term GAD-like symptoms. Liver

damage remains a potentially devastating concern, however, and even the preferred aqueous extract cannot be regarded as entirely safe, particularly at kava dosages above 250 mg/day ([Teschke and Schulze 2010](#)). Two small placebo-controlled trials suggested that chamomile and *Ginkgo biloba* may have modest anxiolytic effects in patients with mild to moderate GAD ([Amsterdam et al. 2009](#); [Woelk et al. 2007](#)). [Kasper et al. \(2014\)](#) demonstrated that lavender oil extract at dosages of 80 mg/day and 160 mg/day was superior to placebo and was better tolerated than paroxetine in a four-arm trial of subjects with DSM-5 GAD. Later studies by these researchers showed that the compound reduced 5-HT<sub>1A</sub> receptor binding in the hippocampus, anterior cingulate cortex, and fusiform and temporal gyri.

A meta-analysis of GAD studies by [Hidalgo et al. \(2007\)](#) showed that the effect sizes (in diminishing order from strongest to weakest) for each drug or drug group versus placebo were as follows: pregabalin, 0.50; hydroxyzine, 0.45; venlafaxine XR, 0.42; benzodiazepines, 0.38; SSRIs, 0.36; buspirone, 0.17; and homeopathy and herbal treatment, -0.31.

Drugs that have been approved in the United States for treating GAD or historical forerunners of the disorder include a large number of benzodiazepines, buspirone, paroxetine IR, escitalopram, venlafaxine XR, and duloxetine. Pregabalin is not approved in the United States but is approved for GAD in Europe.

There is also convincing evidence in favor of efficacy for CBT in GAD, with sustained benefit over 2 years of follow-up. These findings have been well reviewed by [Swinson et al. \(2006\)](#). There are no clinically informative studies to compare, or combine, CBT and pharmacotherapy in GAD,

but on pragmatic grounds, one may consider their combination in patients who have shown only a partial response to a thorough course of either CBT or medication alone.

---

## Obsessive-Compulsive Disorder

---

Although obsessive-compulsive disorder (OCD) has moved to a new disorder category—Obsessive-Compulsive and Related Disorders—in DSM-5, we have retained it in this chapter because of its similarities to anxiety disorders in presentation and treatment approaches.

According to the National Comorbidity Survey Replication (NCS-R), the lifetime and 12-month prevalence rates for OCD are 1.6% and 1.0%, respectively ([Kessler et al. 2005a, 2005b](#)). OCD has been recognized as the tenth leading cause of disability worldwide ([Murray and Lopez 1996](#)). Treatment can be grouped broadly into psychosocial and psychopharmacological approaches, the latter being our focus here. The chief rating scale for treatment studies of OCD remains the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; [Goodman et al. 1989](#)), a 10-item observer-rated measure.

## Monotherapy

A series of placebo-controlled studies completed in the late 1980s and the early 1990s led to the first approved treatment of OCD in the United States and other countries ([Clomipramine Collaborative Study Group 1991](#)). Clomipramine is a potent serotonin reuptake inhibitor (SRI)



but is not selective for serotonin, because its demethylated metabolite is a norepinephrine reuptake inhibitor (NRI). The anti-OCD effect of clomipramine correlates with the plasma level of the SRI parent drug, suggesting that reuptake inhibition of serotonin is the critical factor underlying the drug's benefit. Moreover, selective noradrenergic reuptake inhibitors such as nortriptyline and desipramine have been shown to lack efficacy in OCD ([Leonard et al. 1988](#); [Thorén et al. 1980](#)).

In the [Clomipramine Collaborative Study Group \(1991\)](#) trial, the Y-BOCS score was reduced by about 40% in the active-drug group compared with a reduction of about 5% in the placebo group, consistent with findings by [Huppert et al. \(2004\)](#) that OCD has a remarkably low placebo response rate. Clomipramine and SSRIs are equivalent in the treatment of OCD ([Koran et al. 1996](#)); however, because of its side effects, clomipramine is considered a second-line treatment.

Today, SSRIs are considered the first-line treatment for OCD, and fluvoxamine, fluoxetine, sertraline, and paroxetine have been approved by the FDA for that indication ([Greist et al. 1995a, 1995b](#); [Tollefson et al. 1994](#)). Clomipramine, fluvoxamine, fluoxetine, and sertraline are also effective and indicated for treating OCD in children ([Flament et al. 1985](#); [Liebowitz et al. 2002](#); [March et al. 1998](#); [Riddle et al. 2001](#)), although CBT and the combination of CBT with an SSRI may be more effective ([Ivarsson et al. 2015](#)). When an SSRI drug is to be used in the treatment of OCD, it may need to be given at higher dosages, and it may take a longer time to work effectively ([Ninan et al. 2006](#); [Stein et al. 2007](#)). Most clinicians believe that treatment should be long-term to reduce the chance of relapse ([Pato et al. 1990](#)), although the dosage

might be lowered without loss of benefit ([Ravizza et al. 1996](#)).

## Long-Term Treatment and Relapse Prevention

Long-term pharmacological treatments of OCD have suggested sustained response beyond the acute treatment phase. In addition, clomipramine, paroxetine, sertraline, and escitalopram all have been shown to be more effective than placebo in prevention of OCD relapse ([Fineberg et al. 2005, 2007](#)). SSRIs appear to be well tolerated in these studies.

## Augmentation, Combination, and Other Strategies

Up to 60% of OCD patients show at least a partial response to SSRIs, although full remission is rare. Relapse can occur even during SSRI treatment, and comorbidity is common. The following augmentation, combination, and other novel strategies have been reported as offering benefit:

- The addition of fluvoxamine to clomipramine ([Szegeedi et al. 1996](#)) may be helpful for partial responders, as fluvoxamine inhibits clomipramine's demethylation, thus increasing the amount of available clomipramine and producing a potentiating effect. Monitoring of plasma levels and electrocardiograms is important with this combination to avoid toxicity and seizures.

- The use of intravenous clomipramine ([Fallon et al. 1992](#)) prevents first-pass metabolism, and side effects may be less severe. A double-blind trial of intravenous clomipramine suggested greater benefit with intravenous loading than with oral loading ([Koran et al. 1997](#)).
- In treatment-naïve (i.e., without refractory OCD) patients, the addition of quetiapine (moderate dosage) to high-dosage citalopram treatment was more effective than placebo augmentation ([Vulink et al. 2009](#)).
- The benzodiazepine clonazepam has been added to clomipramine treatment with mixed benefit ([Pigott et al. 1992](#)) and to sertraline treatment with no added benefit ([Crockett et al. 1999](#)).
- Patients with SRI-refractory OCD may benefit from antipsychotic augmentation. A meta-analysis demonstrated significant benefits for haloperidol and risperidone over placebo augmentation in OCD patients who failed to respond to an adequate SRI trial, whereas evidence for olanzapine and quetiapine was less robust ([Bloch et al. 2006](#)). However, quetiapine was superior to aripiprazole as an augmentation strategy in patients with OCD that was resistant to SRI treatment ([Shoja Shafiti and Kaviani 2015](#)).
- The addition of lithium, buspirone, desipramine, gabapentin, or ondansetron to SRIs has produced very limited benefits in studies to date, although there may be occasional patients for whom such combinations are helpful.
- Topiramate augmentation of maximum-dosage SSRI treatment in patients with treatment-refractory OCD had a beneficial effect on compulsions, but not obsessions, and was poorly tolerated ([Berlin et al. 2011](#)).

- One report suggested that St. John's wort (*Hypericum perforatum*) produced some improvement after 12 weeks of treatment in 12 patients with OCD ([Taylor and Kobak 2000](#)). However, a subsequent and adequately powered placebo-controlled study was negative ([Kobak et al. 2005](#)).
- Inositol, a naturally occurring second-messenger precursor, led to greater OCD symptom improvement than placebo at a dosage of 18 g/day for 6 weeks ([Fux et al. 1996](#)).
- Neurosurgical approaches (cingulotomy or anterior capsulotomy) can be helpful for refractory OCD. Between 25% and 50% of subjects show marked improvement, and the side-effect burden of this procedure is small ([Baer et al. 1995](#); [Jenike et al. 1991](#); [Pepper et al. 2015](#)).
- Small but promising studies also suggest benefits from deep brain stimulation for patients with treatment-refractory OCD ([Denys et al. 2010](#); [Greenberg et al. 2006](#); [Pepper et al. 2015](#)).
- rTMS studies have been limited in number of subjects and methodology and have yielded mixed results in patients with treatment-refractory OCD ([Mantovani et al. 2010](#); [Ruffini et al. 2009](#); [Sachdev et al. 2007](#); [Sarkhel et al. 2010](#)). A recent meta-analysis of rTMS augmentation of SSRI treatment in medication-resistant OCD showed positive results ([Ma and Shi 2014](#)).
- CBT is well established in the treatment of OCD, and evidence for its efficacy is strong, including as maintenance therapy ([Eddy et al. 2004](#); [Foa et al. 2005](#); [Peselow et al. 2015](#)). CBT employing exposure with response prevention is a first-choice option for OCD. One landmark study demonstrated that exposure with response prevention was superior to stress management

training as an augmentation strategy in clomipramine partial responders ([Simpson et al. 2008](#)).

---

## Posttraumatic Stress Disorder and Acute Stress Disorder

---

Although both posttraumatic stress disorder (PTSD) and acute stress disorder (ASD) were moved to a new disorder category—Trauma- and Stressor-Related Disorders—in DSM-5, we continue to include them in this review of anxiety-related conditions because of the similarities between their presentations, treatment interventions, and comorbid conditions and those of the anxiety disorders.

### Posttraumatic Stress Disorder

Posttraumatic stress disorder is a chronic and disabling disorder with a lifetime prevalence of about 7% ([Kessler et al. 2005a](#)). It can lead to significant functional impairment and inflict an enormous burden on society.

Treatment of PTSD must target the core symptoms of the disorder, focusing on improving resilience and quality of life and reducing comorbidity and disability. Widely used instruments (most of which are linked to DSM-IV [[American Psychiatric Association 1994](#)] criteria) include the Clinician-Administered PTSD Scale (CAPS; [Weathers et al. 2001](#)) and the more globally oriented Short PTSD Rating Instrument (SPRINT; [Connor and Davidson 2001](#)). Self-rating scales include the Davidson Trauma Scale (DTS; [Davidson et al. 1997a](#)), the PTSD Checklist (PCL; [Weathers et al. 1991](#)),

and the SPRINT, which also has been validated as a self-rating. DSM-5 ([American Psychiatric Association 2013](#))-based instruments (e.g., CAPS, PCL) have been developed and are in the process of being validated.

## Antidepressants

The TCAs and MAOIs were among the first pharmacological agents studied in controlled trials of PTSD. More recently, several controlled multicenter trials have shown efficacy for the SSRIs and SNRIs. With the documented antidepressant and anxiolytic effects of these agents and the high rates of comorbid depression in PTSD ([Kessler et al. 1995](#)), antidepressants would seem a logical choice for PTSD treatment.

**Tricyclic antidepressants.** Two controlled trials of TCAs in male combat veterans with DSM-III-defined ([American Psychiatric Association 1980](#)) PTSD showed benefit for amitriptyline and imipramine ([Davidson et al. 1990](#); [Kosten et al. 1991](#)). A recent report suggests that the now-ignored TCAs deserve reappraisal, given their efficacy in populations with traditionally SSRI-resistant PTSD ([Davidson 2015](#)) and the superiority of desipramine over paroxetine in improving drinking-related measures in male veterans with comorbid alcohol-related disorders ([Petrakis et al. 2012](#)).

**Monoamine oxidase inhibitors.** In a study of male combat veterans, [Kosten et al. \(1991\)](#) compared phenelzine (15–75 mg/day) with placebo and found a 45% decrease in Impact of Event Scale (IES) scores from baseline for phenelzine, compared with a 5% decrease for placebo, but no improvement was noted in depressive symptoms with

either treatment. The RIMA brofaromine has been assessed in two controlled trials of PTSD: a U.S. sample composed predominantly of combat veterans ( $n=114$ ) ([Baker et al. 1995](#)) and a civilian European sample with few veterans ( $n=68$ ) ([Katz et al. 1994-1995](#)). The U.S. study failed to show a difference between the treatments, and findings from the European study were mixed. Finally, the RIMA moclobemide was assessed in 20 subjects with PTSD meeting DSM-III-R ([American Psychiatric Association 1987](#)) criteria ([Neal et al. 1997](#)). Following 12 weeks of treatment, 11 subjects no longer met the full PTSD criteria, providing a signal that the drug might be effective in PTSD.

### **Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.**

Three controlled trials support the efficacy of fluoxetine in PTSD. In these studies, fluoxetine was administered at dosages of 20-80 mg/day for 5-12 weeks in samples including both civilians and combat veterans with PTSD meeting DSM-III-R ([Connor et al. 1999](#); [van der Kolk et al. 1994](#)) or DSM-IV ([Martenyi et al. 2002a](#)) criteria. Significant improvements in clinician-rated structured interviews from baseline to end of treatment were noted, as were significant improvements in resilience and reduction in disability ([Connor et al. 1999](#)). Symptomatic improvement was noted as early as week 6 ([Martenyi et al. 2002a](#)).

Two studies of maintenance therapy with fluoxetine over a period of 1 year have shown reductions in the rate of relapse, as compared with placebo substitution ([Davidson et al. 2005](#); [Martenyi et al. 2002b](#)).

Sertraline has been compared against placebo in 10 trials, and positive results have emerged in 3 of these

([Brady et al. 2000](#); [Davidson et al. 2001](#); [Panahi et al. 2011](#)), while 7 were either ambiguous or negative. A pooled analysis of the positive trials showed an early effect on anger at 1 week ([Davidson et al. 2002](#)). This finding is of significance, given that angry temperament can be associated with violence and a greater risk for cardiac events ([Williams et al. 2001](#)), as well as increased heart rate and blood pressure, in PTSD ([Beckham et al. 2002](#)). A recent placebo-controlled trial of sertraline in Iranian veterans of the Iran-Iraq war showed that sertraline was superior to placebo and was well tolerated ([Panahi et al. 2011](#)). Other short-term studies of sertraline in PTSD have been negative ([Brady et al. 2005](#); [Davidson et al. 2006b](#); [Friedman et al. 2007](#); [Tucker et al. 2003](#)) or inconclusive ([Zohar et al. 2002](#)). A trial in children by [Robb et al. \(2010\)](#) failed to show any difference between drug and placebo.

Continued sertraline treatment over 9 months was associated with sustained improvement in more than 90% of subjects, and more than 50% of initial nonresponders responded with continued treatment ([Londborg et al. 2001](#)). Improvement was sustained over 15 months, with a relapse rate of 5% for sertraline and 26% for placebo, suggesting that the drug provides prophylactic protection against relapse ([Davidson et al. 2001](#)). Sertraline was also effective in improving quality of life and reducing functional impairment, with more than 55% of patients functioning at levels within 10% of the general population. These gains were maintained with long-term treatment, whereas treatment discontinuation was more likely to lead to deteriorating function, although not to levels observed prior to treatment ([Rapaport et al. 2002](#)).

The efficacy of paroxetine in PTSD has been shown in two 12-week controlled multicenter trials, including flexible-



dose ( $n=307$ ; paroxetine 20–50 mg/day) ([Tucker et al. 2001](#)) and fixed-dose ( $n=451$ ; paroxetine 20 mg/day or 40 mg/day) ([Marshall et al. 2001](#)) regimens. Compared with placebo, paroxetine produced significant improvement in overall PTSD symptomatology, individual symptom clusters, and functional impairment. Response rates ranged from 54% to 62% for paroxetine, compared with 37% to 40% for placebo.

Findings from two open-label studies of fluvoxamine at dosages of 100–250 mg/day—an 8-week study in civilians ( $n=15$ ; [Davidson et al. 1998](#)) and a 10-week study in combat veterans ( $n=10$ ; [Marmar et al. 1996](#))—showed that the drug was effective in treating PTSD symptoms. Treatment with fluvoxamine (mean=194 mg/day) also was associated with significant improvement in autonomic reactivity, with reductions in heart rate and blood pressure on exposure to trauma cues to levels that are indistinguishable from those of control subjects ([Tucker et al. 2000](#)). These findings are encouraging, although larger controlled trials are needed to determine the efficacy of the drug in PTSD.

Two large multicenter studies have established efficacy for venlafaxine XR up to 300 mg per day, in one case for as long as 6 months. Rates of remission exceeded 50% in the longer-term trial, and resilience was significantly improved in one of the two studies ([Davidson et al. 2006a, 2006b](#)).

In summary, the SSRIs are efficacious in the treatment of PTSD, and paroxetine IR and sertraline are approved for PTSD treatment. SSRIs and SNRIs show a broad spectrum of activity, with significant reduction in some symptoms as early as 1–2 weeks after treatment initiation, sustained and continued improvement, and in some cases remission, with long-term treatment up to 15 months. These drugs are

generally well tolerated, although some adverse effects (e.g., sexual dysfunction, sleep disturbances, and weight gain) may lead to treatment discontinuation.

**Other antidepressants.** An 8-week controlled trial of mirtazapine in 29 outpatients with PTSD showed a 65% response rate on clinician-rated global assessment with mirtazapine compared with a rate of 20% with placebo, with significant improvement on several measures of PTSD as well as general anxiety ([Davidson et al. 2003](#)).

Six open-label studies of nefazodone in civilians and combat veterans with PTSD have been reported ([Hidalgo et al. 1999](#)). Treatment with nefazodone (50–600 mg/day) over 6–12 weeks was associated with significant reduction in severity of overall PTSD, as well as in each of the symptom clusters. Of particular note was improvement in sleep, which is often disrupted in PTSD and sometimes worsened by treatment with SSRIs. [Davis et al. \(2004\)](#) have demonstrated superior efficacy for nefazodone relative to placebo in combat veterans. However, concerns about potential liver damage have limited the drug's use in PTSD.

## Anxiolytics

Benzodiazepines are often prescribed to treat acute anxiety in the aftermath of a trauma; however, findings have been disappointing. An open-label study of alprazolam and clonazepam in 13 outpatients with PTSD found reduced hyperarousal symptoms but no change in intrusion or avoidance/numbing ([Gelpin et al. 1996](#)). In a crossover design, subjects received 5 weeks of treatment with either alprazolam or placebo followed by 5 weeks of the alternative therapy ([Braun et al. 1990](#)). Minimal improvement was observed in anxiety symptoms overall,

with no improvement in core PTSD symptoms. Clonazepam 2 mg was not different from placebo in controlling nightmares in a 2-week single-blind crossover study in which the test drug was added to preexisting treatment ([Cates et al. 2004](#)). Thus, the evidence does not support the use of benzodiazepines in the management of core PTSD symptoms, even though they appear to be widely used for that purpose ([Mellman et al. 2003](#)). Furthermore, a recent meta-analysis of the efficacy of benzodiazepines in the treatment of PTSD found them to be not only ineffective but also potentially harmful, in terms of increasing the risk of developing PTSD if prescribed after recent trauma as well as worsening aggression, depression, and comorbid substance use ([Guina et al. 2015](#)). Benzodiazepines should therefore be considered relatively contraindicated for use in PTSD or after recent trauma exposure.

## **Anticonvulsants**

[Lipper et al. \(1986\)](#) proposed that the pathophysiology of PTSD may involve sensitization and kindling processes and, to this end, that anticonvulsants might be of therapeutic benefit. In testing this hypothesis, Lipper and colleagues found that 7 of 10 Vietnam War veterans who received open-label carbamazepine (600–1,000 mg/day) for 5 weeks reported improvement, particularly in intrusion and hyperarousal symptoms. Three subsequent open-label studies, two with sodium valproate in combat veterans ([Clark et al. 1999](#); [Fesler 1991](#)) and one with adjunctive topiramate in a civilian PTSD sample ([Berlant and van Kammen 2002](#)), also reported positive effects. However, two more recent double-blind, placebo-controlled trials of divalproex monotherapy in combat veterans with PTSD

were negative ([Davis et al. 2008a](#),  $n=85$ ; [Hamner et al. 2009](#),  $n=29$ ).

Topiramate has received mixed reports in PTSD. An initial trial was negative ([Tucker et al. 2007](#)); however, a more recent double-blind, placebo-controlled trial in 70 civilians (men and women) showed positive effects on re-experiencing and numbing/avoidance symptoms for topiramate at a mean dosage of 102.9 mg/day ([Yeh et al. 2011](#)). Topiramate at dosages up to 300 mg/day in a prospective 12-week, randomized, placebo-controlled, flexible-dose trial also decreased alcohol consumption and cravings and improved hyperarousal symptoms in 30 veterans diagnosed with PTSD and alcohol use disorder ([Batki et al. 2014](#)).

The largest placebo-controlled trial of an anticonvulsant to date found no difference between tiagabine (at a dosage of up to 16 mg/day) and placebo in a 12-week multicenter trial in 232 patients ([Davidson et al. 2007](#)). In a small placebo-controlled trial of lamotrigine (200–500 mg/day) in 15 outpatients ([Hertzberg et al. 1999](#)), a response rate of 50% was noted with lamotrigine, compared with a placebo response rate of 25%.

## Other Treatments

**Antipsychotics.** In a monotherapy trial of olanzapine ([Butterfield et al. 2001](#)), 15 subjects were randomly assigned 2:1 to treatment with olanzapine (up to 20 mg/day) or placebo. No differences were observed between the treatments; however, it is difficult to interpret the findings in this small sample, especially given the high placebo response rate (60%). In a recent small randomized, placebo-controlled trial of flexible-dose olanzapine

monotherapy in a population with non-combat-related chronic PTSD, olanzapine was found to be superior to placebo, though approximately half of the patient sample experienced significant weight gain (Carey et al. 2012). Other reports of antipsychotics are based on augmentation therapy in SSRI partial responders. Several placebo-controlled studies, mainly of augmentation therapy, have found superior efficacy for low-dosage risperidone in both civilian and veteran populations (Bartzokis et al. 2005; Hamner et al. 2003; Monnelly et al. 2003; Reich et al. 2004; Rothbaum et al. 2008), as well as for olanzapine (Stein et al. 2002). In the Monnelly et al. (2003) study, particular benefit was noted for irritability, and in the Hamner et al. (2003) study, psychotic symptoms were relieved. However, a recent large double-blind, placebo-controlled trial of adjunctive risperidone treatment in a patient population with military-related PTSD and SSRI-resistant symptoms found no major benefit for risperidone, although statistically significant changes occurred on some measures (Krystal et al. 2011).

In a double-blind, placebo-controlled monotherapy trial of quetiapine in 80 patients with chronic PTSD, a significant improvement in CAPS scores, as well as in reexperiencing and hyperarousal subscores, was seen by the end of the 12-week trial at an average dosage of 258 mg/day (range 50–800 mg/day) (Villarreal et al. 2016).

**Prazosin and guanfacine.** Raskind et al. (2003) reported encouraging results for intractable PTSD-related nightmares in a placebo-controlled crossover study of prazosin, an  $\alpha_1$ -adrenergic antagonist, at dosages of up to 10 mg/day. The initial findings were confirmed in a second and larger placebo-controlled, double-blind augmentation trial in combat veterans, using dosages of up to 15 mg

daily; benefits were most apparent for nightmares and sleep quality, but the drug also produced greater global improvement ([Raskind et al. 2007](#)). In a randomized, placebo-controlled crossover study of prazosin in 13 patients with civilian trauma-related PTSD, [Taylor et al. \(2008\)](#) found that prazosin significantly increased total and rapid eye movement (REM) sleep time, reduced trauma-related nightmares and awakenings, and improved PCL and CGI scores. A study comparing prazosin with quetiapine for nighttime PTSD symptoms found similar short-term effectiveness for the two drugs but a greater likelihood of treatment discontinuation due to adverse effects for quetiapine ([Byers et al. 2010](#)). A recent randomized controlled 15-week trial in active-duty soldiers showed prazosin to be effective in decreasing global PTSD symptoms and to be well tolerated at maximum dosages of up to 25 mg/day for men and 12 mg/day for women ([Raskind et al. 2013](#)).

In contrast, two placebo-controlled studies of the  $\alpha_2$ -adrenergic agonist guanfacine in veterans with PTSD found no benefit ([Davis et al. 2008b](#); [Neylan et al. 2006](#)).

**Additional approaches.** Given the prevalence of comorbid depression with PTSD and the effectiveness of triiodothyronine ( $T_3$ ) augmentation in some individuals with treatment-refractory depression, it is possible that  $T_3$  augmentation also may be of benefit in PTSD. Five subjects with PTSD taking an SSRI were treated with open-label  $T_3$  (25  $\mu$ g/day) for 8 weeks ([Agid et al. 2001](#)). Improvement was noted as early as 2 weeks, and by the end of treatment, four of the five subjects showed at least partial improvement in depressive symptoms and hyperarousal.

The mechanism for these effects is unknown, and further controlled studies of this augmentation strategy are needed. Cyproheptadine, an antihistaminic drug, was no more effective than placebo for nightmares over 2 weeks in a series of 69 combat veterans with PTSD ([Jacobs-Rebhun et al. 2000](#)). The naturally occurring compound inositol was ineffective in a small placebo-controlled trial ([Kaplan et al. 1996](#)). Innovative treatments with some promise include the NMDA agonist D-serine ([Heresco-Levy et al. 2009](#); [de Kleine et al. 2012](#)) and the neurokinin-1 receptor antagonist GR205171 ([Mathew et al. 2011](#)).

Low-intensity repetitive transcranial magnetic stimulation (rTMS)—in particular, right-sided rTMS applied to the dorsolateral prefrontal cortex ([Boggio et al. 2010](#))—has shown some promise in PTSD, as has acupuncture ([Hollifield et al. 2007](#)). An open trial of electroconvulsive therapy (ECT) in 20 patients with chronic, treatment-refractory PTSD showed improvement in CAPS-rated PTSD symptoms, independent of depressive symptoms ([Margoob et al. 2010](#)). Larger double-blind studies are needed before these somatic treatments can be recommended for PTSD.

An open trial in 166 active-duty soldiers with multiple combat deployments reported that stellate ganglion block led to improvement in PCL scores that was sustained at 6 months ([Mulvaney et al. 2014](#)). However, a recent randomized, placebo-controlled trial of this procedure in 42 military service members with PTSD found no benefit ([McLay et al. 2015](#)).

Ketamine infusion was compared with an active placebo control (midazolam) in a randomized, double-blind, crossover trial in 41 subjects with chronic PTSD ([Feder et al. 2014](#)). The authors reported rapid and significant reduction in PTSD symptoms 24 hours after the infusion, as



well as improvement in comorbid depression. Larger controlled trials are needed to further assess the benefits of this intervention.

CBT has been extensively studied in PTSD and shows overall efficacy ([Bisson and Andrew 2005](#)). In one large well-designed multicenter trial ([Schnurr et al. 2007](#)), the effect size and number-needed-to-treat results for CBT were of the same order of magnitude as those found in comparable trials of antidepressant drugs for PTSD. However, there are only limited data on the combined use of antidepressants and CBT ([Rothbaum et al. 2006](#); [Schneier et al. 2012](#); [Simon et al. 2008](#)), and there have been no head-to-head trials of CBT and medication monotherapies. Exposure is regarded as the key therapeutic principle in the numerous variants of CBT and is recommended as a first-line treatment for PTSD. Modest preservation of gains is found at long-term follow-up ([Bradley et al. 2005](#)), but much pathology remains.

There has been recent interest in enhancement of exposure therapy by using nonantidepressant drugs that modulate memory through one of the following mechanisms: 1) strengthening fear extinction learning, 2) disrupting memory consolidation, or 3) enhancing engagement in therapy ([Dunlop et al. 2012](#)). Among agents in the first category are D-cycloserine, yohimbine, methylene blue, and hydrocortisone. The second category includes propranolol, mifepristone, and rapamycin. The last category refers specifically to 3,4-methylenedioxymethamphetamine (MDMA), with more than one positive trial of MDMA in facilitation of intensive psychotherapy ([White 2014](#)). At present, the evidence for drug-based enhancement of exposure therapy for PTSD is not clear, and the long-term deleterious effects of such



interventions need to be studied further, but it may be a promising therapeutic approach.

## Acute Stress Disorder and the Immediate Aftermath of Trauma

ASD develops shortly after a traumatic event; it includes symptoms of intrusion, negative mood, dissociation, avoidance, and arousal that persist for at least 3 days and up to 1 month following the trauma and that cause significant distress and/or functional impairment ([American Psychiatric Association 2013](#)). ASD was first included in DSM-IV and further modified in DSM-5, and it has been suggested that early intervention may help to alter the course of PTSD, which would imply early identification and treatment of those with or at risk for ASD.

The effects of open-label treatment with risperidone have been reported in four inpatient survivors of physical trauma with ASD; this drug showed possible benefit in flashback symptoms ([Eidelman et al. 2000](#)).

A controlled pilot study assessed the effects of low-dosage imipramine compared with chloral hydrate in 25 pediatric burn patients with ASD ([Robert et al. 1999a](#)). After 1 week of treatment, 38% of the subjects responded to treatment with placebo, compared with 83% responding to imipramine, and an early report noted reduction in intrusion and hyperarousal symptoms ([Robert et al. 1999b](#)). Unfortunately, a subsequent placebo-controlled trial failed to replicate these promising initial findings ([Robert et al. 2008](#)).

The effects of  $\beta$ -adrenergic blockade in reducing subsequent PTSD following acute trauma were also

evaluated ([Pitman et al. 2002](#)). Within 6 hours of the trauma, subjects were treated with either propranolol ( $n=18$ ; 40 mg four times per day) or placebo ( $n=23$ ) for 10 days, followed by a 9-day taper period. PTSD was noted in 30% of the placebo group compared with 10% of the propranolol group 1 month after the trauma, and at 3-month follow-up, physiological arousal rate to trauma cues was 43% in the placebo group compared with 0% of the propranolol group. However, a follow-up double-blind, randomized controlled 14-day trial of propranolol and gabapentin versus placebo, administered within 48 hours of admission to a surgical trauma unit, did not demonstrate any benefits of the two active drugs over placebo on depressive or PTSD symptoms ([Stein et al. 2007](#)).

A short-term trial with temazepam versus placebo in the acute aftermath of trauma showed no long-term benefits and possibly worse PTSD outcomes at 6-week follow-up ([Mellman et al. 2002](#)).

Three promising studies have found greater long-term benefit for short-term hydrocortisone versus placebo in high-risk subjects recovering from septic shock, cardiac surgery, or acute respiratory distress syndrome ([Hauer et al. 2009](#); [Schelling et al. 2006](#)). In subpopulations with critical illness-related corticosteroid insufficiency, this might be an attractive treatment approach for preventing PTSD. One limitation of the authors' work, however, has been the absence of baseline PTSD ratings before administration of hydrocortisone.

SSRI trials in ASD have been negative so far. [Shalev et al. \(2012\)](#) showed that prolonged exposure therapy and cognitive therapy both initially prevented PTSD in recent trauma survivors with ASD at the 1-month and 5-month follow-ups, whereas escitalopram did not. However, at the

36-month follow-up, the study groups (prolonged exposure, cognitive therapy, escitalopram, placebo, and no intervention) had similar PTSD rates, as measured by the CAPS ([Shalev et al. 2016](#)). Similarly, a double-blind, placebo-controlled 24-week trial in 31 subjects with full or partial ASD showed no difference between escitalopram and placebo ([Suliman et al. 2015](#)).

Treatment with morphine in the immediate aftermath of traumatic injury was associated with lower rates of PTSD in a sample of 696 U.S. military personnel identified through records review ([Holbrook et al. 2010](#)). Morphine may act by inhibiting stress-enhanced fear learning; however, further studies are needed to assess the immediate and long-term effects of this intervention. Shortened forms of CBT appear to be effective for acute PTSD-like states, with persistence of gain at 4-year follow-up ([Bryant et al. 1998, 2003](#)).

---

## Conclusion

---

Twenty years ago, few would have thought that one class of drugs, the SSRIs, all of which were initially introduced for depression, would have established primacy in most major anxiety (or anxiety-related) disorders. Their position is based on numerous placebo-controlled trials, and they are considered first-line drugs for treatment of these disorders, followed closely by the SNRIs. There is evidence that these drugs also offer some protection against relapse. However, they are not 100% successful, they carry some limiting side effects, and they may require supplementation with, or substitution by, drugs from other categories. We have reviewed the main clinical trials of these other drugs and

expect further progress in the pharmacotherapy of anxiety and related disorders, with both established drugs and novel categories. Among many unexplored areas, we need to know more about the treatment of resistant and comorbid anxiety disorders, combined psychotherapy and pharmacotherapy interventions, the comparative efficacy of pharmacotherapy and psychosocial treatments, and possible early interventions that may help prevent and/or alleviate the severity and chronicity of these conditions.

---

## References

---

- Agid O, Shalev AY, Lerer B: Triiodothyronine augmentation of selective serotonin reuptake inhibitors in posttraumatic stress disorder. *J Clin Psychiatry* 62(3): 169-173, 2001 11305702
- Alamy S, Wei Zhang, Varia I, et al: Escitalopram in specific phobia: results of a placebo-controlled pilot trial. *J Psychopharmacol* 22(2):157-161, 2008 18208904
- Allgulander C: Paroxetine in social anxiety disorder: a randomized placebo-controlled study. *Acta Psychiatr Scand* 100(3):193-198, 1999 10493085
- Allgulander C, Hackett D, Salinas E: Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. *Br J Psychiatry* 179:15-22, 2001 11435263
- Allgulander C, Dahl AA, Austin C, et al: Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry* 161(9):1642-1649, 2004 15337655
- Allgulander C, Florea I, Huusom AK: Prevention of relapse in generalized anxiety disorder by escitalopram

treatment. *Int J Neuropsychopharmacol* 9(5):495–505, 2006 16316482

Allgulander C, Hartford J, Russell J, et al: Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin* 23(6):1245–1252, 2007 17559726

Alonso J, Angermeyer MC, Bernert S, et al; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project: Sampling and methods of the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* (420):8–20, 2004 15128383

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC, American Psychiatric Association, 2013

Amsterdam JD, Li Y, Soeller I, et al: A randomized, double-blind, placebo-controlled trial of oral *Matricaria recutita* (chamomile) extract therapy for generalized anxiety disorder. *J Clin Psychopharmacol* 29(4):378–382, 2009 19593179

Andersch S, Rosenberg NK, Kullingsjö H, et al: Efficacy and safety of alprazolam, imipramine and placebo in treating panic disorder. A Scandinavian multicenter study. *Acta Psychiatr Scand Suppl* 365:18–27, 1991 1862730

Asakura S, Tajima O, Koyama T: Fluvoxamine treatment of generalized social anxiety disorder in Japan: a

- randomized double-blind, placebo-controlled study. *Int J Neuropsychopharmacol* 10(2):263-274, 2007 16573847
- Asnis GM, Hameedi FA, Goddard AW, et al: Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients. *Psychiatry Res* 103(1):1-14, 2001 11472786
- Baer L, Rauch SL, Ballantine HT Jr, et al: Cingulotomy for intractable obsessive-compulsive disorder. Prospective long-term follow-up of 18 patients. *Arch Gen Psychiatry* 52(5):384-392, 1995 7726719
- Baker DG, Diamond BI, Gillette G, et al: A double-blind, randomized, placebo-controlled, multi-center study of brofaromine in the treatment of post-traumatic stress disorder. *Psychopharmacology (Berl)* 122(4):386-389, 1995 8657838
- Baldwin D, Bobes J, Stein DJ, et al; Paroxetine Study Group: Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 175:120-126, 1999 10627793
- Baldwin DS, Huusom AK, Maehlum E: Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. *Br J Psychiatry* 189:264-272, 2006 16946363
- Ballenger JC, Wheadon DE, Steiner M, et al: Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. *Am J Psychiatry* 155(1):36-42, 1998 9433336
- Bandelow B, Hajak G, Holzrichter S, et al: Assessing the efficacy of treatments for panic disorder and agoraphobia, I: methodological problems. *Int Clin Psychopharmacol* 10(2):83-93, 1995 7673660
- Bandelow B, Chouinard G, Bobes J, et al: Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and

- active-controlled study. *Int J Neuropsychopharmacol* 13(3):305-320, 2010 19691907
- Barnett SD, Kramer ML, Casat CD, et al: Efficacy of olanzapine in social anxiety disorder: a pilot study. *J Psychopharmacol* 16(4):365-368, 2002 12503837
- Bartzokis G, Lu PH, Turner J, et al: Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry* 57(5):474-479, 2005 15737661
- Batki SL, Pennington DL, Lasher B, et al: Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: a randomized controlled pilot trial. *Alcohol Clin Exp Res* 38(8):2169-2177, 2014 25092377
- Beckham JC, Vrana SR, Barefoot JC, et al: Magnitude and duration of cardiovascular responses to anger in Vietnam veterans with and without posttraumatic stress disorder. *J Consult Clin Psychol* 70(1):228-234, 2002 11860049
- Bell J, DeVeaugh-Geiss J: Multicenter trial of a 5-HT antagonist, ondansetron, in social phobia. Paper presented at the 33rd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 12-16, 1994
- Bellew KM, McCafferty JP, Iyengar M: Short-term efficacy of paroxetine in generalized anxiety disorder: a double-blind placebo-controlled trial (NR253). Paper presented at the 153rd Annual Meeting of the American Psychiatric Association, Chicago, IL, May 13-18, 2000
- Benjamin J, Ben-Zion IZ, Karbofsky E, Dannon P: Double-blind placebo-controlled pilot study of paroxetine for specific phobia. *Psychopharmacology (Berl)* 149(2):194-196, 2000 10805616
- Bergink V, Westenberg HG: Metabotropic glutamate II receptor agonists in panic disorder: a double blind

- clinical trial with LY354740. *Int Clin Psychopharmacol* 20(6):291-293, 2005 16192835
- Berigan TR: Panic attacks during escalation of mirtazapine (abstract). *Prim Care Companion J Clin Psychiatry* 5(2):93, 2003 15156239
- Berlant J, van Kammen DP: Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry* 63(1):15-20, 2002 11838620
- Berlin HA, Koran LM, Jenike MA, et al: Double-blind, placebo-controlled trial of topiramate augmentation in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry* 72(5):716-721, 2011 20816027
- Bertani A, Perna G, Migliarese G, et al: Comparison of the treatment with paroxetine and reboxetine in panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 37(5):206-210, 2004 15359375
- Bielski RJ, Bose A, Chang CC: A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. *Ann Clin Psychiatry* 17(2):65-69, 2005 16075658
- Bisson J, Andrew M: Psychological treatment of post-traumatic stress disorder (PTSD). *Cochrane Database Syst Rev* (2):CD003388, 2005 15846661
- Black DW, Wesner R, Bowers W, Gabel J: A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. *Arch Gen Psychiatry* 50(1):44-50, 1993 8422221
- Blanco C, Heimberg RG, Schneier FR, et al: A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. *Arch Gen Psychiatry* 67(3):286-295, 2010 20194829
- Blanco C, Rubio JM, Wall M, et al: The latent structure and comorbidity patterns of generalized anxiety disorder and



- major depressive disorder: a national study. *Depress Anxiety* 31(3):214-222, 2014 23776155
- Bloch MH, Landeros-Weisenberger A, Kelmendi B, et al: A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry* 11(7):622-632, 2006 16585942
- Blomhoff S, Haug TT, Hellström K, et al: Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *Br J Psychiatry* 179:23-30, 2001 11435264
- Boggio PS, Rocha M, Oliveira MO, et al: Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *J Clin Psychiatry* 71(8):992-999, 2010 20051219
- Bonne O, Shemer Y, Goral Y, et al: A randomized, double-blind, placebo-controlled study of classical homeopathy in generalized anxiety disorder. *J Clin Psychiatry* 64(3):282-287, 2003 12716269
- Boshuisen ML, Slaap BR, Vester-Blokland ED, den Boer JA: The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol* 16(6):363-368, 2001 11712626
- Boyer W: Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. *Int Clin Psychopharmacol* 10(1):45-49, 1995 7622804
- Bradley R, Greene J, Russ E, et al: A multidimensional meta-analysis of psychotherapy for PTSD. *Am J Psychiatry* 162(2): 214-227, 2005 15677582
- Bradwejn J, Ahokas A, Stein DJ, et al: Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry* 187:352-359, 2005 16199795

- Brady K, Pearlstein T, Asnis GM, et al: Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* 283(14):1837-1844, 2000 10770145
- Brady KT, Sonne S, Anton RF, et al: Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. *Alcohol Clin Exp Res* 29(3):395-401, 2005 15770115
- Braun P, Greenberg D, Dasberg H, Lerer B: Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *J Clin Psychiatry* 51(6):236-238, 1990 2189869
- Brawman-Mintzer O, Knapp RG, Rynn M, et al: Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 67(6):874-881, 2006 16848646
- Bruscky SB, Caldeira MV, Bueno JR: [Clinical trial with sulpiride]. *Arq Neuropsiquiatr* 32(3):234-239, 1974 4408939
- Bryant RA, Harvey AG, Dang ST, et al: Treatment of acute stress disorder: a comparison of cognitive-behavioral therapy and supportive counseling. *J Consult Clin Psychol* 66(5):862-866, 1998 9803707
- Bryant RA, Moulds ML, Nixon RV: Cognitive behaviour therapy of acute stress disorder: a four-year follow-up. *Behav Res Ther* 41(4):489-494, 2003 12643970
- Butterfield MI, Becker ME, Connor KM, et al: Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. *Int Clin Psychopharmacol* 16(4):197-203, 2001 11459333
- Byers MG, Allison KM, Wendel CS, Lee JK: Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. *J Clin Psychopharmacol* 30(3):225-229, 2010 20473055

- Byrne SP, Rapee RM, Richardson R, et al: D-cycloserine enhances generalization of fear extinction in children. *Depress Anxiety* 32(6):408-414, 2015 25775435
- Bystritsky A, Kerwin L, Feusner JD, Vapnik T: A pilot controlled trial of bupropion XL versus escitalopram in generalized anxiety disorder. *Psychopharmacol Bull* 41(1):46-51, 2008 18362870
- Carey P, Suliman S, Ganesan K, et al: Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. *Hum Psychopharmacol* 27(4):386-391, 2012 22730105
- Cates ME, Bishop MH, Davis LL, et al: Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. *Ann Pharmacother* 38(9):1395-1399, 2004 15252193
- Charney DS, Woods SW, Goodman WK, et al: Drug treatment of panic disorder: the comparative efficacy of imipramine, alprazolam, and trazodone. *J Clin Psychiatry* 47(12):580-586, 1986 3536889
- Chen A, Zhao Y, Yu X: The clinical study of antianxiety and antidepressant effect of sulpiride. *Chin J Neurol Psychiatry* 27: 220-222, 1994
- Clark DM, Ehlers A, McManus F, et al: Cognitive therapy versus fluoxetine in generalized social phobia: a randomized placebo-controlled trial. *J Consult Clin Psychol* 71(6):1058-1067, 2003 14622081
- Clark RD, Cañive JM, Calais LA, et al: Divalproex in posttraumatic stress disorder: an open-label clinical trial. *J Trauma Stress* 12(2):395-401, 1999 10378177
- Clomipramine Collaborative Study Group: Clomipramine in the treatment of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry* 48(8):730-738, 1991 1883256
- Clum GA, Clum GA, Surls R: A meta-analysis of treatments for panic disorder. *J Consult Clin Psychol* 61(2):317-326, 1993 8097212

- Cohn JB, Bowden CL, Fisher JG, Rodos JJ: Double-blind comparison of buspirone and clorazepate in anxious outpatients. *Am J Med* 80(3B):10-16, 1986 2870640
- Connor KM, Davidson JR: SPRINT: a brief global assessment of post-traumatic stress disorder. *Int Clin Psychopharmacol* 16(5):279-284, 2001 11552771
- Connor KM, Davidson JR: A placebo-controlled study of Kava kava in generalized anxiety disorder. *Int Clin Psychopharmacol* 17(4):185-188, 2002 12131602
- Connor KM, Davidson JR, Potts NL, et al: Discontinuation of clonazepam in the treatment of social phobia. *J Clin Psychopharmacol* 18(5):373-378, 1998 9790154
- Connor KM, Sutherland SM, Tupler LA, et al: Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. *Br J Psychiatry* 175:17-22, 1999 10621763
- Connor KM, Davidson JR, Churchill LE, et al: Psychometric properties of the Social Phobia Inventory (SPIN). New self-rating scale. *Br J Psychiatry* 176:379-386, 2000 10827888
- Connor KM, Cook JL, Davidson JR: Botulinum toxin treatment of social anxiety disorder with hyperhidrosis: a placebo-controlled double-blind trial. *J Clin Psychiatry* 67(1):30-36, 2006 16426085
- Crockett BA, Davidson JR, Churchill LE: Treatment of obsessive-compulsive disorder with clonazepam and sertraline versus placebo and sertraline. Paper presented at the 39th Annual Meeting of the New Clinical Drug Evaluation Unit, Boca Raton, FL, June 1, 1999
- Cross-National Collaborative Panic Study: Drug treatment of panic disorder. Comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 160: 191-202; discussion 202-205, 1992 1540759
- Dahl AA, Ravindran A, Allgulander C, et al: Sertraline in generalized anxiety disorder: efficacy in treating the

- psychic and somatic anxiety factors. *Acta Psychiatr Scand* 111(6):429-435, 2005 15877709
- Davidson J: Vintage treatments for PTSD: a reconsideration of tricyclic drugs. *J Psychopharmacol* 29(3):264-269, 2015 25586404
- Davidson JR, Moroz G: Pivotal studies of clonazepam in panic disorder. *Psychopharmacol Bull* 34(2):169-174, 1998 9640996
- Davidson J, Kudler H, Smith R, et al: Treatment of posttraumatic stress disorder with amitriptyline and placebo. *Arch Gen Psychiatry* 47(3):259-266, 1990 2407208
- Davidson JR, Hughes DL, George LK, Blazer DG: The epidemiology of social phobia: findings from the Duke Epidemiological Catchment Area Study. *Psychol Med* 23(3):709-718, 1993 8234577
- Davidson JR, Tupler LA, Potts NL: Treatment of social phobia with benzodiazepines. *J Clin Psychiatry* 55 (suppl):28-32, 1994 8077166
- Davidson JR, Book SW, Colket JT, et al: Assessment of a new self-rating scale for post-traumatic stress disorder. *Psychol Med* 27(1):153-160, 1997a 9122295
- Davidson JR, Miner CM, De Vaugh-Geiss J, et al: The Brief Social Phobia Scale: a psychometric evaluation. *Psychol Med* 27(1):161-166, 1997b 9122296
- Davidson JR, Weisler RH, Malik M, Tupler LA: Fluvoxamine in civilians with posttraumatic stress disorder. *J Clin Psychopharmacol* 18(1):93-95, 1998 9472854
- Davidson JR, DuPont RL, Hedges D, Haskins JT: Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *J Clin Psychiatry* 60(8):528-535, 1999 10485635
- Davidson J, Pearlstein T, Lonnberg P, et al: Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-

controlled study. *Am J Psychiatry* 158(12):1974-1981, 2001 11729012

Davidson JR, Landerman LR, Farfel GM, Clary CM: Characterizing the effects of sertraline in post-traumatic stress disorder. *Psychol Med* 32(4):661-670, 2002 12102380

Davidson JR, Weisler RH, Butterfield MI, et al: Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry* 53(2):188-191, 2003 12547477

Davidson JR, Bose A, Korotzer A, Zheng H: Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 19(4):234-240, 2004a 15274172

Davidson JR, Foa EB, Huppert JD, et al: Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry* 61(10):1005-1013, 2004b 15466674

Davidson J, Yaryura-Tobias J, DuPont R, et al: Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol* 24(2):118-125, 2004c 15206657

Davidson JR, Connor KM, Hertzberg MA, et al: Maintenance therapy with fluoxetine in posttraumatic stress disorder: a placebo-controlled discontinuation study. *J Clin Psychopharmacol* 25(2):166-169, 2005 15738748

Davidson J, Baldwin D, Stein DJ, et al: Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry* 63(10):1158-1165, 2006a 17015818

Davidson J, Rothbaum BO, Tucker P, et al: Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J Clin Psychopharmacol* 26(3):259-267, 2006b 16702890

Davidson JR, Brady K, Mellman TA, et al: The efficacy and tolerability of tiagabine in adult patients with post-

- traumatic stress disorder. *J Clin Psychopharmacol* 27(1):85–88, 2007 17224720
- Davis LL, Jewell ME, Ambrose S, et al: A placebo-controlled study of nefazodone for the treatment of chronic posttraumatic stress disorder: a preliminary study. *J Clin Psychopharmacol* 24(3):291–297, 2004 15118483
- Davis LL, Davidson JR, Ward LC, et al: Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. *J Clin Psychopharmacol* 28(1):84–88, 2008a 18204347
- Davis LL, Ward C, Rasmusson A, et al: A placebo-controlled trial of guanfacine for the treatment of posttraumatic stress disorder in veterans. *Psychopharmacol Bull* 41(1):8–18, 2008b 18362867
- Davis ML, Smits JA, Hofmann SG: Update on the efficacy of pharmacotherapy for social anxiety disorder: a meta-analysis. *Expert Opin Pharmacother* 15(16):2281–2291, 2014 25284086
- de Kleine RA, Hendriks GJ, Kusters WJ, et al: A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. *Biol Psychiatry* 71(11):962–968, 2012 22480663
- Den Boer JA, Westenberg HG: Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder; a double-blind comparative study with fluvoxamine and maprotiline. *Int Clin Psychopharmacol* 3(1):59–74, 1988 2833543
- Denys D, Mantione M, Figee M, et al: Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 67(10):1061–1068, 2010 20921122
- Dunlop BW, Mansson E, Gerardi M: Pharmacological innovations for posttraumatic stress disorder and medication-enhanced psychotherapy. *Curr Pharm Des* 18(35): 5645–5658, 2012 22632469

- Eddy KT, Dutra L, Bradley R, Westen D: A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin Psychol Rev* 24(8):1011-1030, 2004 15533282
- Eidelman I, Seedat S, Stein DJ: Risperidone in the treatment of acute stress disorder in physically traumatized in-patients. *Depress Anxiety* 11(4):187-188, 2000 10945142
- Emmanuel NP, Lydiard RB, Ballenger JC: Treatment of social phobia with bupropion. *J Clin Psychopharmacol* 11(4):276-277, 1991 1918431
- Enkelmann R: Alprazolam versus buspirone in the treatment of outpatients with generalized anxiety disorder. *Psychopharmacology (Berl)* 105(3):428-432, 1991 1798836
- European Medicines Agency: 13 February 2015. EMA/85678/2015  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2015/02/WC500182462.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/02/WC500182462.pdf). Accessed March 22, 2015.
- Fahlén T, Nilsson HL, Borg K, et al: Social phobia: the clinical efficacy and tolerability of the monoamine oxidase -A and serotonin uptake inhibitor brofaromine. A double-blind placebo-controlled study. *Acta Psychiatr Scand* 92(5):351-358, 1995 8619339
- Fahy TJ, O'Rourke D, Brophy J, et al: The Galway Study of Panic Disorder. I: Clomipramine and lofepramine in DSM-III-R panic disorder: a placebo controlled trial. *J Affect Disord* 25(1):63-75, 1992 1624646
- Fallon BA, Campeas R, Schneier FR, et al: Open trial of intravenous clomipramine in five treatment-refractory patients with obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci* 4(1):70-75, 1992 1627966
- Fava M, Asnis GM, Shrivastava R, et al: Zolpidem extended-release improves sleep and next-day symptoms in



- comorbid insomnia and generalized anxiety disorder. *J Clin Psychopharmacol* 29(3):222-230, 2009 19440075
- Feder A, Parides MK, Murrough JW, et al: Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry* 71(6):681-688, 2014 24740528
- Fedoroff IC, Taylor S: Psychological and pharmacological treatments of social phobia: a meta-analysis. *J Clin Psychopharmacol* 21(3):311-324, 2001 11386495
- Feltner DE, Crockatt JG, Dubovsky SJ, et al: A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol* 23(3):240-249, 2003 12826986
- Feltner D, Wittchen HU, Kavoussi R, et al: Long-term efficacy of pregabalin in generalized anxiety disorder. *Int Clin Psychopharmacol* 23(1):18-28, 2008 18090504
- Ferguson JM, Khan A, Mangano R, et al: Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. *J Clin Psychiatry* 68(1):58-68, 2007 17284131
- Ferreri M, Hantouche EG: Recent clinical trials of hydroxyzine in generalized anxiety disorder. *Acta Psychiatr Scand Suppl* 393:102-108, 1998 9777055
- Fesler FA: Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 52(9):361-364, 1991 1894587
- Fineberg NA, Sivakumaran T, Roberts A, Gale T: Adding quetiapine to SRI in treatment-resistant obsessive-compulsive disorder: a randomized controlled treatment study. *Int Clin Psychopharmacol* 20(4):223-226, 2005 15933483
- Fineberg NA, Tonnoir B, Lemming O, Stein DJ: Escitalopram prevents relapse of obsessive-compulsive disorder. *Eur Neuropsychopharmacol* 17(6-7):430-439, 2007 17240120

- Flament MF, Rapoport JL, Berg CJ, et al: Clomipramine treatment of childhood obsessive-compulsive disorder. A double-blind controlled study. *Arch Gen Psychiatry* 42(10):977-983, 1985 3899048
- Foa EB, Liebowitz MR, Kozak MJ, et al: Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. *Am J Psychiatry* 162(1):151-161, 2005 15625214
- Fontaine R, Beaudry P, Beauclair L, Chouinard G: Comparison of withdrawal of buspirone and diazepam: a placebo controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* 11(2-3):189-197, 1987 2888159
- Friedman MJ, Marmar CR, Baker DG, et al: Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry* 68(5):711-720, 2007 17503980
- Furmark T, Appel L, Michelgård A, et al: Cerebral blood flow changes after treatment of social phobia with the neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biol Psychiatry* 58(2):132-142, 2005 16038684
- Fux M, Levine J, Aviv A, Belmaker RH: Inositol treatment of obsessive-compulsive disorder. *Am J Psychiatry* 153(9):1219-1221, 1996 8780431
- Gambi F, De Berardis D, Campanella D, et al: Mirtazapine treatment of generalized anxiety disorder: a fixed dose, open label study. *J Psychopharmacol* 19(5):483-487, 2005 16166185
- Gelenberg AJ, Lydiard RB, Rudolph RL, et al: Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. *JAMA* 283(23):3082-3088, 2000 10865302
- Gelernter CS, Uhde TW, Cimbolic P, et al: Cognitive-behavioral and pharmacological treatments of social

- phobia. A controlled study. *Arch Gen Psychiatry* 48(10):938-945, 1991 1929764
- Gelpin E, Bonne O, Peri T, et al: Treatment of recent trauma survivors with benzodiazepines: a prospective study. *J Clin Psychiatry* 57(9):390-394, 1996 9746445
- Goddard AW, Brouette T, Almai A, et al: Early coadministration of clonazepam with sertraline for panic disorder. *Arch Gen Psychiatry* 58(7):681-686, 2001 11448376
- Goldberg DP, Lecrubier Y: Form and frequency of mental disorders across centers, in *Mental Illness in General Health Care: An International Study*. Edited by Üstürn TB, Sartorius N. New York, Wiley, 1995, pp 323-334
- Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Arch Gen Psychiatry* 46(11):1012-1016, 1989 2510699
- Goodman WK, Bose A, Wang Q: Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. *J Affect Disord* 87(2-3):161-167, 2005 15982747
- Goodnick PJ, Puig A, DeVane CL, Freund BV: Mirtazapine in major depression with comorbid generalized anxiety disorder. *J Clin Psychiatry* 60(7):446-448, 1999 10453798
- Greenberg BD, Malone DA, Friehs GM, et al: Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* 31(11):2384-2393, 2006 16855529
- Greenblatt DJ, Shader RI, Abernethy DR: Drug therapy. Current status of benzodiazepines. *N Engl J Med* 309(7):410-416, 1983 6135990
- Greist J, Chouinard G, DuBoff E, et al: Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. *Arch Gen Psychiatry* 52(4):289-295, 1995a 7702445

- Greist JH, Jefferson JW, Kobak KA, et al: Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. *Arch Gen Psychiatry* 52(1):53-60, 1995b 7811162
- Greist JH, Liu-Dumaw M, Schweizer E, Feltner D: Efficacy of pregabalin in preventing relapse in patients with generalized social anxiety disorder: results of a double-blind, placebo-controlled 26-week study. *Int Clin Psychopharmacol* 26(5):243-251, 2011 21734588
- Guina J, Rossetter SR, DeRhodes BJ, et al: Benzodiazepines for PTSD: a systematic review and meta-analysis. *J Psychiatr Pract* 21(4):281-303, 2015 26164054
- Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 32(1):50-55, 1959 13638508
- Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56-62, 1960 14399272
- Hamner MB, Faldowski RA, Ulmer HG, et al: Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. *Int Clin Psychopharmacol* 18(1):1-8, 2003 12490768
- Hamner MB, Faldowski RA, Robert S, et al: A preliminary controlled trial of divalproex in posttraumatic stress disorder. *Ann Clin Psychiatry* 21(2):89-94, 2009 19439158
- Hauer D, Weis F, Krauseneck T, et al: Traumatic memories, post-traumatic stress disorder and serum cortisol levels in long-term survivors of the acute respiratory distress syndrome. *Brain Res* 1293:114-120, 2009 19376097
- Haug TT, Hellstrøm K, Blomhoff S, et al: The treatment of social phobia in general practice. is exposure therapy feasible? *Fam Pract* 17(2):114-118, 2000 10758071
- Heimberg RG, Liebowitz MR, Hope DA, et al: Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. *Arch Gen Psychiatry* 55(12):1133-1141, 1998 9862558

- Heresco-Levy U, Vass A, Bloch B, et al: Pilot controlled trial of D-serine for the treatment of post-traumatic stress disorder. *Int J Neuropsychopharmacol* 12(9):1275–1282, 2009 19366490
- Hertzberg MA, Butterfield MI, Feldman ME, et al: A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 45(9):1226–1229, 1999 10331117
- Hidalgo R, Hertzberg MA, Mellman T, et al: Nefazodone in post-traumatic stress disorder: results from six open-label trials. *Int Clin Psychopharmacol* 14(2):61–68, 1999 10220119
- Hidalgo RB, Tupler LA, Davidson JR: An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. *J Psychopharmacol* 21(8):864–872, 2007 17984162
- Hoehn-Saric R, McLeod DR, Zimmerli WD: Differential effects of alprazolam and imipramine in generalized anxiety disorder: somatic versus psychic symptoms. *J Clin Psychiatry* 49(8):293–301, 1988 3045099
- Hofmann SG, Meuret AE, Smits JA, et al: Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch Gen Psychiatry* 63(3):298–304, 2006 16520435
- Hofmann SG, Smits JA, Rosenfield D, et al: D-Cycloserine as an augmentation strategy with cognitive-behavioral therapy for social anxiety disorder. *Am J Psychiatry* 170(7):751–758, 2013 23599046
- Holbrook TL, Galarneau MR, Dye JL, et al: Morphine use after combat injury in Iraq and post-traumatic stress disorder. *N Engl J Med* 362(2):110–117, 2010 20071700
- Hollifield M, Thompson PM, Ruiz JE, Uhlenhuth EH: Potential effectiveness and safety of olanzapine in refractory panic disorder. *Depress Anxiety* 21(1):33–40, 2005 15786486

- Hollifield M, Sinclair-Lian N, Warner TD, Hammerschlag R: Acupuncture for posttraumatic stress disorder: a randomized controlled pilot trial. *J Nerv Ment Dis* 195(6):504-513, 2007 17568299
- Huppert JD, Schultz LT, Foa EB, et al: Differential response to placebo among patients with social phobia, panic disorder, and obsessive-compulsive disorder. *Am J Psychiatry* 161(8):1485-1487, 2004 15285978
- International Multicenter Clinical Trial Group on Moclobemide in Social Phobia: Moclobemide in social phobia. A double-blind, placebo-controlled clinical study. *Eur Arch Psychiatry Clin Neurosci* 247(2):71-80, 1997 9177952
- Ivarsson T, Skarphedinsson G, Kornør H, et al: The place of and evidence for serotonin reuptake inhibitors (SRIs) for obsessive compulsive disorder (OCD) in children and adolescents: views based on a systematic review and meta-analysis. *Psychiatry Res* 227(1):93-103, 2015 25769521
- Jacobs RJ, Davidson JR, Gupta S, Meyerhoff AS: The effects of clonazepam on quality of life and work productivity in panic disorder. *Am J Manag Care* 3(8):1187-1196, 1997 10170301
- Jacobs-Rebhun S, Schnurr PP, Friedman MJ, et al: Posttraumatic stress disorder and sleep difficulty. *Am J Psychiatry* 157(9):1525-1526, 2000 10964881
- Jenike MA, Baer L, Ballantine T, et al: Cingulotomy for refractory obsessive-compulsive disorder. A long-term follow-up of 33 patients. *Arch Gen Psychiatry* 48(6):548-555, 1991 2039338
- Kaplan Z, Amir M, Swartz M, Levine J: Inositol treatment of post-traumatic stress disorder. *Anxiety* 2(1):51-52, 1996 9160600
- Kasper S, Stein DJ, Loft H, Nil R: Escitalopram in the treatment of social anxiety disorder: randomised,

- placebo-controlled, flexible-dosage study. *Br J Psychiatry* 186:222-226, 2005 15738503
- Kasper S, Gastpar M, Müller WE, et al: Lavender oil preparation Silexan is effective in generalized anxiety disorder—a randomized, double-blind comparison to placebo and paroxetine. *Int J Neuropsychopharmacol* 17(6):859-869, 2014 24456909
- Katschnig H, Amering M, Stolk JM, et al: Long-term follow-up after a drug trial for panic disorder. *Br J Psychiatry* 167(4):487-494, 1995 8829718
- Katz RJ, Lott MH, Arbus P, et al: Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic. *Anxiety* 1(4):169-174, 1994-1995 9160569
- Katzelnick DJ, Kobak KA, Greist JH, et al: Sertraline for social phobia: a double-blind, placebo-controlled crossover study. *Am J Psychiatry* 152(9):1368-1371, 1995 7653696
- Katzman MA, Brawman-Mintzer O, Reyes EB, et al: Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. *Int Clin Psychopharmacol* 26(1):11-24, 2011 20881846
- Keck PE Jr, McElroy SL, Tugrul KC, et al: Antiepileptic drugs for the treatment of panic disorder. *Neuropsychobiology* 27(3):150-153, 1993 8232830
- Kessler RC, Sonnega A, Bromet E, et al: Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 52(12):1048-1060, 1995 7492257
- Kessler RC, Berglund P, Demler O, et al: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62(6):593-602, 2005a 15939837
- Kessler RC, Chiu WT, Demler O, et al: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the

- National Comorbidity Survey Replication (see comment).  
Arch Gen Psychiatry 62(6):617-627, 2005b 15939839
- Klesmer J, Sarcevic A, Fomari V: Panic attacks during discontinuation of mirtazepine. Can J Psychiatry 45(6):570-571, 2000 10986577
- Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ: Fluoxetine in social phobia: a double-blind, placebo-controlled pilot study. J Clin Psychopharmacol 22(3):257-262, 2002 12006895
- Kobak KA, Taylor LV, Bystritsky A, et al: St John's wort versus placebo in obsessive-compulsive disorder: results from a double-blind study. Int Clin Psychopharmacol 20(6):299-304, 2005 16192837
- Koran LM, McElroy SL, Davidson JR, et al: Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol 16(2):121-129, 1996 8690827
- Koran LM, Sallee FR, Pallanti S: Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. Am J Psychiatry 154(3):396-401, 1997 9054789
- Kosten TR, Frank JB, Dan E, et al: Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. J Nerv Ment Dis 179(6):366-370, 1991 2051152
- Krystal JH, Rosenheck RA, Cramer JA, et al; Veterans Affairs Cooperative Study No. 504 Group: Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA 306(5): 493-502, 2011 21813427
- Lader M, Scotto JC: A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. Psychopharmacology (Berl) 139(4):402-406, 1998 9809861



- Lader M, Stender K, Bürger V, Nil R: Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 19(4):241-248, 2004 15274173
- Lecrubier Y, Judge R; Collaborative Paroxetine Panic Study Investigators: Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatr Scand* 95(2):153-160, 1997 9065681
- Lecrubier Y, Bakker A, Dunbar G, Judge R; Collaborative Paroxetine Panic Study Investigators: A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. *Acta Psychiatr Scand* 95(2):145-152, 1997 9065680
- Leonard H, Swedo S, Rapoport JL, et al: Treatment of childhood obsessive compulsive disorder with clomipramine and desmethyylimipramine: a double-blind crossover comparison. *Psychopharmacol Bull* 24(1):93-95, 1988 3290954
- Lepola UM, Wade AG, Leinonen EV, et al: A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. *J Clin Psychiatry* 59(10):528-534, 1998 9818634
- Lepola U, Bergtholdt B, St Lambert J, et al: Controlled-release paroxetine in the treatment of patients with social anxiety disorder. *J Clin Psychiatry* 65(2):222-229, 2004 15003077
- Liebowitz MR: Social phobia. *Mod Probl Pharmacopsychiatry* 22:141-173, 1987 2885745
- Liebowitz MR, Schneier F, Campeas R, et al: Phenelzine vs atenolol in social phobia. A placebo-controlled comparison. *Arch Gen Psychiatry* 49(4):290-300, 1992 1558463
- Liebowitz MR, Turner SM, Piacentini J, et al: Fluoxetine in children and adolescents with OCD: a placebo-controlled

- trial. J Am Acad Child Adolesc Psychiatry 41(12):1431-1438, 2002 12447029
- Liebowitz MR, DeMartinis NA, Weihs K, et al: Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. J Clin Psychiatry 64(7):785-792, 2003 12934979
- Liebowitz MR, Mangano RM, Bradwejn J, Asnis G; SAD Study Group: A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. J Clin Psychiatry 66(2):238-247, 2005 15705011
- Lipper S, Davidson JR, Grady TA, et al: Preliminary study of carbamazepine in post-traumatic stress disorder. Psychosomatics 27(12):849-854, 1986 3543990
- Lipsitz JD, Mannuzza S, Klein DF, et al: Specific phobia 10-16 years after treatment. Depress Anxiety 10(3):105-111, 1999 10604083
- Llorca PM, Spadone C, Sol O, et al: Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study (see comment). J Clin Psychiatry 63(11):1020-1027, 2002 12444816
- Londborg PD, Wolkow R, Smith WT, et al: Sertraline in the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose investigation. Br J Psychiatry 173:54-60, 1998 9850204
- Londborg PD, Hegel MT, Goldstein S, et al: Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. J Clin Psychiatry 62(5):325-331, 2001 11411812
- Lott M, Greist JH, Jefferson JW, et al: Brofaromine for social phobia: a multicenter, placebo-controlled, double-blind study. J Clin Psychopharmacol 17(4):255-260, 1997 9241003
- Lydiard RB, Ballenger JC: Antidepressants in panic disorder and agoraphobia. J Affect Disord 13(2):153-168, 1987 2960710

- Lydiard RB, Laraia MT, Ballenger JC, Howell EF: Emergence of depressive symptoms in patients receiving alprazolam for panic disorder. *Am J Psychiatry* 144(5):664-665, 1987 3578580
- Lydiard RB, Lesser IM, Ballenger JC, et al: A fixed-dose study of alprazolam 2 mg, alprazolam 6 mg, and placebo in panic disorder. *J Clin Psychopharmacol* 12(2):96-103, 1992 1573046
- Lydiard RB, Morton WA, Emmanuel NP, et al: Preliminary report: placebo-controlled, double-blind study of the clinical and metabolic effects of desipramine in panic disorder. *Psychopharmacol Bull* 29(2):183-188, 1993 8290663
- Lydiard RB, Steiner M, Burnham D, Gergel I: Efficacy studies of paroxetine in panic disorder. *Psychopharmacol Bull* 34(2):175-182, 1998 9640997
- Lydiard RB, Rickels K, Herman B, Feltner DE: Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. *Int J Neuropsychopharmacol* 13(2):229-241, 2010 19737439
- Ma ZR, Shi LJ: Repetitive transcranial magnetic stimulation (rTMS) augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant obsessive-compulsive disorder (OCD): a meta-analysis of randomized controlled trials. *Int J Clin Exp Med* 7(12):4897-4905, 2014 25663986
- Magee WJ, Eaton WW, Wittchen HU, et al: Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. *Arch Gen Psychiatry* 53(2):159-168, 1996 8629891
- Mantovani A, Simpson HB, Fallon BA, et al: Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. *Int J Neuropsychopharmacol* 13(2):217-227, 2010 19691873

- March JS, Biederman J, Wolkow R, et al: Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA* 280(20):1752-1756, 1998 9842950
- March JS, Entusah AR, Rynn M, et al: A Randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biol Psychiatry* 62(10):1149-1154, 2007 17553467
- Margoob MA, Ali Z, Andrade C: Efficacy of ECT in chronic, severe, antidepressant- and CBT-refractory PTSD: an open, prospective study. *Brain Stimulat* 3(1):28-35, 2010 20633428
- Marks IM, Mathews AM: Brief standard self-rating for phobic patients. *Behav Res Ther* 17(3):263-267, 1979 526242
- Marmar CR, Schoenfeld F, Weiss DS, et al: Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder. *J Clin Psychiatry* 57 (suppl 8):66-70, discussion 71-72, 1996 8698684
- Marshall RD, Beebe KL, Oldham M, Zaninelli R: Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry* 158(12):1982-1988, 2001 11729013
- Martenyi F, Brown EB, Zhang H, et al: Fluoxetine versus placebo in posttraumatic stress disorder. *J Clin Psychiatry* 63(3): 199-206, 2002a 11926718
- Martenyi F, Brown EB, Zhang H, et al: Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. *Br J Psychiatry* 181:315-320, 2002b 12356658
- Mathew SJ, Amiel JM, Coplan JD, et al: Open-label trial of riluzole in generalized anxiety disorder. *Am J Psychiatry* 162(12):2379-2381, 2005 16330605
- Mathew SJ, Vythilingam M, Murrough JW, et al: A selective neurokinin-1 receptor antagonist in chronic PTSD: a randomized, double-blind, placebo-controlled, proof-of-

- concept trial. *Eur Neuropsychopharmacol* 21(3):221-229, 2011 21194898
- Mavissakalian MR, Perel JM: Imipramine dose-response relationship in panic disorder with agoraphobia. Preliminary findings. *Arch Gen Psychiatry* 46(2):127-131, 1989 2643933
- Mavissakalian MR, Perel JM: Imipramine treatment of panic disorder with agoraphobia: dose ranging and plasma level-response relationships. *Am J Psychiatry* 152(5):673-682, 1995 7726306
- McLay R, Hanling S, Drastal CA, et al: A randomized, double-blind, placebo-controlled trial of stellate ganglion block in the treatment of post-traumatic stress disorder. Paper presented at the American Academy of Pain Medicine (AAPM) 31st Annual Meeting, National Harbor, MD, March 20-22, 2015
- Mellman TA, Bustamante V, David D, Fins AI: Hypnotic medication in the aftermath of trauma. *J Clin Psychiatry* 63(12):1183-1184, 2002 12530420
- Mellman TA, Clark RE, Peacock WJ: Prescribing patterns for patients with posttraumatic stress disorder. *Psychiatr Serv* 54(12):1618-1621, 2003 14645801
- Meoni P, Hackett D: Characterization of the longitudinal course of long-term venlafaxine-ER treatment of GAD. Paper presented at the 13th Annual Meeting of the European College of Neuropsychopharmacology, Munich, Germany, September 11, 2000
- Michelson D, Lydiard RB, Pollack MH, et al; The Fluoxetine Panic Disorder Study Group: Outcome assessment and clinical improvement in panic disorder: evidence from a randomized controlled trial of fluoxetine and placebo. *Am J Psychiatry* 155(11):1570-1577, 1998 9812120
- Michelson D, Pollack M, Lydiard RB, et al; The Fluoxetine Panic Disorder Study Group: Continuing treatment of panic disorder after acute response: randomised,

- placebo-controlled trial with fluoxetine. *Br J Psychiatry* 174:213–218, 1999 10448445
- Michelson D, Allgulander C, Dantendorfer K, et al: Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder: randomised, placebo-controlled trial. *Br J Psychiatry* 179:514–518, 2001 11731354
- Modigh K, Westberg P, Eriksson E: Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo-controlled trial. *J Clin Psychopharmacol* 12(4):251–261, 1992 1527228
- Monnelly EP, Ciraulo DA, Knapp C, Keane T: Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. *J Clin Psychopharmacol* 23(2):193–196, 2003 12640221
- Montgomery SA: Pregabalin for the treatment of generalised anxiety disorder. *Expert Opin Pharmacother* 7(15):2139–2154, 2006 17020438
- Montgomery SA, Nil R, Dürr-Pal N, et al: A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. *J Clin Psychiatry* 66(10): 1270–1278, 2005 16259540
- Muehlbacher M, Nickel MK, Nickel C, et al: Mirtazapine treatment of social phobia in women: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 25(6):580–583, 2005 16282842
- Mulvaney SW, Lynch JH, Hickey MJ, et al: Stellate ganglion block used to treat symptoms associated with combat-related post-traumatic stress disorder: a case series of 166 patients. *Mil Med* 179(10):1133–1140, 2014 25269132
- Murray CJL, Lopez AD: *The Global Burden of Disease*. Cambridge, MA, Harvard School of Public Health, 1996
- Nardi AE, Machado S, Almada LF, et al: Clonazepam for the treatment of panic disorder. *Curr Drug Targets* 14(3):353–364, 2013 23256724

- Neal LA, Shapland W, Fox C: An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol* 12(4):231-237, 1997 9347385
- Neylan TC, Lenoci M, Samuelson KW, et al: No improvement of posttraumatic stress disorder symptoms with guanfacine treatment. *Am J Psychiatry* 163(12):2186-2188, 2006 17151174
- Ninan PT, Koran LM, Kiev A, et al: High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. *J Clin Psychiatry* 67(1):15-22, 2006 16426083
- Noyes R Jr, Moroz G, Davidson JR, et al: Moclobemide in social phobia: a controlled dose-response trial. *J Clin Psychopharmacol* 17(4):247-254, 1997 9241002
- Oehrberg S, Christiansen PE, Behnke K, et al: Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 167(3):374-379, 1995 7496647
- Olajide D, Lader M: A comparison of buspirone, diazepam, and placebo in patients with chronic anxiety states. *J Clin Psychopharmacol* 7(3):148-152, 1987 2885344
- Otto MW, Pollack MH, Sachs GS, et al: Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. *Am J Psychiatry* 150(10):1485-1490, 1993 8379551
- Otto MW, Tuby KS, Gould RA, et al: An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry* 158(12):1989-1992, 2001 11729014
- Pages KP, Ries RK: Use of anticonvulsants in benzodiazepine withdrawal. *Am J Addict* 7(3):198-204, 1998 9702287
- Panahi Y, Moghaddam BR, Sahebkar A, et al: A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-

- traumatic stress disorder. *Psychol Med* 41(10):2159–2166, 2011 21349225
- Pande AC, Davidson JR, Jefferson JW, et al: Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol* 19(4):341–348, 1999a 10440462
- Pande AC, Greiner M, Adams JB, et al: Placebo-controlled trial of the CCK-B antagonist, CI-988, in panic disorder. *Biol Psychiatry* 46(6):860–862, 1999b 10494457
- Pande AC, Pollack MH, Crockatt J, et al: Placebo-controlled study of gabapentin treatment of panic disorder. *J Clin Psychopharmacol* 20(4):467–471, 2000 10917408
- Pande AC, Crockatt JG, Feltner DE, et al: Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 160(3):533–540, 2003 12611835
- Papp LA: Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study. *J Clin Psychiatry* 67(10):1573–1576, 2006 17107249
- Pato MT, Hill JL, Murphy DL: A clomipramine dosage reduction study in the course of long-term treatment of obsessive-compulsive disorder patients. *Psychopharmacol Bull* 26(2):211–214, 1990 2236458
- Pecknold J, Luthe L, Munjack D, Alexander P: A double-blind, placebo-controlled, multicenter study with alprazolam and extended-release alprazolam in the treatment of panic disorder. *J Clin Psychopharmacol* 14(5):314–321, 1994 7806686
- Pepper J, Hariz M, Zrinzo L: Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: a review of the literature. *J Neurosurg* 122(5):1028–1037, 2015 25635480
- Peselow ED, Pizano DR, IsHak WW: Maintenance treatment for obsessive-compulsive disorder: findings from a naturalistic setting. *Ann Clin Psychiatry* 27(1):25–32, 2015 25696778



- Petracca A, Nisita C, McNair D, et al: Treatment of generalized anxiety disorder: preliminary clinical experience with buspirone. *J Clin Psychiatry* 51 (suppl):31-39, 1990 2211564
- Petrakis IL, Ralevski E, Desai N, et al: Noradrenergic vs serotonergic antidepressant with or without naltrexone for veterans with PTSD and comorbid alcohol dependence. *Neuropsychopharmacology* 37(4):996-1004, 2012 22089316
- Piacentini J, Bennett S, Compton SN, et al: 24- and 36-week outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS). *J Am Acad Child Adolesc Psychiatry* 53(3):297-310, 2014 24565357
- Pigott T, L'Hereux F, Rubinstein CS: A controlled trial of clonazepam augmentation in OCD patients treated with clomipramine or fluoxetine (NR82). Paper presented at the 145th Annual Meeting of the American Psychiatric Association, Washington, DC, May 2-7, 1992
- Pitman RK, Sanders KM, Zusman RM, et al: Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol Psychiatry* 51(2):189-192, 2002 11822998
- Pohl RB, Feltner DE, Fieve RR, Pande AC: Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. *J Clin Psychopharmacol* 25(2):151-158, 2005 15738746
- Pollack MH, Zaninelli R, Goddard A, et al: Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 62(5):350-357, 2001 11411817
- Pollack MH, Simon NM, Worthington JJ, et al: Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. *J Psychopharmacol* 17(3):276-282, 2003 14513919

- Pollack M, Mangano R, Entsuah R, et al: A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. *Psychopharmacology (Berl)* 194(2):233-242, 2007 17589833
- Pollack M, Kinrys G, Krystal A, et al: Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. *Arch Gen Psychiatry* 65(5):551-562, 2008a 18458207
- Pollack MH, Tiller J, Xie F, Trivedi MH: Tiagabine in adult patients with generalized anxiety disorder: results from 3 randomized, double-blind, placebo-controlled, parallel-group studies. *J Clin Psychopharmacol* 28(3):308-316, 2008b 18480688
- Pollack MH, Van Ameringen M, Simon NM, et al: A double-blind randomized controlled trial of augmentation and switch strategies for refractory social anxiety disorder. *Am J Psychiatry* 171(1):44-53, 2014 24399428
- Prosser JM, Yard S, Steele A, et al: A comparison of low-dose risperidone to paroxetine in the treatment of panic attacks: a randomized, single-blind study. *BMC Psychiatry* 9:25, 2009 19470174
- Rapaport MH, Wolkow R, Rubin A, et al: Sertraline treatment of panic disorder: results of a long-term study. *Acta Psychiatr Scand* 104(4):289-298, 2001 11722304
- Rapaport MH, Endicott J, Clary CM: Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. *J Clin Psychiatry* 63(1):59-65, 2002 11838628
- Raskind MA, Peskind ER, Kanter ED, et al: Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 160(2):371-373, 2003 12562588
- Raskind MA, Peskind ER, Hoff DJ, et al: A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans

- with post-traumatic stress disorder. *Biol Psychiatry* 61(8):928-934, 2007 17069768
- Raskind MA, Peterson K, Williams T, et al: A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry* 170(9):1003-1010, 2013 23846759
- Ravizza L, Barzega G, Bellino S, et al: Drug treatment of obsessive-compulsive disorder (OCD): long-term trial with clomipramine and selective serotonin reuptake inhibitors (SSRIs). *Psychopharmacol Bull* 32(1):167-173, 1996 8927668
- Reich DB, Winternitz S, Hennen J, et al: A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. *J Clin Psychiatry* 65(12):1601-1606, 2004 15641864
- Research Unit on Pediatric Psychopharmacology Anxiety Study Group: Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 344(17):1279-1285, 2001 11323729
- Ressler KJ, Rothbaum BO, Tannenbaum L, et al: Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry* 61(11):1136-1144, 2004 15520361
- Ribeiro L, Busnello JV, Kauer-Sant'Anna M, et al: Mirtazapine versus fluoxetine in the treatment of panic disorder. *Braz J Med Biol Res* 34(10):1303-1307, 2001 11593305
- Rickels K, Weisman K, Norstad N, et al: Buspirone and diazepam in anxiety: a controlled study. *J Clin Psychiatry* 43(12 Pt 2): 81-86, 1982 6130078
- Rickels K, Case WG, Downing RW, Winokur A: Long-term diazepam therapy and clinical outcome. *JAMA* 250(6):767-771, 1983 6348314
- Rickels K, Fox IL, Greenblatt DJ, et al: Clorazepate and lorazepam: clinical improvement and rebound anxiety.

- Am J Psychiatry 145(3):312-317, 1988a 2894175
- Rickels K, Schweizer E, Csanalosi I, et al: Long-term treatment of anxiety and risk of withdrawal. Prospective comparison of clorazepate and buspirone. Arch Gen Psychiatry 45(5):444-450, 1988b 2895993
- Rickels K, Amsterdam JD, Clary C, et al: Buspirone in major depression: a controlled study. J Clin Psychiatry 52(1):34-38, 1991 1988416
- Rickels K, Downing R, Schweizer E, Hassman H: Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 50(11):884-895, 1993 8215814
- Rickels K, Pollack MH, Sheehan DV, Haskins JT: Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 157(6):968-974, 2000 10831478
- Rickels K, Zaninelli R, McCafferty J, et al: Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry 160(4):749-756, 2003 12668365
- Rickels K, Pollack MH, Feltner DE, et al: Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry 62(9):1022-1030, 2005 16143734
- Riddle MA, Reeve EA, Yaryura-Tobias JA, et al: Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. J Am Acad Child Adolesc Psychiatry 40(2):222-229, 2001 11211371
- Robb AS, Cueva JE, Sporn J, et al: Sertraline treatment of children and adolescents with posttraumatic stress disorder: a double-blind, placebo-controlled trial. J Child Adolesc Psychopharmacol 20(6):463-471, 2010 21186964

- Robert R, Blakeney PE, Villarreal C, et al: Imipramine treatment in pediatric burn patients with symptoms of acute stress disorder: a pilot study. *J Am Acad Child Adolesc Psychiatry* 38(7):873-882, 1999a 10405506
- Robert R, Meyer WJ 3rd, Villarreal C, et al: An approach to the timely treatment of acute stress disorder. *J Burn Care Rehabil* 20(3):250-258, 1999b 10342481
- Robert R, Tcheung WJ, Rosenberg L, et al: Treating thermally injured children suffering symptoms of acute stress with imipramine and fluoxetine: a randomized, double-blind study. *Burns* 34(7):919-928, 2008 18675519
- Rocca P, Fonzo V, Scotta M, et al: Paroxetine efficacy in the treatment of generalized anxiety disorder. *Acta Psychiatr Scand* 95(5):444-450, 1997 9197912
- Rosenbaum JF, Woods SW, Groves JE, Klerman GL: Emergence of hostility during alprazolam treatment. *Am J Psychiatry* 141(6):792-793, 1984 6145358
- Rosenbaum JF, Moroz G, Bowden CL; Clonazepam Panic Disorder Dose-Response Study Group: Clonazepam in the treatment of panic disorder with or without agoraphobia: a dose-response study of efficacy, safety, and discontinuance. *J Clin Psychopharmacol* 17(5):390-400, 1997 9315990
- Ross CA, Matas M: A clinical trial of buspirone and diazepam in the treatment of generalized anxiety disorder. *Can J Psychiatry* 32(5):351-355, 1987 3308052
- Rothbaum BO, Cahill SP, Foa EB, et al: Augmentation of sertraline with prolonged exposure in the treatment of posttraumatic stress disorder. *J Trauma Stress* 19(5):625-638, 2006 17075912
- Rothbaum BO, Killeen TK, Davidson JR, et al: Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. *J Clin Psychiatry* 69(4):520-525, 2008 18278987

- Roy-Byrne PP, Clary CM, Miceli RJ, et al: The effect of selective serotonin reuptake inhibitor treatment of panic disorder on emergency room and laboratory resource utilization. *J Clin Psychiatry* 62(9):678-682, 2001 11681762
- Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Panic Disorder and Agoraphobia: Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia. *Aust N Z J Psychiatry* 37(6):641-656, 2003 14636376
- Ruffini C, Locatelli M, Lucca A, et al: Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. *Prim Care Companion J Clin Psychiatry* 11(5):226-230, 2009 19956460
- Rynn M, Russell J, Erickson J, et al: Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety* 25(3):182-189, 2008 17311303
- Sachdev PS, Loo CK, Mitchell PB, et al: Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. *Psychol Med* 37(11):1645-1649, 2007 17655805
- Sarchiapone M, Amore M, De Risio S, et al: Mirtazapine in the treatment of panic disorder: an open-label trial. *Int Clin Psychopharmacol* 18(1):35-38, 2003 12490773
- Sarkhel S, Sinha VK, Praharaj SK: Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. *J Anxiety Disord* 24(5):535-539, 2010 20392594

- Sarris J, Kavanagh DJ, Byrne G, et al: The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*. *Psychopharmacology (Berl)* 205(3):399-407, 2009 19430766
- Schelling G, Roozendaal B, Krauseneck T, et al: Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. *Ann N Y Acad Sci* 1071:46-53, 2006 16891561
- Schneier FR, Goetz D, Campeas R, et al: Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry* 172:70-77, 1998 9534836
- Schneier FR, Neria Y, Pavlicova M, et al: Combined prolonged exposure therapy and paroxetine for PTSD related to the World Trade Center attack: a randomized controlled trial. *Am J Psychiatry* 169(1):80-88, 2012 21908494
- Schnurr PP, Friedman MJ, Engel CC, et al: Cognitive behavioral therapy for PTSD in women: a randomized controlled trial. *JAMA* 297:820-830, 2007 17327524
- Schutters SI, Van Megen HJ, Van Veen JF, et al: Mirtazapine in generalized social anxiety disorder: a randomized, double-blind, placebo-controlled study. *Int Clin Psychopharmacol* 25(5):302-304, 2010 20715300
- Schweizer E, Rickels K: Buspirone in the treatment of panic disorder: a controlled pilot comparison with clorazepate (abstract). *J Clin Psychopharmacol* 8(4):303, 1988 2905363
- Schweizer E, Rickels K: Pharmacological treatment for generalized anxiety disorder, in *Long-term Treatments of Anxiety Disorders*. Edited by Mavissakalian M, Prien RF. Washington, DC, American Psychiatric Press, 1996, pp 201-220
- Schweizer E, Rickels K, Lucki I: Resistance to the anti-anxiety effect of buspirone in patients with a history of

- benzodiazepine use. N Engl J Med 314(11):719-720, 1986 2869408
- Schweizer E, Patterson W, Rickels K, Rosenthal M: Double-blind, placebo-controlled study of a once-a-day, sustained-release preparation of alprazolam for the treatment of panic disorder. Am J Psychiatry 150(8):1210-1215, 1993 8328566
- Sepede G, De Berardis D, Gambi F, et al: Olanzapine augmentation in treatment-resistant panic disorder: a 12-week, fixed-dose, open-label trial. J Clin Psychopharmacol 26(1):45-49, 2006 16415705
- Shader RI, Greenblatt DJ: Use of benzodiazepines in anxiety disorders. N Engl J Med 328(19):1398-1405, 1993 8292115
- Shalev AY, Ankri Y, Israeli-Shalev Y, et al: Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach And Prevention study. Arch Gen Psychiatry 69(2):166-176, 2012 21969418
- Shalev AY, Ankri Y, Gilad M, et al: Long-term outcome of early interventions to prevent posttraumatic stress disorder. J Clin Psychiatry 77(5):e580-e587, 2016 27135249
- Shear MK, Brown TA, Barlow DH, et al: Multicenter collaborative panic disorder severity scale. Am J Psychiatry 154(11):1571-1575, 1997 9356566
- Sheehan DV: The Anxiety Disease. Bantam Books, New York, 1986
- Sheehan DV, Ballenger J, Jacobsen G: Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. Arch Gen Psychiatry 37(1):51-59, 1980 7352840
- Sheehan DV, Davidson J, Manschreck T, Van Wyck Fleet J: Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. J Clin Psychopharmacol 3(1):28-31, 1983 6403599



- Sheehan DV, Raj AB, Sheehan KH, Soto S: Is buspirone effective for panic disorder? *J Clin Psychopharmacol* 10(1):3-11, 1990 2407755
- Sheehan DV, Burnham DB, Iyengar MK, Perera P; Paxil CR Panic Disorder Study Group: Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. *J Clin Psychiatry* 66(1):34-40, 2005 15669886
- Sheehan DV, Harnett-Sheehan K, Hidalgo RB, et al: Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient. *J Affect Disord* 145(1):83-94, 2013 22920718
- Shoja Shafiti S, Kaviani H: Aripiprazole versus quetiapine in treatment-resistant obsessive-compulsive disorder: a double-blind clinical trial. *Ther Adv Psychopharmacol* 5(1):32-37, 2015 25653829
- Silverstone PH, Salinas E: Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder. *J Clin Psychiatry* 62(7):523-529, 2001 11488362
- Simon NM, Emmanuel N, Ballenger J, et al: Bupropion sustained release for panic disorder. *Psychopharmacol Bull* 37(4):66-72, 2003 15131517
- Simon NM, Hoge EA, Fischmann D, et al: An open-label trial of risperidone augmentation for refractory anxiety disorders. *J Clin Psychiatry* 67(3):381-385, 2006 16649823
- Simon NM, Connor KM, Lang AJ, et al: Paroxetine CR augmentation for posttraumatic stress disorder refractory to prolonged exposure therapy. *J Clin Psychiatry* 69(3):400-405, 2008 18348595
- Simpson HB, Schneier FR, Marshall RD, et al: Low dose selegiline (L-Deprenyl) in social phobia. *Depress Anxiety* 7(3):126-129, 1998 9656093
- Simpson HB, Foa EB, Liebowitz MR, et al: A randomized, controlled trial of cognitive-behavioral therapy for

- augmenting pharmacotherapy in obsessive-compulsive disorder. *Am J Psychiatry* 165(5):621-630, 2008 18316422
- Snyderman SH, Rynn MA, Rickels K: Open-label pilot study of ziprasidone for refractory generalized anxiety disorder. *J Clin Psychopharmacol* 25(5):497-499, 2005 16160630
- Stahl SM, Gergel I, Li D: Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 64(11):1322-1327, 2003 14658946
- Stein DJ, Andersen EW, Tonnoir B, Fineberg N: Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin* 23(4):701-711, 2007 17407626
- Stein DJ, Ahokas AA, de Bodinat C: Efficacy of agomelatine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 28(5):561-566, 2008 18794654
- Stein MB, Chartier MJ, Hazen AL, et al: Paroxetine in the treatment of generalized social phobia: open-label treatment and double-blind placebo-controlled discontinuation. *J Clin Psychopharmacol* 16(3): 218-222, 1996 8784653
- Stein MB, Liebowitz MR, Lydiard RB, et al: Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. *JAMA* 280(8): 708-713, 1998 9728642
- Stein MB, Fyer AJ, Davidson JR, et al: Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. *Am J Psychiatry* 156(5):756-760, 1999 10327910
- Stein MB, Kline NA, Matloff JL: Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind,

- placebo-controlled study. *Am J Psychiatry* 159(10): 1777-1779, 2002 12359687
- Stein MB, Ravindran LN, Simon NM, et al: Levetiracetam in generalized social anxiety disorder: a double-blind, randomized controlled trial. *J Clin Psychiatry* 71(5):627-631, 2010 20021997
- Stinson FS, Dawson DA, Patricia Chou S, et al: The epidemiology of DSM-IV specific phobia in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol Med* 37(7):1047-1059, 2007 17335637
- Strand M, Hetta J, Rosen A, et al: A double-blind, controlled trial in primary care patients with generalized anxiety: a comparison between buspirone and oxazepam. *J Clin Psychiatry* 51 (suppl):40-45, 1990 2211567
- Strawn JR, Prakash A, Zhang Q, et al: A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. *J Am Acad Child Adolesc Psychiatry* 54(4):283-293, 2015 25791145
- Suliman S, Seedat S, Pingo J, et al: Escitalopram in the prevention of posttraumatic stress disorder: a pilot randomized controlled trial. *BMC Psychiatry* 15(1):24, 2015 25885650
- Sutherland SM, Tupler LA, Colket JT, Davidson JR: A 2-year follow-up of social phobia. Status after a brief medication trial. *J Nerv Ment Dis* 184(12):731-738, 1996 8994456
- Swinson RP, Antony MM, Bleau P, et al; Canadian Psychiatric Association: Clinical practice guidelines. Management of anxiety disorders. *Can J Psychiatry* 51 (8 suppl 2):9S-91S, 2006 16933543
- Szegedi A, Wetzel H, Leal M, et al: Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety, and tolerability data. *J Clin Psychiatry* 57(6):257-264, 1996 8666564

- Taylor LH, Kobak KA: An open-label trial of St. John's Wort (*Hypericum perforatum*) in obsessive-compulsive disorder. *J Clin Psychiatry* 61(8):575-578, 2000 10982200
- Taylor FB, Martin P, Thompson C, et al: Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. *Biol Psychiatry* 63(6): 629-632, 2008 17868655
- Tesar GE, Rosenbaum JF, Pollack MH, et al: Double-blind, placebo-controlled comparison of clonazepam and alprazolam for panic disorder. *J Clin Psychiatry* 52(2):69-76, 1991 1993639
- Teschke R, Schulze J: Risk of kava hepatotoxicity and the FDA consumer advisory. *JAMA* 304(19):2174-2175, 2010 21081732
- Thorén P, Asberg M, Cronholm B, et al: Clomipramine treatment of obsessive-compulsive disorder. I. A controlled clinical trial. *Arch Gen Psychiatry* 37(11):1281-1285, 1980 7436690
- Tollefson GD, Rampey AH Jr, Potvin JH, et al: A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 51(7):559-567, 1994 8031229
- Tucker P, Smith KL, Marx B, et al: Fluvoxamine reduces physiologic reactivity to trauma scripts in posttraumatic stress disorder. *J Clin Psychopharmacol* 20(3):367-372, 2000 10831026
- Tucker P, Zaninelli R, Yehuda R, et al: Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 62(11):860-868, 2001 11775045
- Tucker P, Potter-Kimball R, Wyatt DB, et al: Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram,

- sertraline, and placebo. *Psychopharmacol Bull* 37(3):135-149, 2003 14608246
- Tucker P, Trautman RP, Wyatt DB, et al: Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 68(2):201-206, 2007 17335317
- Turner SM, Beidel DC, Jacob RG: Social phobia: a comparison of behavior therapy and atenolol. *J Consult Clin Psychol* 62(2):350-358, 1994 8201073
- Van Ameringen M, Mancini C, Oakman JM: Nefazodone in social phobia. *J Clin Psychiatry* 60(2):96-100, 1999 10084635
- Van Ameringen MA, Lane RM, Walker JR, et al: Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. *Am J Psychiatry* 158(2):275-281, 2001 11156811
- Van Ameringen M, Mancini C, Oakman J, et al: Nefazodone in the treatment of generalized social phobia: a randomized, placebo-controlled trial. *J Clin Psychiatry* 68(2):288-295, 2007 17335328
- van der Kolk BA, Dreyfuss D, Michaels M, et al: Fluoxetine in posttraumatic stress disorder (see comment). *J Clin Psychiatry* 55(12):517-522, 1994 7814344
- van Vliet IM, den Boer JA, Westenberg HG: Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine, a selective MAO-A inhibitor. *Eur Neuropsychopharmacol* 2(1):21-29, 1992 1638170
- van Vliet IM, den Boer JA, Westenberg HG: Psychopharmacological treatment of social phobia; a double blind placebo controlled study with fluvoxamine. *Psychopharmacology (Berl)* 115(1-2):128-134, 1994 7862884
- van Vliet IM, den Boer JA, Westenberg HG, Pian KL: Clinical effects of buspirone in social phobia: a double-blind

placebo-controlled study. *J Clin Psychiatry* 58(4): 164-168, 1997 9164427

Versiani M, Nardi AE, Mundim FD, et al: Pharmacotherapy of social phobia. A controlled study with moclobemide and phenelzine. *Br J Psychiatry* 161:353-360, 1992 1393304

Versiani M, Nardi AE, Figueria J: Double-blind placebo-controlled trial with bromazepam in social phobia. *J Bras Psiquiatr* 46(3):167-171, 1997

Versiani M, Cassano G, Perugi G, et al: Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *J Clin Psychiatry* 63(1):31-37, 2002 11838623

Villarrreal G, Hamner MB, Cañive JM, et al: Efficacy of quetiapine monotherapy in posttraumatic stress disorder: a randomized, placebo-controlled trial. *Am J Psychiatry* 173(12):1205-1212, 2016 27418378

Vulink NC, Denys D, Fluitman SB, et al: Quetiapine augments the effect of citalopram in non-refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled study of 76 patients. *J Clin Psychiatry* 70(7):1001-1008, 2009 19497245

Wade AG, Lepola U, Koponen HJ, et al: The effect of citalopram in panic disorder. *Br J Psychiatry* 170:549-553, 1997 9330022

Wagner KD, Berard R, Stein MB, et al: A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry* 61(11): 1153-1162, 2004 15520363

Walker JR, Van Ameringen MA, Swinson R, et al: Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. *J Clin Psychopharmacol* 20(6):636-644, 2000 11106135

- Walkup JT, Albano AM, Piacentini J, et al: Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med* 359(26):2753–2766, 2008 18974308
- Weathers FW, Huska JA, Keane TM: PCL-C for DSM-IV. Boston, MA, National Center for PTSD—Behavioral Science Division, 1991
- Weathers FW, Keane TM, Davidson JR: Clinician-administered PTSD scale: a review of the first ten years of research. *Depress Anxiety* 13(3):132–156, 2001 11387733
- Westenberg HG, Stein DJ, Yang H, et al: A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol* 24(1): 49–55, 2004 14709947
- White CM: 3,4-Methylenedioxymethamphetamine's (MDMA's) impact on posttraumatic stress disorder. *Ann Pharmacother* 48(7):908–915, 2014 24740469
- Williams JE, Nieto FJ, Sanford CP, Tyroler HA: Effects of an angry temperament on coronary heart disease risk: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 154(3):230–235, 2001 11479187
- Wittchen HU, Hoyer J: Generalized anxiety disorder: nature and course. *J Clin Psychiatry* 62 (suppl 11):15–19, discussion 20–21, 2001 11414546
- Woelk H, Arnoldt KH, Kieser M, Hoerr R: Ginkgo biloba special extract EGb 761 in generalized anxiety disorder and adjustment disorder with anxious mood: a randomized, double-blind, placebo-controlled trial. *J Psychiatr Res* 41(6):472–480, 2007 16808927
- Wurthmann C, Klieser E, Lehmann E: [Differential pharmacologic therapy of generalized anxiety disorders—results of a study with 30 individual case experiments]. *Fortschr Neurol Psychiatr* 63(8):303–309, 1995 7557813

- Yeh MS, Mari JJ, Costa MC, et al: A double-blind randomized controlled trial to study the efficacy of topiramate in a civilian sample of PTSD. *CNS Neurosci Ther* 17(5):305-310, 2011 21554564
- Zhang X, Norton J, Carrière I, et al: Generalized anxiety in community-dwelling elderly: Prevalence and clinical characteristics. *J Affect Disord* 172C(172C):24-29, 2014 25451391
- Zigmond AS, Snaith RP: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67(6):361-370, 1983 6880820
- Zimmerman M, Mattia JI: Principal and additional DSM-IV disorders for which outpatients seek treatment. *Psychiatr Serv* 51(10):1299-1304, 2000 11013331
- Zitrin CM, Klein DF, Woerner MG, Ross DC: Treatment of phobias. I. Comparison of imipramine hydrochloride and placebo. *Arch Gen Psychiatry* 40(2):125-138, 1983 6337578
- Zohar J, Amital D, Miodownik C, et al: Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clin Psychopharmacol* 22(2):190-195, 2002 11910265
- Zwanzger P, Baghai TC, Schüle C, et al: Tiagabine improves panic and agoraphobia in panic disorder patients. *J Clin Psychiatry* 62(8):656-657, 2001 11561942
- Zwanzger P, Eser D, Nothdurfter C, et al: Effects of the GABA-reuptake inhibitor tiagabine on panic and anxiety in patients with panic disorder. *Pharmacopsychiatry* 42(6):266-269, 2009 19924586



## CHAPTER 49

# Treatment of Schizophrenia

Tsung-Ung W. Woo, M.D., Ph.D.

Carla M. Canuso, M.D.

Joanne D. Wojcik, Ph.D., P.M.H.C.N.S.-B.C.

Douglas Noordsy, M.D.

Mary F. Brunette, M.D.

Alan I. Green, M.D.

**Schizophrenia** is a debilitating brain disorder characterized by a chronic relapsing and remitting course of psychosis that is superimposed on persistent “deficit” features such as cognitive dysfunction and negative symptoms. It appears to be equally prevalent across geographical and cultural boundaries (see [Jablensky et al. 1992](#)), affecting approximately 1% of the population ([Perälä et al. 2007](#)).

Considerable progress has been made in the pharmacological treatment of schizophrenia since the serendipitous discovery in the early 1950s of chlorpromazine as the first effective antipsychotic medication ([Lehmann and Hanrahan 1954](#)). Many other antipsychotic agents, all sharing chlorpromazine’s dopamine D<sub>2</sub> receptor-blocking ability, were subsequently developed. These “conventional,” or first-generation, antipsychotics are all effective in the treatment of positive symptoms of psychosis, but they all have limited beneficial effects on negative symptoms and cognitive deficits.

Since 1990, a second generation of antipsychotic drugs has been available in the United States. These second-generation agents are also commonly referred to as “atypical” or “novel” antipsychotics, largely because of their reduced propensity (compared with the conventional agents) to cause extrapyramidal side effects (EPS). It has been postulated that this unique property (i.e., the low risk of EPS) may reflect the potent serotonin type 2A (5-HT<sub>2A</sub>) receptor antagonistic effects—or, more specifically, the high ratio of 5-HT<sub>2A</sub>-to-D<sub>2</sub> receptor occupancy—of these drugs ([Meltzer 1989](#)). More recently, it has been

proposed that the rapid dissociation (high dissociation constant) of these drugs from D<sub>2</sub> receptors may be another very important pharmacological property that determines “atypicality” ([Kapur and Remington 2001](#); [Seeman 2002](#)).

The focus of schizophrenia treatment has been gradually expanding beyond the targeting of psychotic or positive symptoms of the illness alone. Second-generation agents have been reported by some (but not all) investigators to improve some aspects of negative symptoms and cognitive impairment. Moreover, development of compounds that can improve cognition has become one of the main foci in schizophrenia research ([Barch 2010](#); [Buchanan et al. 2007](#); [Fenton et al. 2003](#); [Hyman and Fenton 2003](#); [Marder 2006](#); [Young and Geyer 2015](#)). In recent years, schizophrenia has been increasingly conceptualized as a neurodevelopmental disorder ([Insel 2010](#)). In this context, the field has developed a focused interest on early diagnosis and early intervention during the prodromal phase before the onset of overt psychosis, in an attempt to improve the overall course or perhaps even prevent the actual onset of overt illness in individuals who appear likely to develop schizophrenia.

---

## Clinical Manifestations of Schizophrenia

---

There is a general consensus, following the seminal work of several investigators (e.g., [Andreasen 1985](#); [Crow 1985](#)), that schizophrenia can be conceptualized as a disorder with at least two more or less orthogonal dimensions of symptomatology: positive and negative symptoms.

### Positive Symptoms

Positive symptoms are perceptual or cognitive features that individuals without psychiatric disorders usually do not experience. They include hallucinations, delusions, and disorganized thinking, although disorganization also can be conceptualized as an independent symptom dimension ([Liddle et al. 1989](#)). As a general rule, positive symptoms tend to respond to treatment with antipsychotic medications. These symptoms do not appear to bear any significant association with or predict the long-term functional outcome of the illness ([Green et al. 2000](#)). It also should be emphasized that psychotic symptoms are not unique to schizophrenia; they can occur in a wide spectrum of other psychiatric, neurological, and medical disorders. Therefore, it is essential to rule out other possible causes of psychosis before a diagnosis of schizophrenia is made.

### Negative Symptoms

Negative symptoms represent a “loss” of functions or abilities that people without schizophrenia normally possess. They include anhedonia, affective flattening, alogia, avolition, and asociality. Negative symptoms are somewhat associated with intellectual and neurocognitive impairment ([Dickerson et al. 1996](#); [Harvey and Keefe 1998](#)), and they are better predictors of long-term functional outcome and psychosocial functioning of schizophrenia patients than are positive symptoms ([Buchanan et al. 1994](#); [Dickerson et al. 1996](#); [Harvey and Keefe 1998](#)). However, neurocognitive deficits in schizophrenia (see subsection with that name later in this chapter) remain the strongest predictors of outcome ([Green 1996](#)). It is important to remember that EPS produced by antipsychotic medications can sometimes resemble negative symptoms of schizophrenia.

The concept of primary versus secondary negative symptoms may provide a useful framework for assessing symptoms ([Carpenter et al. 1988](#)). According to this construct, *primary* negative symptoms represent the core negative symptoms reflecting the schizophrenia disease process. *Secondary* negative symptoms, on the other hand, are caused by or are secondary to positive symptoms of psychosis or the antipsychotic medications themselves. A reduction in medication dosage may alleviate some secondary negative symptoms, but this strategy is unlikely to have a beneficial effect on primary negative symptoms.

---

## Diagnosis of Schizophrenia

---

According to DSM-5 ([American Psychiatric Association 2013](#)), to make the diagnosis of schizophrenia, there must be evidence of continuous symptomatic disturbance for at least 6 months accompanied by a decline from the premorbid level of functioning. Thus, in line with the Kraepelinian concept ([Kraepelin 1919/1971](#)), DSM-5 emphasizes the longitudinal course of deterioration of the illness. This 6-month period can include functional deterioration occurring during the prodromal phase before the onset of overt psychosis. Within the 6-month period, the patient must have experienced two or more of the following symptoms for at least 1 month: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms; and one of these symptoms must be a positive symptom (delusions, hallucinations, or disorganized speech). If the duration of psychotic symptoms is less than 1 month because of successful treatment with antipsychotic medication, a diagnosis of schizophrenia may still be made. In DSM-IV-TR ([American Psychiatric Association 2000](#)), only one of the five symptoms was required if delusions were bizarre or if Schneiderian first-rank auditory hallucinations (i.e., a voice keeping up a running commentary on the person’s behavior or thoughts or two or more voices conversing with each other) were present. However, because of the poor specificity of Schneiderian symptoms and bizarre delusions, this special designation was removed in DSM-5. Another major change in DSM-5 was the

removal of the subtypes of schizophrenia because of their limited reliability and validity.

---

## Neurocognitive Deficits in Schizophrenia

---

Schizophrenia appears to be associated with a decline in general cognitive functions, including verbal declarative memory, working memory, executive function, and attention. There is strong evidence that cognitive deficits predate the onset of psychosis, followed by a significant decline during the early course of the illness ([Aylward et al. 1984](#); [David et al. 1997](#); [Keefe 2014](#), [Nelson et al. 1990](#); [Reichenberg 2010](#); [Russell et al. 1997](#); [Simon et al. 2007](#)). It appears that after this initial decline, the level of cognitive impairment follows a relatively stable course for several decades without evidence of significant further deterioration ([Bozikas and Andreou 2011](#); [Elvevåg and Goldberg 2000](#); [Goldberg et al. 1993](#); [Lewandowski et al. 2011](#)).

---

## Course of Schizophrenia

---

Schizophrenia is a chronic illness, with the onset of psychotic symptoms usually occurring around late adolescence or early adulthood ([Lewis and Lieberman 2000](#)). The age at onset is approximately 5 years later in women than in men ([Angermeyer et al. 1990](#); [Faraone et al. 1994](#); [Hambrecht et al. 1992](#); [Szymanski et al. 1995](#)). Although there may be no clear sex differences in cross-sectional symptomatology of the illness ([Häfner et al. 1993](#); [Szymanski et al. 1995](#)), women in general tend to have more favorable outcomes.

Accumulating evidence suggests that schizophrenia is a neurodevelopmental disorder ([Lewis and Levitt 2002](#); [Murray 1994](#); [Pilowsky et al. 1993](#); [Waddington 1993](#); [Weinberger 1987, 1996](#)). It has been postulated that disturbances in brain development during the first and second trimesters may contribute to the pathophysiology of the illness ([Waddington 1993](#)). Other factors such as obstetrical complications may further alter the course of brain development ([Cannon 1997](#); [Geddes and Lawrie 1995](#)).

For a period of 2–5 years before the onset of the first overt psychotic episode, up to three-quarters of the patients who eventually develop schizophrenia show a wide spectrum of “prodromal” symptoms and reduced functioning ([Docherty et al. 1978](#); [Freedman and Chapman 1973](#); [Häfner et al. 1992, 1993, 1994](#); [Huber et al. 1980](#); [Lieberman 2006](#); [Simon et al. 2007](#); [Varsamis and Adamson 1971](#); [Yung and McGorry 1996a, 1996b](#)). Prodromal symptoms are usually affective or cognitive in nature (e.g., depressed mood, social withdrawal, decreased concentration and attention, decreased motivation, agitation, anxiety, and sleep disturbances) and can also include attenuated positive symptoms.

After the onset of the first episode of psychosis, the course of the illness is often characterized by a gradual deterioration, especially over the first 2–5 years ([McGlashan 1998](#)). Some evidence suggests that functional deterioration may be accompanied by a gradual loss of gray matter volume in the cerebral cortex ([DeLisi et al. 1997](#); [Kasai et al. 2003a, 2003b](#); [Salisbury et al. 2007](#); [van Haren et al. 2008](#); [Zipursky et al. 1992](#)). In fact, increasing evidence suggests that gray matter reduction may have already begun prior to the onset of frank illness ([Moorhead et al. 2013](#); [Pantelis et al. 2003](#); [Takahashi et al. 2009](#); [Witthaus et al. 2009](#)). Although there has been speculation that these observations of functional and structural brain changes around the onset of psychosis may reflect a neurodegenerative process ([DeLisi 1999](#); [DeLisi et al. 1997](#); [Lieberman 1999](#)), the available evidence in support of the neurodegeneration hypothesis of schizophrenia remains weak ([Carpenter 1998](#); [Weinberger and McClure 2002](#)). An alternative interpretation of these findings is that they represent the dysregulation of late developmental processes that involve refinement of brain circuits through pruning of synaptic connectivities ([Sekar et al. 2016](#)).

After an initial period of functional deterioration, symptoms tend to become more or less stabilized. Positive symptoms often respond to treatment, whereas negative symptoms are believed to be relatively treatment resistant and may tend to become increasingly prominent during the course of the illness ([Breier et al. 1991](#)). Most studies ([Ho et al. 2000](#); [Kane et al. 2016](#); [Marshall et al. 2005](#)) have suggested that early intervention during the very first episode of psychosis could be associated with better overall prognosis; thus, a major goal in the treatment of schizophrenia is early recognition and timely treatment of the illness.

---

## Management of Schizophrenia

---

### Acute Psychosis

The acute phase of schizophrenia is characterized by psychotic symptoms and often by agitation. Affective symptoms such as depression and mania also may be present. Patients who are unable to care for themselves or who show a risk of harming themselves or others may require hospitalization. Acute psychosis requires treatment with antipsychotic medication.

Management of an acutely agitated and psychotic patient may require physical restraint and parenterally administered antipsychotic medication. Many physicians still use a high-potency first-generation antipsychotic either alone or in conjunction with a benzodiazepine (such as lorazepam) and/or an anticholinergic drug (such as benztropine) for acute symptom management. Additionally, intramuscular administration of a second-generation antipsychotic, such as olanzapine or ziprasidone, is also increasingly common.

If the patient has a history of treatment with antipsychotic medications, the clinician must ascertain whether the current psychosis is the result of nonadherence to the medication regimen or a “breakthrough” episode due to loss of therapeutic response to the medications. Noncompliance with antipsychotic medications is common and is one of the major causes of symptom exacerbation or full-blown relapse ([Crow et al. 1986](#); [Lieberman et al. 1993](#); [Robinson et al. 1999](#)). Causes of noncompliance vary, but the most common reasons are unpleasant side effects, lack of insight into the illness, delusional interpretations about medication, substance use, and lack of a supportive environment ([Kampman and Lehtinen 1999](#)). With noncompliant patients, it is imperative to focus on improving adherence by providing psychoeducation to the patient (and family, if available), discussing with the patient the reasons for nonadherence, and developing a plan for improved adherence (which may include daily support and monitoring of medication dosages). Depot or long-acting injectable medications also should be considered if noncompliance is a persistent or recurring problem. In the case of apparent breakthrough psychosis, a change in the patient’s medication regimen may be indicated. Other causes of exacerbation of psychosis include comorbid substance use disorders and comorbid depression, as well as psychosocial stressors such as difficulties with housing, employment, benefits, insurance, disability, family, or friends. Therefore, although medications are undoubtedly the mainstay of initial treatment of psychosis, other interventions such as psychotherapy, group therapy, family therapy, dual-diagnosis treatment, social skills training, and case management are important adjuncts to pharmacological management.

## First-Episode Psychosis

Emphasis on the early diagnosis and treatment of the first psychotic episode of schizophrenia arises from evidence suggesting that longer durations of untreated psychosis may be associated with poorer long-term outcomes ([Birchwood 1992](#); [Cechnicki et al. 2014](#); [Harris et al. 2005](#); [Loebel et al. 1992](#); [Marshall et al. 2005](#); [Penttilä et al. 2014](#); [Perkins et al. 2005](#); [Wyatt 1991](#)). Unfortunately, the average time between onset of symptoms and initiation of treatment in the United States is a year and a half ([Addington et al. 2015](#)). Coordinated specialty care provided to patients and their families as early as possible in the course of illness improves outcomes and may reduce disability ([Kane et al. 2016](#)).

Because of their more favorable neurological side-effect profiles (mainly the reduced risks of adverse neurological events such as parkinsonism, akathisia, and tardive dyskinesia), the second-generation antipsychotics are often used in the initial treatment of first-episode psychosis. Because patients are likely to require long-term treatment, clinicians often choose medications with the lowest risk for cardiometabolic side effects (weight gain, hyperlipidemia, and



glucose intolerance), monitor all side effects regularly in accordance with published guidelines ([American Diabetes Association et al. 2004](#)), and adjust medication types and dosages on the basis of efficacy and tolerability. In general, a conservative titration schedule is appropriate for first-episode patients, in part to minimize side effects but also to take into account that these patients may require only low dosages for the control and remission of symptoms ([Remington et al. 1998](#); [Robinson et al. 1999](#); [Schooler et al. 2005](#); [Wyatt 1995](#)).

After remission of an initial episode of psychosis, discontinuation of medication, even if done very gradually, is controversial and often not attempted. Any such decision should be made in light of studies showing that the relapse rate is very high after medication discontinuation in first-episode schizophrenia ([Crow et al. 1986](#); [Johnson 1985](#); [Kane et al. 1982](#); [Robinson et al. 1999](#)). [Gitlin et al. \(2001\)](#), using a low threshold to define recurrence of symptoms, reported that the relapse rate in the first year after medication discontinuation was 78%, and this rate had increased to 98% by the end of the second year.

## Choice of Antipsychotics

Since the early 1990s, second-generation antipsychotics have been used widely. The National Institute of Mental Health (NIMH) sponsored the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study ([Lieberman et al. 2005](#)), which was designed to compare the effectiveness of four second-generation antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) and a representative first-generation antipsychotic (perphenazine) in “real-world” schizophrenia patients. The primary outcome measure was treatment discontinuation. Of the 1,432 subjects who received at least one dose of medication, 74% discontinued the study medication before 18 months: 64% of the subjects taking olanzapine discontinued, compared with 74%–82% of those taking perphenazine, quetiapine, risperidone, or ziprasidone. More subjects receiving olanzapine discontinued because of weight gain and metabolic effects, whereas more subjects assigned to perphenazine discontinued because of EPS ([Lieberman et al. 2005](#)). Of interest, individuals assigned to olanzapine or risperidone who were continuing with their baseline medication had significantly longer times until discontinuation than did those assigned to switch antipsychotics ([Essock et al. 2006](#)).

Phase II of the CATIE study involved two treatment pathways—efficacy and tolerability—with randomized follow-up medication based on the reason for discontinuation of the previous antipsychotic drug ([McEvoy et al. 2006](#); [Stroup et al. 2006](#)). For patients who failed to improve with an atypical antipsychotic, clozapine was more effective than switching to another atypical antipsychotic ([McEvoy et al. 2006](#)), and in patients who failed to respond to perphenazine,

olanzapine or quetiapine was more effective than risperidone ([Stroup et al. 2006](#)). Moreover, in subjects who discontinued a second-generation agent for tolerability or efficacy reasons but who were unwilling to be randomly assigned to clozapine, risperidone or olanzapine was more effective than quetiapine or ziprasidone ([Stroup et al. 2006](#)). (Note: Since the CATIE study was published, several new antipsychotics—asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, and paliperidone—have been approved by the U.S. Food and Drug Administration [FDA]. A very limited number of direct comparison studies appear to suggest that these new antipsychotics are neither more nor less efficacious compared with older second-generation antipsychotics ([Fu et al. 2014a, 2014b](#)), but little is known about the effectiveness of these newer agents relative to the older agents.) Finally, although the CATIE cost-effectiveness analysis found perphenazine to be less costly than—and similar in effectiveness (based on quality-adjusted life-years) to—each of the atypical antipsychotics tested, the investigators noted that their results could not be generalized to all patient populations; they therefore concluded that the study findings did not warrant policies that would unconditionally restrict access to a particular medication ([Rosenheck et al. 2006](#)).

Similar to the NIMH-sponsored CATIE study, the United Kingdom's National Health Service funded the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS). This study of 227 schizophrenia-spectrum patients randomly assigned to first- and second-generation antipsychotics (other than clozapine) found no difference between the groups in quality of life, symptoms, or health care costs at 1 year ([Jones et al. 2006](#)).

Neither the CATIE nor the CUtLASS study addressed the comparative effects of oral versus long-acting injectable antipsychotics. Mirror-image studies in which patients served as their own control subjects provide evidence of substantial benefit for first-generation long-acting injectable antipsychotics over oral antipsychotic medications ([Kane et al. 2013](#); [Kishimoto et al. 2014](#); [Schooler 2003](#)), although this putative superiority is in general not supported by findings from randomized controlled trials ([Kishimoto et al. 2014](#); [Rosenheck et al. 2011](#)). At present, risperidone, paliperidone, olanzapine, and aripiprazole are the only second-generation antipsychotics available in long-acting injectable formulations.

Taken together, the CATIE and the CUtLASS studies indicate that antipsychotic medications are generally effective but have a variety of shortcomings. Physicians need to be well informed about the differential tolerability profiles among the antipsychotics. Several of the first-generation agents clearly have a high risk of EPS and tardive dyskinesia ([Glazer 2000b](#); [Jeste et al. 1998](#); [Tollefson et al. 1997](#)). Risperidone and paliperidone tend to elevate serum prolactin levels and may cause EPS at higher dosages. Iloperidone may elevate serum prolactin to a lesser degree. Akathisia and other EPS also may be common with aripiprazole, brexpiprazole, cariprazine, and lurasidone. Although weight gain and metabolic disturbances are associated



with most of the second-generation agents, olanzapine and clozapine appear to have the highest likelihood of causing these side effects ([Allison et al. 1999](#); [American Diabetes Association et al. 2004](#)). Sedation is most commonly observed in patients receiving asenapine, quetiapine, olanzapine, ziprasidone, or clozapine. Ziprasidone, paliperidone, and iloperidone carry product labeling for QTc prolongation and should be used with caution in patients at risk for QTc prolongation. Finally, clozapine, because of its side effects of agranulocytosis, seizures, and myocarditis, is generally reserved for patients with treatment-resistant illness or suicidality. [Table 49-1](#) lists the available formulations for the most commonly used first-generation antipsychotic medications and all of the second-generation agents.

**TABLE 49-1. Antipsychotic medications**

Antipsychotic name	Tablet/capsule	Orally disintegrating	Liquid	Short-acting	Long-acting
		tablets		injection	injection
Commonly used first-generation agents					
Chlorpromazine (low potency)	X		X	X	
Perphenazine (midpotency)	X		X	X	X
Fluphenazine (high potency)	X		X	X	X
Haloperidol (high potency)	X		X	X	X
Second-generation agents					
Aripiprazole	X	X	X	X	X
Asenapine		X			
Brexpiprazole	X				
Cariprazine	X				
Clozapine	X	X			
Iloperidone	X				
Lurasidone	X				
Olanzapine	X	X		X	X
Paliperidone	X				X
Risperidone	X	X	X		X
Ziprasidone	X			X	

# Maintenance Treatment

The major goals of maintenance treatment are prevention of relapse and improvement in psychosocial and vocational functioning. The primary methods used to achieve these goals consist of an integration of optimal psychopharmacological and psychosocial treatments. Treatment and prevention of other psychiatric comorbidities, such as substance use disorders, are important aspects of maintenance treatment. Also, prevention and treatment of medical comorbidities that may be associated with second-generation antipsychotics, as well as those that may result from the lifestyles of some patients with schizophrenia who are given these drugs, have become a very important part of long-term management.

Prevention of relapse improves long-term clinical outcomes ([Wyatt et al. 1998](#)) and reduces the associated economic burden of the illness ([Bernardo et al. 2006](#)). With each relapse, the time required to regain clinical stability lengthens, with the possible consequence of ultimate unresponsiveness to treatment ([Lieberman et al. 1993](#); [Wyatt et al. 1998](#)). Nonadherence to medication is a significant predictor of relapse ([Schooler 2006](#)); long-acting injectable antipsychotics may have the potential to improve medication adherence and thus improve long-term outcomes.

## Treatment-Resistant Schizophrenia

At least 30% of patients with schizophrenia have an incomplete to poor response to antipsychotics, with persistent psychotic symptoms ([Kane et al. 1988, 2007](#); [Tamminga 1999](#)). For research purposes, [Kane et al. \(1988\)](#) operationally defined *treatment resistance* as 1) lack of significant response to at least three adequate trials of antipsychotics from at least two different chemical classes in the past 5 years and 2) persistently poor social and occupational functioning.

Most of the available data suggest that clozapine is the most effective drug for treatment-resistant schizophrenia ([Kane et al. 2001](#); [Lewis et al. 2006](#); [McEvoy et al. 2006](#)). However, because of the serious side effects that may be associated with clozapine and the requirement for frequent white blood cell count monitoring, some patients and some psychiatrists are reluctant to use it, and some patients are unable to tolerate it. Whether the other second-generation agents even approach the effectiveness of clozapine for the treatment of these chronically ill patients is also unclear. Evidence regarding whether either risperidone ([Bondolfi et al. 1998](#); [Breier et al. 1999](#); [Volavka et al. 2002](#)) or olanzapine ([Buchanan et al. 2005](#); [Tollefson et al. 2001](#); [Volavka et al. 2002](#)) is as effective as clozapine is mixed. Other preliminary data also suggest the possible utility of quetiapine, aripiprazole, and ziprasidone in treatment-resistant illness ([Emsley et al. 2000](#); [Kane et al. 2006, 2007](#)).

Multiple controlled trials have assessed whether combining two antipsychotics is more effective than antipsychotic monotherapy. Thus far, the evidence is mixed and inconclusive ([Barbui 2008](#); [Correll et al. 2009](#); [Evins et al. 2005](#)), and many patients taking two antipsychotics are able to switch back to a single agent without destabilization ([Essock et al. 2011](#)). In summary, clozapine remains the primary medication for treatment-resistant schizophrenia, although some studies suggest that other second-generation agents also may have a role in the management of this disorder. Clinically, judicious addition of adjunctive agents, such as mood stabilizers, may be beneficial. Clearly, more research is needed to guide treatment in patients with severe and resistant symptoms.

## Neurocognitive Deficits

Neurocognitive deficits, especially disturbances in executive functioning, memory, and attention ([Green 1996](#); [Green et al. 2000](#)), are closely associated with the long-term functional outcome of patients with schizophrenia. It appears that second-generation antipsychotics may improve some aspects of cognition in schizophrenia, as found in meta-analysis reports ([Bilder et al. 2002](#); [Désaméricq et al. 2014](#); [Woodward et al. 2005](#)). The therapeutic effects of the newer antipsychotics are most notable in measures of verbal fluency and executive functioning, whereas improvement in memory may be more limited. However, data obtained from the CATIE trial showed that at 18 months of treatment, perphenazine was actually more effective than any of the second-generation drugs in improving all domains of neurocognitive deficits ([Keefe et al. 2007](#)). The investigators postulated that several factors might potentially explain this unexpected finding, such as sample size, differences between midpotency drugs such as perphenazine and high-potency drugs (e.g., haloperidol) that were commonly used in prior studies, the real-world features of the CATIE sample, and prior drug trials before entering the study ([Keefe et al. 2007](#)). Interestingly, a meta-analysis of 34 studies found that first-generation antipsychotics do appear to have some cognition-enhancing properties, although effect sizes tend to be quite small ([Mishara and Goldberg 2004](#)). Finally, it is not clear whether any of the apparent statistically significant improvements in neurocognitive deficits measured in the laboratory can actually be translated into improved functional outcomes, for example, in terms of employment, school performance, or social role (see [Green 2002](#)).

---

## Psychosocial Treatment of Schizophrenia

---

Despite the proven efficacy of antipsychotics in the treatment of schizophrenia, most patients continue to have some degree of residual positive symptoms, negative symptoms, and cognitive deficits, and many have difficulty attaining or

regaining their desired level of social and occupational functioning. To address functional goals, treatment is ideally offered by a multidisciplinary team that includes, at a minimum, a medication prescriber and a clinician skilled in psychosocial rehabilitation but also may include employment and housing specialists. Programs that use clinical case managers to directly assist patients in accessing services and to provide the psychosocial interventions are ideal ([Rapp and Goscha 2004](#)). In the first episode of psychosis, specialized programs are tailored for young people and their families to maximize engagement, rapid stabilization, and return to psychosocial functioning ([Mueser et al. 2015](#)). To date, several different types of psychosocial interventions have been empirically shown to reduce rates of relapse and rehospitalization, and a variety of treatments may assist patients in acquiring social and vocational skills and possibly in managing residual psychotic symptoms ([Bustillo et al. 2001](#); [Lauriello et al. 1999](#); [Penn and Mueser 1996](#)). Initial studies have shown that psychosocial treatments can be effective when delivered via technology ([Ben-Zeev et al. 2014](#); [Brunette et al. 2011b](#); [Gottlieb et al. 2013](#); [Rotondi et al. 2010](#)), potentially increasing their reach while maintaining quality and lowering the cost of psychosocial treatment. Importantly, the interaction between pharmacological and psychosocial treatments appears to be more than additive, because each can enhance the effects of the other and affect different domains of outcome ([Marder 2000](#)).

## Relapse Prevention

It has long been noted that patients with highly critical or overinvolved family members (so-called high-expressed-emotion [EE] families) have a higher risk of relapse ([Brown and Rutter 1966](#)). In a classic study, [Goldstein et al. \(1978\)](#) reported that a 6-week therapy focusing on teaching families more effective communication and dispute-resolution skills reduced relapse rates for up to 6 months. Many other studies have since confirmed the efficacy of family psychoeducational interventions (involving education and training in problem-solving techniques and/or cognitive and behavioral management strategies) to prevent relapse and to improve other outcomes ([Falloon et al. 1982](#); [Pilling et al. 2002](#); [Pitschel-Walz et al. 2001](#); [Tarrier et al. 1988](#)). In addition, the positive effect of family interventions seems to persist beyond the time of intervention ([Sellwood et al. 2001](#)) and is independent of either the specific form or the intensity of the intervention ([Bustillo et al. 2001](#)).

Another psychosocial intervention that has been shown to be effective in preventing relapse or rehospitalization in schizophrenia is assertive community treatment (ACT). This intervention, which involves intensive multidisciplinary team management and service delivery in both community and inpatient settings, is designed for individuals who experience intractable symptoms and high levels of functional impairment. At least 30 studies of ACT have shown

advantages over standard community treatment in reducing symptoms, family burden, and hospitalization and in improving independent living, housing stability, and quality of life ([McFarlane et al. 2015](#); [Mueser et al. 1998](#); [Phillips et al. 2001](#); [Stein and Test 1980](#)). However, it appears that the advantages of ACT do not persist after discontinuation of the program, even after prolonged delivery of services.

## Improvement of Psychosocial Functioning

Most patients with schizophrenia have personal goals that involve social and occupational functioning in the community; therefore, psychosocial treatment for patients with schizophrenia targets impairments in these areas. In a 3-year study, [Hogarty et al. \(1997a\)](#) found that weekly individual personal therapy, in which an incremental psychoeducational approach based on the patient's phase of recovery was used, had a significant advantage over supportive therapy, family therapy, and combined treatment in improving social adjustment but not in preventing relapse ([Hogarty et al. 1997b](#)). Interestingly, cognitive-behavioral therapy (CBT) may have a role in the management of persistent psychotic symptoms ([Chadwick et al. 1994](#); [Granholtz et al. 2005](#); [Tarrier et al. 2000](#)). CBT involves the use of techniques such as distraction, cognitive reframing of psychotic beliefs or experiences, and verbal challenge followed by reality testing ([Beck and Rector 2005](#); [Kingdon et al. 2008](#)). Reviews and meta-analyses of CBT for psychosis suggest a positive effect for reducing symptoms ([Mueser et al. 2013](#); [Wykes et al. 2008](#)).

Social skills training (SST) is one treatment strategy to help individuals acquire interpersonal disease management and independent living skills. Reviews of SST ([Bellack and Mueser 1993](#); [Kopelowicz et al. 2006](#)) have described three models of SST: basic model, social problem-solving model, and cognitive remediation model. Within the *basic model*, complex social scenarios are broken down to simpler components, the therapist models correct behaviors, and the patient learns through repeated role-play. The combination of this form of SST with antipsychotic medication appears to be more effective than medication alone in reducing relapse ([Hogarty et al. 1986](#)).

The *social problem-solving model* focuses on impaired information processing, which is thought to cause social skills deficits. This model targets symptom and medication management, recreation, basic conversation, and self-care in educational modules, and it has been shown to be modestly effective in enhancing skills ([Eckman et al. 1992](#); [Liberman et al. 1998](#); [Marder et al. 1996](#)). Interventions that use cueing and support in everyday community interactions by friends or family seem to improve transfer of newly learned social skills to community functioning (e.g., [Glynn et al. 2002](#)).

Finally, the *cognitive remediation model* of SST targets more fundamental cognitive deficits, in areas such as attention, memory, and planning, with the

aim of supporting more complex cognitive processes used in learning social and other skills. Small studies have reported mixed results for more complex cognitive and social skills ([Hodel and Brenner 1994](#); [Spencer et al. 1994](#); [Wykes et al. 1999](#)). An integrated approach to the concomitant training of neurocognitive and social cognitive abilities as well as social skills resulted in long-term improvement in social adjustment ([Hogarty et al. 2006](#); [McGurk et al. 2007](#)). One recent trial reported greater cognitive and functional gains when cognitive remediation was combined with physical exercise ([Malchow et al. 2015](#)).

Work to improve social functioning has focused on social cognition—the capacity to perceive the intentions and dispositions of others ([Penn et al. 2006](#)). A preliminary study of social cognition and interaction training—an intervention offered in 18 weekly sessions that focused on emotion training, figuring out situations, and integrating skills into real life—suggested that this treatment may be a promising approach for improving interpersonal functioning and managing symptoms of psychosis ([Combs et al. 2007](#)).

Illness management and recovery (IMR) is a manualized package of empirically supported approaches (psychoeducation, cognitive-behavioral approaches for medication adherence, relapse prevention planning, SST, and coping skills training) delivered in weekly group or individual sessions that are used with a recovery focus that targets each individual's personal life goals ([Mueser et al. 2006](#)). This combination of approaches results in improved symptoms, better community functioning, and reduced hospital readmission ([Bartholomew and Zechner 2014](#); [McGuire et al. 2014](#)).

Although family psychoeducation, CBT, SST, and IMR may improve symptoms and social functioning, they do not appear to affect employment status. However, more than 14 studies suggest that supported employment programs, which use rapid job searches, on-the-job training, continuous job support, and integration with mental health treatment, are more effective than traditional methods in helping patients obtain competitive employment ([Bond 2004](#); [Kinoshita et al. 2013](#); [Mueser et al. 2013](#)). For young people early in the course of their illness, this effective approach has been expanded to include return to education as well as employment ([Bond et al. 2015](#)).

In addition to employment, the ability to maintain a residence in the community is an important marker of community functioning. Simple provision of access to affordable housing by Section 8 certificates improves housing stability ([Hurlburt et al. 1996b](#)). Supported housing, broadly defined as access to independent housing of the patient's choice (often supported with housing subsidies), that is coupled with access to community mental health and support services improves residential stability and reduces hospitalization ([Rog 2004](#)). ACT for homeless individuals also has been shown to reduce homelessness ([Coldwell and Bender 2007](#)).

Because multiple effective psychosocial interventions exist and are still being developed, the choice of which intervention to apply should depend not only on



therapeutic efficacy but also on each individual's goals and preferences. Patients and their families need to be given information about treatment options and should be engaged in discussions with their treatment providers about how treatments can be useful in the context of an individual's symptoms, comorbidities, needs, and preferences.

---

## Management of Medical Comorbidity

---

### Obesity, Diabetes Mellitus, and Metabolic Syndrome

Medication side effects, as well as lifestyle and disease factors, place patients with schizophrenia at increased risk for developing obesity and metabolic side effects, including glucose intolerance, type 2 diabetes, diabetic ketoacidosis, and hyperlipidemia ([Dixon et al. 2000](#); [Meyer and Koro 2004](#); [Wirshing et al. 2002, 2003](#)). Although clinically significant weight gain occurs in a substantial proportion of patients receiving an antipsychotic medication ([Baptista 1999](#)), a convincing body of evidence indicates that certain atypical antipsychotics cause more weight gain than other agents ([Allison et al. 1999](#); [Lieberman et al. 2005](#); [Wirshing et al. 1999](#)). A large meta-analytic study of atypical and typical antipsychotics ([Wirshing et al. 1999](#)) found a mean weight gain of 9.8 lbs with clozapine, 9.1 lbs with olanzapine, and 4.6 lbs with risperidone, compared with 2.4 lbs with haloperidol, whereas the atypical antipsychotic ziprasidone was associated with a less than 1-lb weight gain. Furthermore, the CATIE study found a greater than 7% weight gain from baseline in 30% of the patients receiving olanzapine, 16% of those receiving quetiapine, 14% of those receiving risperidone, 12% of those receiving perphenazine, and 7% of those receiving ziprasidone ([Lieberman et al. 2005](#)). Compared with risperidone, iloperidone may have a higher risk of weight gain ([Weiden et al. 2008](#)) and asenapine ([Potkin et al. 2007](#)) and lurasidone ([Citrome 2011a, 2011b](#)) may have a lower risk. An antipsychotic's propensity to cause weight gain and other cardiometabolic side effects may be substantially greater in children and young adults who are using an antipsychotic for the first time ([Correll et al. 2009](#); [O'Donoghue et al. 2014](#)).

Diabetes mellitus is estimated to occur two to four times more frequently in patients with schizophrenia compared with the general population ([Dixon et al. 2000](#); [Goff et al. 2005](#); [Henderson et al. 2000](#); [Mukherjee et al. 1996](#); [Wirshing et al. 1998](#)). The risk of diabetes in schizophrenia is likely multifactorial, but accrued evidence clearly indicates that atypical antipsychotics are associated with glucose dysregulation ([Jin et al. 2004](#)). Numerous studies of hyperglycemia, new-onset diabetes mellitus, and diabetic ketoacidosis ([Dixon et](#)

al. 2000; Gianfrancesco et al. 2002; Henderson et al. 2000; Wirshing et al. 2002) led to heightened concern, the issuance of warnings by regulatory authorities and class labeling (Jin et al. 2004), and published consensus guidelines on monitoring for cardiometabolic risk (American Diabetes Association et al. 2004). Some atypical antipsychotics appear to increase risk for diabetes beyond typical agents: clozapine and olanzapine are described as having the greatest risk for diabetes (Kessing et al. 2010; Leslie and Rosenheck 2004; Yood et al. 2009). The risk associated with other antipsychotics is not as clear, although the risk associated with aripiprazole, ziprasidone, and lurasidone is described as being low or not different from the risk associated with typical agents in adults with chronic schizophrenia.

Certain atypical antipsychotics (particularly clozapine, olanzapine, and quetiapine) and low-potency conventional agents have been shown to be associated with hyperlipidemia (Henderson et al. 2000; Meyer and Koro 2004; Osser et al. 1999), whereas ziprasidone and aripiprazole do not appear to carry this adverse effect (Kingsbury et al. 2001; Meyer and Koro 2004). The co-occurrence of atherogenic dyslipidemia with abdominal adiposity, insulin resistance, impaired fasting glucose or overt diabetes mellitus, and hypertension constitutes the cluster of clinical features known as the metabolic syndrome. Baseline data from the CATIE study indicated that more than 40% of subjects had metabolic syndrome, with women carrying greater risk than men (McEvoy et al. 2005). The presence of metabolic syndrome is associated with decreased aerobic fitness and increased functional impairment (Vancampfort et al. 2015).

Controlled studies of metformin have reported benefits for reducing weight gain at initiation of antipsychotic therapy, as well as for achieving weight loss during continuing therapy (Ellinger et al. 2010; Mizuno et al. 2014; Praharaj et al. 2011). Moreover, metformin in combination with lifestyle changes was found to be effective in decreasing cardiometabolic risks (Curtis et al. 2012). Controlled studies of topiramate, reboxetine, and modafinil have also shown beneficial effects on cardiometabolic risk factors, although topiramate treatment was associated with substantial side effects (Ellinger et al. 2010). Orlistat, the non-centrally acting weight-control drug, was not better than placebo in one controlled study (Joffe et al. 2008). A case series (Hamoui et al. 2004) suggested that bariatric surgery was as effective in promoting weight loss in patients with schizophrenia as it is in other populations of obese patients. Centrally acting weight-loss drugs (e.g., diethylpropion, fenproporex, amfepramone) that have the potential to increase the activity of biogenic amines could theoretically exacerbate symptoms of psychosis in this population.

Given the high rates of cardiometabolic disease and early mortality in schizophrenia, all other things being equal, prescribers should strongly consider selecting an antipsychotic with lower risk for cardiometabolic side effects first. Clinicians should use pre- and posttreatment monitoring such as that recommended by the American Diabetes Association-American Psychiatric



Association consensus panel ([American Diabetes Association et al. 2004](#)) and deploy pharmacological and/or behavioral strategies to prevent weight gain. Patients who develop cardiometabolic abnormalities may require a medication switch, monitoring, and management of the new abnormalities with behavioral and pharmacological strategies in collaboration with an internist. Although a medication switch may lower the risk of cardiometabolic abnormalities, a dosage reduction may be helpful in decreasing EPS, agitation, and amenorrhea ([Newcomer et al. 2013](#)).

## Tobacco Use Disorder

The rate of smoking in people with schizophrenia continues to be three to four times that seen in the general population ([McClave et al. 2010](#)). Cigarette smoke causes cardiovascular diseases, diabetes, lung diseases, and cancers and is partially responsible for the excess medical disease burden in schizophrenia. Smoking can complicate the treatment of schizophrenia, because cigarette smoke alters liver enzyme metabolism of some antipsychotics, changing the medication blood levels as patients transition in and out of smoke-free hospital settings ([Desai et al. 2001](#)), and nicotine withdrawal in emergency departments and hospitals can contribute to (treatable) agitation during acute psychosis ([Allen et al. 2011](#)).

Treatment of nicotine addiction appears to be more difficult in the schizophrenia population compared with both the general population and other psychiatric populations ([Covey et al. 1994](#)). Nonetheless, evidence suggests that a multimodality approach that integrates motivation-based treatment ([Brunette et al. 2011b](#); [Steinberg et al. 2004](#)), addiction treatment strategies, and tobacco dependence treatment into mental health settings is beneficial ([Ziedonis et al. 2003](#)). FDA-approved tobacco cessation medications combined with individual or group CBT lead to cessation in up to half of patients who initiate treatment ([Evins et al. 2005, 2014](#); [Ferron et al. 2009](#); [George et al. 2000](#); [Weiner et al. 2001](#); [Williams et al. 2004, 2012](#)). As in the general population, relapse can occur rapidly after short-term treatment is discontinued but can be prevented by continuing treatment for 1 year ([Evins et al. 2014](#)). Patients with schizophrenia who use cessation treatment are able to quit smoking and thereby improve their long-term health without adverse effects on the psychotic illness.

## Extrapyramidal Side Effects

Parkinsonism and acute dystonia are associated with the degree of dopamine D<sub>2</sub> receptor occupancy in the striatum ([Kapur and Remington 1996](#)). Thus, high-potency first-generation antipsychotics such as haloperidol have the greatest propensity (especially at high dosages) to cause these side effects, but many

second-generation agents also may cause EPS in a dose-dependent manner. The CATIE study found that the rate of drug discontinuation due to reported EPS was 8% in the patient group receiving the typical antipsychotic perphenazine, with rates of 4% for ziprasidone, 3% for risperidone and quetiapine, and 2% for olanzapine (Lieberman et al. 2005). Among the second-generation agents, iloperidone, asenapine, aripiprazole, olanzapine, quetiapine, and clozapine do not appear to produce clinically significant parkinsonism or dystonia (Citrome 2011a; Kane et al. 2008; Lieberman et al. 2005; Schoemaker et al. 2010; Stip and Tourjman 2010), whereas lurasidone, risperidone, and paliperidone carry some risk (Leucht et al. 2013).

Akathisia, a disturbing sense of inner restlessness and the inability of the patient to stay still, is associated with seemingly purposeless movements (such as tapping or pacing) that may be noticeable to the examiner. Akathisia occurs less frequently with second-generation than with first-generation medication (Kane et al. 2009) and least often with clozapine, olanzapine, quetiapine, iloperidone, and low-potency first-generation antipsychotic medications (Citrome 2011a; Kane et al. 2008; Lieberman et al. 2005; Schoemaker et al. 2010; Stip and Tourjman 2010). Although lowering the dosage of the antipsychotic is an obvious treatment for akathisia, addition of a  $\beta$ -blocker (e.g., propranolol) is often effective. Anticholinergic drugs and benzodiazepines are generally not that effective but can be tried in patients who do not respond to  $\beta$ -blockers, and anticholinergics also may be useful in patients with coexisting parkinsonism.

Parkinsonism (Osser 1999), characterized by tremor, rigidity, and bradykinesia, can occur early in treatment, usually within the initial weeks or months. Bradykinesia includes generalized slowing of movement and a masklike face (with a loss of facial expression); it may be confused with depression or negative symptoms. One variant of parkinsonism, akinesia, can coexist with bradykinesia (but without tremor or rigidity) and may be associated with symptoms of apathy and fatigue. The “rabbit syndrome” (Casey 1999), occurring after months or years of antipsychotic drug treatment, is also a variant of parkinsonism and is characterized by a perioral and jaw tremor. Anticholinergic medications are the treatment of choice for parkinsonism and usually are effective. Reducing the antipsychotic dosage or switching to an antipsychotic less likely to produce EPS also may be helpful.

Acute dystonia occurs most commonly in young males during the week after initiation of antipsychotics or following an abrupt or rapid dosage increase (Ayd 1961; Barnes and Spence 2000; Remington and Kapur 1996). The dystonia may appear as torticollis, trismus, tongue protrusion, pharyngeal constriction, laryngospasm, blepharospasm, oculogyric crisis, or abnormal contractions of any part of the body. Clinically, in addition to the dystonic muscular contractions that may be immediately noticeable, the patient may complain of tongue thickening, throat tightening, and difficulty speaking or swallowing. Acute treatment with either an anticholinergic agent or an antihistamine is usually

highly effective but may need to be repeated at intervals. Should respiratory difficulty develop, medications may need to be given parenterally.

## Tardive Dyskinesia and Tardive Dystonia

Tardive dyskinesia, which is a syndrome of potentially irreversible involuntary movements, and tardive dystonia, which is characterized by sustained muscle contractions, can gradually emerge after a prolonged period of treatment with antipsychotic medications. Accumulating evidence suggests that the second-generation antipsychotics are less likely to cause these tardive syndromes than are the first-generation drugs (Jeste et al. 1998; Kane et al. 1993; Marder et al. 2002; Margolese et al. 2005; Shirzadi and Ghaemi 2006; Tarsy and Baldessarini 2006; Tollefson et al. 1997). However, because many patients have had exposure to more than one second-generation agent, it is difficult to determine the risk associated with individual agents. It appears that in comparison with the first-generation agents, the second-generation drugs collectively carry one-third to one-twelfth the risk of causing tardive dyskinesia and tardive dystonia (Correll et al. 2004, 2009; Kane 2004; Leucht et al. 2003; Margolese et al. 2005).

The most common form of tardive dyskinesia involves dyskinetic movements of the orofacial and buccolingual musculature, manifesting as grimacing, facial tics, lip smacking, chewing, and wormlike movements of the tongue. Involvement of the neck, axial, and extremity musculature also may occur in the form of choreoathetoid movements, which on rare occasions may involve laryngopharyngeal and respiratory muscles. Tardive dystonia may occur earlier in treatment than tardive dyskinesia and is characterized by slow, sustained twisting movements of the head, neck, trunk, and extremities; blepharospasm, torticollis, facial grimacing, back arching, and hyperextension and rotation of the limbs also may be seen (Simpson 2000).

Risk factors for tardive dyskinesia include older age and female sex (Kane 2004), whereas tardive dystonia is more common in younger patients and males. Other important risk factors for tardive dyskinesia include high medication dosages (Glazer 2000a, 2000c) and the presence of other extrapyramidal syndromes (Kane 2004).

Although no treatment has been demonstrated to be effective for tardive dyskinesia, several management strategies may be clinically useful. Clinicians should screen patients taking antipsychotic medications on a regular basis. If tardive dyskinesia develops, switching from a first-generation to a second-generation drug may be helpful. For those patients who are taking a second-generation agent, a switch to another second-generation drug may be considered. Among the second-generation drugs, evidence suggests that clozapine may reduce symptoms of tardive dyskinesia (Glazer 2000a; Lieberman et al. 1991). Patients with tardive dyskinesia who are taking anticholinergic

medications should discontinue these medications, because they can worsen tardive dyskinesia. Finally, the symptoms of tardive dystonia may be alleviated by reducing the dosages of the antipsychotics, by switching from first-generation to second-generation agents (including clozapine), by using anticholinergics, and/or by administering dopamine-depleting agents, such as reserpine or tetrabenazine ([Simpson 2000](#)).

## Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS), which occurs in about 1%-2% of patients receiving typical antipsychotic medication and is potentially fatal in up to 20% of cases (without treatment), has been reported to occur during treatment with both the typical ([Caroff and Mann 1993](#)) and the atypical ([Ananth et al. 2004](#); [S. Hasan and Buckley 1998](#); [Wirshing et al. 2000](#)) antipsychotics. Risk factors include intramuscular injections, rapid escalation to high dosages, dehydration, restraint use, and high temperatures. Catatonia and severe disorganization are clinical symptoms that may be associated with a high risk for NMS ([Berardi et al. 2002](#)). Symptoms of NMS include hyperpyrexia, altered consciousness, muscle rigidity and dystonia, and autonomic nervous system dysfunction, as well as laboratory test results indicating elevated creatine phosphokinase, liver enzymes, and white blood cell count. Early detection and rapid treatment of this medical emergency are crucial and include discontinuation of the antipsychotic, treatment in a medical setting that can support vital functioning, and in some cases the use of a dopamine agonist such as bromocriptine or dantrolene, a muscle relaxant ([Koppel 1998](#); [Susman 2001](#)).

## Hyperprolactinemia

Antipsychotic medications—particularly some of the typical agents, as well as risperidone, paliperidone, and lurasidone—can produce an increase in serum prolactin levels ([Dickson and Glazer 1999](#); [Marder et al. 2004](#)). It is well known that hyperprolactinemia secondary to medical disorders (e.g., pituitary tumor) can produce galactorrhea, hypogonadism, and osteoporosis, all of which have also been reported in patients with schizophrenia ([Abraham et al. 1996](#); [Ghadirian et al. 1982](#); [Riecher-Rössler et al. 1994](#); [Windgassen et al. 1996](#); [Yazigi et al. 1997](#)). Yet the relations between antipsychotic-induced hyperprolactinemia and these conditions, perhaps with the exception of galactorrhea ([Windgassen et al. 1996](#)), remain unclear, with conflicting reports in the literature ([Canuso et al. 2002](#); [Costa et al. 2007](#); [Hummer et al. 2005](#); [Kinon et al. 2006](#); [Kleinberg et al. 1999](#); [O'Keane and Meaney 2005](#)).

Clinicians should ask patients about possible symptoms of hyperprolactinemia. If a patient is symptomatic, prolactin levels should be obtained and medical

causes of hyperprolactinemia ruled out. Prolactin elevation-associated symptoms of galactorrhea or of sexual or menstrual dysfunction may be minimized through a dosage reduction or through a medication change to an atypical antipsychotic with less prolactin-elevating potential ([Canuso et al. 1998](#); [Dickson and Glazer 1999](#)).

---

## Psychiatric Conditions Comorbid With Schizophrenia and Their Treatment

---

### Substance-Related Disorders

Nearly one-half of the patients with schizophrenia are reported to have a lifetime history of an alcohol or a substance use disorder, compared with 16% of the general population ([Regier et al. 1990](#)). Alcohol is the most commonly abused substance in chronically ill patients, followed by cannabis and cocaine ([Selzer and Lieberman 1993](#); [Sevy et al. 1990](#)). As in the general population, men with schizophrenia are more likely to abuse substances than are women ([Mueser et al. 1995](#)).

Comorbid substance use has a deleterious effect on the course of schizophrenia ([Grech et al. 1999](#)); use of even small amounts can produce negative effects ([Drake et al. 2001](#); [D'Souza et al. 2005](#)). Patients with schizophrenia and substance use disorders are at increased risk for infectious diseases such as HIV, hepatitis B, and hepatitis C ([Rosenberg et al. 2001](#)); in addition, alcohol and substance use are associated with clinical worsening, poor functioning, and increased rates of hospitalizations and homelessness ([Dixon et al. 1990](#); [Drake and Mueser 1996](#); [Hurlburt et al. 1996a](#); [Negrete et al. 1986](#); [Soni and Brownlee 1991](#)). In some studies, more than 50% of the first-episode patients were reported to have cannabis use disorder ([Rolfe et al. 1999](#)), which often complicates the diagnosis of a psychotic disorder ([Addington 1999](#)).

Although obtaining information from patients about their use of substances of abuse should be a standard part of a medical history, problematic alcohol or substance use is often underrecognized and undertreated in mental health settings ([Ananth et al. 1989](#)). Because patients often deny use of alcohol and drugs, clinicians also should pursue collateral reports from family members, case managers, and others involved in the delivery of services to patients. Patients with schizophrenia and a comorbid alcohol or substance use disorder require treatment for both disorders ([Bellack and DiClemente 1999](#)), optimally in programs that provide long-term comprehensive services along with integrated mental health and substance abuse treatment, including medication management ([Drake and Mueser 2001](#); [Minkoff 1989](#); [Osher and Kofoed 1989](#)).

Although there is no agreed-on pharmacological treatment approach for patients with schizophrenia and comorbid alcohol or substance use disorders (Green et al. 2007, 2008; Wilkins 1997), some investigators have been interested in the potential role of atypical antipsychotics in reducing substance use in these patients. The atypical antipsychotic that has been studied most in this population is clozapine. Preliminary studies of clozapine have reported promising results for reducing alcohol and drug use (Brunette et al. 2006; Buckley et al. 1999; Drake et al. 2000; Green et al. 2003; Lee et al. 1998; Zimmet et al. 2000). A small randomized trial provided some confirmation of these preliminary studies (Brunette et al. 2011a).

Data concerning the potential effects of other atypical antipsychotics on substance use reduction and relapse prevention are even more preliminary. Findings have been mixed for risperidone (Albanese 2000; Green et al. 2003; Petrakis et al. 2006; Rubio et al. 2006; Smelson et al. 2000), olanzapine (Littrell et al. 2001; Noordsy et al. 2001; Sayers et al. 2005; Smelson et al. 2006), quetiapine (Brown et al. 2003; Potvin et al. 2006), and aripiprazole (Beresford et al. 2005; Brown et al. 2005). No research has assessed the effects of brexpiprazole, cariprazine, ziprasidone, asenapine, iloperidone, or lurasidone on substance craving or use.

Other possible pharmacological options with evidence for efficacy in the treatment of substance use disorders in schizophrenia include the following: 1) disulfiram for co-occurring alcohol use disorder (note that use requires monitoring in patients with schizophrenia) (Kofoed et al. 1986; Mueser et al. 2003; Petrakis et al. 2005); 2) naltrexone for co-occurring alcohol use disorder (Petrakis et al. 2004, 2005); 3) the tricyclic antidepressants desipramine and imipramine for comorbid cocaine use disorder (Siris et al. 1993; Ziedonis et al. 1992); and 4) bupropion, nicotine replacement therapy, and varenicline for tobacco use disorder (Evins et al. 2005; George et al. 2002; Nino-Gomez et al. 2010). Acamprosate, although shown to be effective for alcohol use disorder in placebo-controlled trials, has yet to be studied in patients with schizophrenia.

## Depression

Schizophrenia is often associated with depressive states ranging from dysphoria to major depressive disorder (Blum et al. 2015). The Epidemiologic Catchment Area study suggested that individuals with schizophrenia have a 14-fold greater risk of depression compared with the general population (Fenton 2001). At various times, depression has been viewed as an aspect of schizophrenia (McGlashan and Carpenter 1976; Sax et al. 1996), as a response to psychosis (McGlashan and Carpenter 1976; Sax et al. 1996), or as a state occurring after the cessation of frank psychotic symptoms (Birchwood et al. 2000). The DSM-5 Psychotic Disorders Work Group recommended that depressive symptoms that do not meet full criteria for an episode of major depressive disorder be



considered a component of schizophrenia, and in accordance with this view, depression was included as one of eight Clinician-Rated Dimensions of Psychosis Symptom Severity ([American Psychiatric Association 2013](#); [Malaspina et al. 2013](#)).

Depression in patients with schizophrenia must be differentiated from negative symptoms and EPS; the presence of a core depressed mood and related neurovegetative symptoms should be distinguished from flatness of affect, parkinsonism, and anhedonia ([McGlashan and Carpenter 1976](#)). Depression occurring during an exacerbation of psychosis may remit with treatment of the psychosis ([Birchwood et al. 2000](#); [Koreen et al. 1993](#); [Tollefson et al. 1999](#)). However, postpsychotic depression classically develops after the resolution or improvement of psychotic symptoms (see [Birchwood et al. 2000](#); [Koreen et al. 1993](#)). Dysphoria and demoralization ([Iqbal et al. 2000](#); [Siris 2000a](#)) may occur as patients struggle with illness-related disability ([Bartels and Drake 1988](#)).

Treatment of depression in patients with schizophrenia may include both psychopharmacological and psychosocial components ([A. Hasan et al. 2015](#); [Siris 2000b](#)). Because depression may presage an increase in psychosis, the pharmacological treatment of psychotic symptoms should be optimized. Treatment of depression in acute psychosis may be accomplished through the use of antipsychotic medication alone, especially second-generation antipsychotics ([Banov et al. 1994](#); [Levinson et al. 1999](#); [Marder et al. 1997](#); [Tollefson et al. 1998](#)). However, an episode of major depressive disorder that develops after the remission of psychosis often requires the addition of antidepressants to the medication regimen ([Hogarty et al. 1995](#); [Kirli and Caliskan 1998](#); [Levinson et al. 1999](#); [Siris et al. 1987](#)). Psychosocial interventions can help with demoralization and dysphoria ([Siris 2000b](#)). Severe depression also may be treated with electroconvulsive therapy (ECT; [Pompili et al. 2013](#)).

## Suicide

Suicide is one of the leading causes of premature death in patients with schizophrenia, who have a 10% lifetime risk of suicide. Nearly 50% of the patients with schizophrenia attempt suicide during their lifetime ([Black et al. 1985](#); [Tsuang et al. 1999](#)). Risk factors include depression and the diagnosis of schizoaffective disorder ([Harkavy-Friedman et al. 2004](#); [Radomsky et al. 1999](#)), social isolation ([Drake et al. 1986](#); [Goldstein et al. 2006](#); [Potkin et al. 2003](#)), and feelings of hopelessness and disappointment over failure to meet high self-expectations ([Kim et al. 2003](#); [Westermeyer et al. 1991](#)). Patients with a higher level of insight and awareness of their illness may be at increased risk ([Amador et al. 1996](#); [Bourgeois et al. 2004](#); [Crumlish et al. 2005](#)), as may patients with a low level of functioning ([Kaplan and Harrow 1996](#)).

A history of suicide attempts is one of the strongest predictors of suicide in patients with schizophrenia (Potkin et al. 2003; Rossau and Mortensen 1997; Roy 1982). A meta-analysis of 29 case-control and cohort studies indicated that suicide risk factors included previous depressive disorders, substance use disorders, agitation or motor restlessness, fear of mental disintegration, poor adherence to treatment, and recent loss (Hawton et al. 2005).

An increased risk of suicide is present in the early phase of the illness (Drake et al. 1985; Kuo et al. 2005; Nordentoft et al. 2015). Suicide risk peaks immediately after admission and shortly after discharge (Qin and Nordentoft 2005; Rossau and Mortensen 1997). Patients in an active phase of the illness (Heilä et al. 1997) or with positive symptoms (Kelly et al. 2004) may be at particular risk, especially if they have prominent symptoms of suspiciousness and delusions (Fenton et al. 1997).

The treating clinician should regularly evaluate the patient's condition, assess for suicide risk factors, and aim to enhance protective factors such as social support and positive coping skills (Montross et al. 2005). Patients who present with suicidal thoughts or behavior require close follow-up and intensive outreach (Drake et al. 1986; Harkavy-Friedman and Nelson 1997). Improved ward safety, effective substance use disorder therapy, treatment of mood symptoms, and ensured medication adherence are all measures that may help prevent suicide (Hawton et al. 2005; Hunt et al. 2006).

Psychopharmacological treatment plays a crucial role in the prevention of suicide. In one study, more than half of the patients who committed suicide either were noncompliant with their medication regimens or had been prescribed inadequate dosages of antipsychotics, and 23% were estimated to be nonresponsive to their medication (Heilä et al. 1999). Moreover, a landmark study of nearly 1,000 patients with schizophrenia and schizoaffective disorder who were at risk for suicide (but who were not necessarily classically treatment resistant) indicated that treatment with clozapine was more likely to decrease suicidality than was treatment with olanzapine (Meltzer et al. 2003). ECT also may be helpful for suicidal symptoms among people with schizophrenia (Pompili et al. 2013).

## Obsessive-Compulsive Symptoms

Obsessive-compulsive symptoms are seen in 9%-30% of patients with schizophrenia (Berman et al. 1995a; Byerly et al. 2005; Cassano et al. 1998; Ongür and Goff 2005). Although obsessive-compulsive symptoms may be difficult to distinguish from delusions (Eisen et al. 1997), they are important to identify because they may indicate a poor prognosis yet may be responsive to specialized treatment regimens (Byerly et al. 2005; Fenton and McGlashan 1986; Hwang et al. 2000; Ongür and Goff 2005). The obsessive-compulsive symptoms in schizophrenia are similar to those in obsessive-compulsive disorder



([Tibbo et al. 2000](#)), although the symptoms may not be ego-dystonic in patients with schizophrenia.

Treatment of obsessive-compulsive schizophrenia may require the addition of a serotonergic antidepressant to the antipsychotic regimen ([Berman et al. 1995b](#); [Chang and Berman 1999](#); [Poyurovsky et al. 2000](#)). However, prescribers should be mindful of the risk of drug interactions, because the combined use of serotonin reuptake inhibitors with some antipsychotics, particularly clozapine, may lead to excessive antipsychotic serum levels. CBT also may be useful for managing obsessive-compulsive symptoms ([Hagen et al. 2014](#)).

---

## Future Directions

---

Despite advances in understanding of the neurobiology of schizophrenia, and a variety of novel-mechanism agents currently being evaluated in clinical trials, it remains the case that all approved antipsychotic medications primarily modulate the dopamine system. Although postsynaptic dopamine D<sub>2</sub> antagonists and partial D<sub>2</sub> agonists have proven antipsychotic efficacy, these agents are mostly prescribed in oral formulations. Because inconsistent patient adherence can limit the utility of these agents in clinical practice, several longer-acting injectable formulations of existing dopaminergic agents have been developed. These agents traditionally have been dosed every 2–4 weeks, but a 3-month formulation of paliperidone was recently approved, and a 6-week formulation of aripiprazole is available. In earlier stages of drug development are several novel and established dopamine-modulating agents with combined pharmacological activity at other important neurotransmitter receptors, including serotonin, glutamate,  $\sigma_2$ , and the  $\mu$  opioid receptor. Such agents may confer some efficacy or safety benefit over existing medications.

Although dopaminergic drugs will continue to play a major role in treatment of the positive symptoms of schizophrenia, more effective treatments are needed against the functionally disabling negative and neurocognitive symptoms of the illness. Recent drug development efforts, particularly for negative symptoms, have targeted the glutamatergic system. Although promising Phase II findings were reported for a metabotropic glutamate 2/3 receptor agonist ([Patil et al. 2007](#)) and a glycine transport reuptake inhibitor ([Umbricht et al. 2014](#)), later-phase programs yielded disappointing results ([Downing et al. 2014](#); [Kinon et al. 2011](#); [Roche 2014](#)). Several  $\alpha_7$ -nicotinic receptor agonists also have been studied in the treatment of cognitive impairment in schizophrenia. Other novel-mechanism agents that are either under investigation or of theoretical interest for the treatment of cognitive impairment in schizophrenia include  $\alpha_2$   $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptor agonists ([Lewis and Gonzalez-Burgos 2006](#)), muscarinic agonists ([Shekhar et al. 2008](#)), serotonin 5-HT<sub>6</sub> ([Roth et al. 2004](#)) and 5-HT<sub>7</sub> ([Horiguchi](#)

et al. 2011; Horisawa et al. 2011; Nikiforuk et al. 2013) receptor antagonists, and phosphodiesterase 10A inhibitors (Kehler and Nielsen 2011).

In addition to recent pharmacological advances in the treatment of schizophrenia, emerging evidence suggests that novel psychosocial approaches, including computerized cognitive remediation, may be of benefit in treating cognitive impairment in schizophrenia (Fisher et al. 2009; Lindenmayer et al. 2008, 2013). Moreover, the use of pro-cognitive medications along with software targeted to engage specific neuronal circuits could facilitate use-dependent plasticity. Such combined therapies, along with social and vocational skills training, could lead to better outcomes in the functioning and quality of life for people with schizophrenia.

The future is also likely to see further progress in the development of treatments for prodromal schizophrenia, with the goal of improving symptoms and delaying or preventing conversion to the full expression of the illness. Interestingly, the risk-benefit ratio of antipsychotic therapy does not appear to be particularly favorable in this population, with studies showing inconsistent benefit in preventing conversion to psychosis and high side-effect burden (McGlashan et al. 2006; McGorry et al. 2002; Yung et al. 2011). Alternatively, promising data from studies of long-chain omega-3 fatty acids (Amminger et al. 2010) and CBT (Morrison et al. 2004) have been reported. Taken together, these results suggest that the therapeutic targets for preventing the progression to schizophrenia differ from the target for treating psychosis. It is hoped that as new treatments for the negative and cognitive systems of schizophrenia emerge, these therapeutics will also be found to have a role in the treatment of prodromal symptoms and the prevention of schizophrenia.

---

## References

---

- Abraham G, Friedman RH, Vergheze C: Osteoporosis demonstrated by dual energy x-ray absorptiometry in chronic schizophrenic patients. *Biol Psychiatry* 40(5): 430-431, 1996 8874849
- Addington J: Early intervention strategies for co-morbid cannabis use and psychosis. Presented at the Inaugural International Cannabis and Psychosis Conference, Melbourne, Australia, February 16-19, 1999
- Addington J, Heinssen RK, Robinson DG, et al: Duration of untreated psychosis in community treatment settings in the United States. *Psychiatr Serv* 66(7):753-756, 2015 25588418
- Albanese MJ: Risperidone in substance abusers with bipolar disorder. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, 2000
- Allen MH, Debanné M, Lazignac C, et al: Effect of nicotine replacement therapy on agitation in smokers with schizophrenia: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 168(4):395-399, 2011 21245085

- Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156(11):1686-1696, 1999 10553730
- Amador XF, Friedman JH, Kasapis C, et al: Suicidal behavior in schizophrenia and its relationship to awareness of illness. *Am J Psychiatry* 153(9):1185-1188, 1996 8780423
- American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity: Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry* 65(2):267-272, 2004 15003083
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Amminger GP, Schäfer MR, Papageorgiou K, et al: Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 67(2):146-154, 2010 20124114
- Ananth J, Vandewater S, Kamal M, et al: Missed diagnosis of substance abuse in psychiatric patients. *Hosp Community Psychiatry* 40(3):297-299, 1989 2917741
- Ananth J, Parameswaran S, Gunatilake S, et al: Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 65(4):464-470, 2004 15119907
- Andreasen NC: Positive vs. negative schizophrenia: a critical evaluation. *Schizophr Bull* 11(3):380-389, 1985 2863870
- Angermeyer MC, Kühn L, Goldstein JM: Gender and the course of schizophrenia: differences in treated outcomes. *Schizophr Bull* 16(2):293-307, 1990 2374885
- Ayd FJ Jr: A survey of drug-induced extrapyramidal reactions. *JAMA* 175:1054-1060, 1961 13685365
- Aylward E, Walker E, Bettles B: Intelligence in schizophrenia: meta-analysis of the research. *Schizophr Bull* 10(3):430-459, 1984 6382590
- Banov MD, Zarate CA Jr, Tohen M, et al: Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. *J Clin Psychiatry* 55(7):295-300, 1994 8071290
- Baptista T: Body weight gain induced by antipsychotic drugs: mechanisms and management. *Acta Psychiatr Scand* 100(1):3-16, 1999 10442434
- Barbui C: Intramuscular haloperidol plus promethazine is more effective and safer than haloperidol alone for rapid tranquillisation of agitated mentally ill patients. *Evid Based Ment Health* 11(3):86-87, 2008 18669688
- Barch DM: Pharmacological strategies for enhancing cognition in schizophrenia. *Curr Top Behav Neurosci* 4:43-96, 2010 21312397
- Barnes TR, Spence SA: Movement disorders associated with antipsychotic drugs: clinical and biological implications, in *Psychopharmacology of Schizophrenia*. Edited by Reverly MA, Deakin JFW. New York, Oxford University Press, 2000, pp 178-210

- Bartels SJ, Drake RE: Depressive symptoms in schizophrenia: comprehensive differential diagnosis. *Compr Psychiatry* 29(5): 467–483, 1988 3053027
- Bartholomew T, Zechner M: The relationship of illness management and recovery to state hospital readmission. *J Nerv Ment Dis* 202(9):647–650, 2014 25099301
- Beck AT, Rector NA: Cognitive approaches to schizophrenia: theory and therapy. *Annu Rev Clin Psychol* 1:577–606, 2005 17716100
- Bellack AS, DiClemente CC: Treating substance abuse among patients with schizophrenia. *Psychiatr Serv* 50(1):75–80, 1999 9890583
- Bellack AS, Mueser KT: Psychosocial treatment for schizophrenia. *Schizophr Bull* 19(2):317–336, 1993 8322036
- Ben-Zeev D, Brenner CJ, Begale M, et al: Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. *Schizophr Bull* 40(6):1244–1253, 2014 24609454
- Berardi D, Dell’Atti M, Amore M, et al: Clinical risk factors for neuroleptic malignant syndrome. *Hum Psychopharmacol* 17(2):99–102, 2002 12404699
- Beresford TP, Clapp L, Martin B, et al: Aripiprazole in schizophrenia with cocaine dependence: a pilot study. *J Clin Psychopharmacol* 25(4):363–366, 2005 16012280
- Berman I, Kalinowski A, Berman SM, et al: Obsessive and compulsive symptoms in chronic schizophrenia. *Compr Psychiatry* 36(1):6–10, 1995a 7705089
- Berman I, Sapers BL, Chang HH, et al: Treatment of obsessive-compulsive symptoms in schizophrenic patients with clomipramine. *J Clin Psychopharmacol* 15(3):206–210, 1995b 7635998
- Bernardo M, Ramón Azanza J, Rubio-Terrés C, et al: Cost-effectiveness analysis of schizophrenia relapse prevention: an economic evaluation of the ZEUS (Ziprasidone-Extended-Use-in-Schizophrenia) study in Spain. *Clin Drug Investig* 26(8):447–457, 2006 17163277
- Bilder RM, Goldman RS, Volavka J, et al: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *Am J Psychiatry* 159(6):1018–1028, 2002 12042192
- Birchwood M: Early intervention in schizophrenia: theoretical background and clinical strategies. *Br J Clin Psychol* 31(pt 3):257–278, 1992 1393156
- Birchwood M, Iqbal Z, Chadwick P, et al: Cognitive approach to depression and suicidal thinking in psychosis, 1: ontogeny of post-psychotic depression. *Br J Psychiatry* 177:516–521, 2000 11102326
- Black DW, Warrack G, Winokur G: The Iowa record-linkage study, I: suicides and accidental deaths among psychiatric patients. *Arch Gen Psychiatry* 42(1):71–75, 1985 3966854
- Blum LH, Vakhrusheva J, Saperstein A, et al: Depressed mood in individuals with schizophrenia: a comparison of retrospective and real-time measures. *Psychiatr Res* 227(2–3):318–323, 2015 25895490
- Bond GR: Supported employment: evidence for an evidence-based practice. *Psychiatr Rehabil J* 27(4):345–359, 2004 15222147
- Bond GR, Drake RE, Luciano A: Employment and educational outcomes in early intervention programmes for early psychosis: a systematic review. *Epidemiol*

- Psychiatr Sci 24(5):446-457, 2015 25016950
- Bondolfi G, Dufour H, Patris M, et al; The Risperidone Study Group: Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. *Am J Psychiatry* 155(4):499-504, 1998 9545995
- Bourgeois M, Swendsen J, Young F, et al; InterSePT Study Group: Awareness of disorder and suicide risk in the treatment of schizophrenia: results of the International Suicide Prevention Trial. *Am J Psychiatry* 161(8):1494-1496, 2004 15285981
- Bozikas VP, Andreou C: Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. *Aust N Z J Psychiatry* 45(2):93-108, 2011 21320033
- Breier A, Schreiber JL, Dyer J, et al: National Institute of Mental Health longitudinal study of chronic schizophrenia: prognosis and predictors of outcome. *Arch Gen Psychiatry* 48(3):239-246, 1991 1671741
- Breier AF, Malhotra AK, Su TP, et al: Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. *Am J Psychiatry* 156(2):294-298, 1999 9989566
- Brown ES, Nejtek VA, Perantie DC, et al: Cocaine and amphetamine use in patients with psychiatric illness: a randomized trial of typical antipsychotic continuation or discontinuation. *J Clin Psychopharmacol* 23(4):384-388, 2003 12920415
- Brown ES, Jeffress J, Liggin JD, et al: Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. *J Clin Psychiatry* 66(6):756-760, 2005 15960570
- Brown GW, Rutter M: The measurement of family activities and relationships: a methodological study. *Human Relations* 19(3):241-263, 1966
- Brunette MF, Drake RE, Xie H, et al: Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 32(4):637-643, 2006 16782758
- Brunette MF, Dawson R, O'Keefe CD, et al: A randomized trial of clozapine vs. other antipsychotics for cannabis use disorder in patients with schizophrenia. *J Dual Diagn* 7(1-2):50-63, 2011a 25914610
- Brunette MF, Ferron JC, McHugo GJ, et al: An electronic decision support system to motivate people with severe mental illnesses to quit smoking. *Psychiatr Serv* 62(4):360-366, 2011b 21459986
- Buchanan RW, Strauss ME, Kirkpatrick B, et al: Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. *Arch Gen Psychiatry* 51(10):804-811, 1994 7944870
- Buchanan RW, Ball MP, Weiner E, et al: Olanzapine treatment of residual positive and negative symptoms. *Am J Psychiatry* 162(1):124-129, 2005 15625210
- Buchanan RW, Freedman R, Javitt DC, et al: Recent advances in the development of novel pharmacological agents for the treatment of cognitive impairments in schizophrenia. *Schizophr Bull* 33(5):1120-1130, 2007 17641146

- Buckley P, McCarthy M, Chapman P, et al: Clozapine treatment of comorbid substance abuse in patients with schizophrenia. *Schizophr Res* 36(1-3):272, 1999
- Bustillo J, Lauriello J, Horan W, et al: The psychosocial treatment of schizophrenia: an update. *Am J Psychiatry* 158(2):163-175, 2001 11156795
- Byerly M, Goodman W, Acholonu W, et al: Obsessive compulsive symptoms in schizophrenia: frequency and clinical features. *Schizophr Res* 76(2-3):309-316, 2005 15949663
- Cannon TD: On the nature and mechanisms of obstetric influences in schizophrenia: a review and synthesis of epidemiologic studies. *Int Rev Psychiatry* 9(4):387-398, 1997
- Canuso CM, Hanau M, Jhamb KK, et al: Olanzapine use in women with antipsychotic-induced hyperprolactinemia. *Am J Psychiatry* 155(10):1458, 1998 9766782
- Canuso CM, Goldstein JM, Wojcik J, et al: Antipsychotic medication, prolactin elevation, and ovarian function in women with schizophrenia and schizoaffective disorder. *Psychiatry Res* 111(1):11-20, 2002 12140115
- Caroff SN, Mann SC: Neuroleptic malignant syndrome. *Med Clin North Am* 77(1):185-202, 1993 8093494
- Carpenter WT Jr: New views on the course and treatment of schizophrenia. *J Psychiatr Res* 32(3-4):191-195, 1998 9793872
- Carpenter WT Jr, Heinrichs DW, Wagman AM: Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 145(5):578-583, 1988 3358462
- Casey DE: Rabbit syndrome, in *Movement Disorders in Neurology and Neuropsychiatry*. Edited by Joseph AB, Young RR. Malden, MA, Blackwell Science, 1999, pp 119-122
- Cassano GB, Pini S, Sauttoni M, et al: Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. *J Clin Psychiatry* 59(2): 60-68, 1998 9501887
- Cechnicki A, Cichocki Ł, Kalisz A, et al: Duration of untreated psychosis (DUP) and the course of schizophrenia in a 20-year follow-up study. *Psychiatry Res* 219(3): 420-425, 2014 24999174
- Chadwick PD, Lowe CF, Horne PJ, Higson PJ: Modifying delusions: the role of empirical testing: innovations in cognitive-behavioral approaches to schizophrenia. *Behav Ther* 25(1):35-49, 1994
- Chang HH, Berman I: Treatment issues for patients with schizophrenia who have obsessive-compulsive symptoms. *Psychiatric Annals* 29(9):529-532, 1999
- Citrome L: Lurasidone for schizophrenia: a brief review of a new second-generation antipsychotic. *Clin Schizophr Relat Psychoses* 4(4):251-257, 2011a 21177242
- Citrome L: Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. *Int J Clin Pract* 65(2):189-210, 2011b 21129135
- Coldwell CM, Bender WS: The effectiveness of assertive community treatment for homeless populations with severe mental illness: a meta-analysis. *Am J Psychiatry* 164(3):393-399, 2007 17329462

- Combs DR, Adams SD, Penn DL, et al: Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: preliminary findings. *Schizophr Res* 91(1-3):112-116, 2007 17293083
- Correll CU, Leucht S, Kane JM: Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 161(3):414-425, 2004 14992963
- Correll CU, Rummel-Kluge C, Corves C, et al: Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophr Bull* 35(2):443-457, 2009 18417466
- Costa AM, de Lima MS, Faria M, et al: A naturalistic, 9-month follow-up, comparing olanzapine and conventional antipsychotics on sexual function and hormonal profile for males with schizophrenia. *J Psychopharmacol* 21(2):165-170, 2007 17329296
- Covey LS, Hughes DC, Glassman AH, et al: Ever-smoking, quitting, and psychiatric disorders: evidence from the Durham, North Carolina, Epidemiologic Catchment Area. *Tob Control* 3(3):222-227, 1994
- Crow TJ: The two-syndrome concept: origins and current status. *Schizophr Bull* 11(3): 471-486, 1985 2863873
- Crow TJ, MacMillan JF, Johnson AL, et al: A randomised controlled trial of prophylactic neuroleptic treatment. *Br J Psychiatry* 148:120-127, 1986 2870753
- Crumlish N, Whitty P, Kamali M, et al: Early insight predicts depression and attempted suicide after 4 years in first-episode schizophrenia and schizophreniform disorder. *Acta Psychiatr Scand* 112(6):449-455, 2005 16279874
- Curtis J, Newall H, Myles N, et al: Considering metformin in cardiometabolic protection in psychosis. *Acta Psychiatr Scand* 126(4):302-303, 2012 22804349
- David AS, Malmberg A, Brandt L, et al: IQ and risk for schizophrenia: a population-based cohort study. *Psychol Med* 27(6):1311-1323, 1997 9403903
- DeLisi LE: Defining the course of brain structural change and plasticity in schizophrenia. *Psychiatry Res* 92(1):1-9, 1999 10688156
- DeLisi LE, Sakuma M, Tew W, et al: Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res* 74(3):129-140, 1997 9255858
- Desai HD, Seabolt J, Jann MW: Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs* 15(6):469-494, 2001 11524025
- Désaméricq G, Schurhoff F, Meary A, et al: Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. *Eur J Clin Pharmacol* 70(2):127-134, 2014 24145817
- Dickerson F, Boronow JJ, Ringel N, et al: Neurocognitive deficits and social functioning in outpatients with schizophrenia. *Schizophr Res* 21(2):75-83, 1996 8873775
- Dickson RA, Glazer WM: Neuroleptic-induced hyperprolactinemia. *Schizophr Res* 35 (suppl):S75-S86, 1999 10190228

- Dixon L, Haas G, Weiden P, et al: Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self-reports. *Schizophr Bull* 16(1):69-79, 1990 2185536
- Dixon L, Weiden P, Delahanty J, et al: Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull* 26(4):903-912, 2000 11087022
- Docherty JP, Van Kammen DP, Siris SG, et al: Stages of onset of schizophrenic psychosis. *Am J Psychiatry* 135(4):420-426, 1978 637135
- Downing AM, Kinon BJ, Millen BA, et al: A double-blind, placebo-controlled comparator study of LY2140023 monohydrate in patients with schizophrenia. *BMC Psychiatry* 14:351, 2014 25539791
- Drake RE, Mueser KT: Alcohol-use disorder and severe mental illness. *Alcohol Health and Research World* 20(2):87-93, 1996
- Drake RE, Mueser KT: Substance abuse comorbidity, in *Comprehensive Care of Schizophrenia*. Edited by Lieberman JA, Murray RM. London, Martin Dunitz, 2001, pp 243-254
- Drake RE, Gates C, Whitaker A, et al: Suicide among schizophrenics: a review. *Compr Psychiatry* 26(1):90-100, 1985 3881217
- Drake RE, Gates C, Cotton PG: Suicide among schizophrenics: a comparison of attempters and completed suicides. *Br J Psychiatry* 149:784-787, 1986 3790880
- Drake RE, Xie H, McHugo GJ, et al: The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophr Bull* 26(2):441-449, 2000 10885642
- Drake RE, Essock SM, Shaner A, et al: Implementing dual diagnosis services for clients with severe mental illness. *Psychiatr Serv* 52(4):469-476, 2001 11274491
- D'Souza DC, Abi-Saab WM, Madonick S, et al: Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 57(6):594-608, 2005 15780846
- Eckman TA, Wirshing WC, Marder SR, et al: Technique for training schizophrenic patients in illness self-management: a controlled trial. *Am J Psychiatry* 149(11): 1549-1555, 1992 1384364
- Eisen JL, Beer DA, Pato MT, et al: Obsessive-compulsive disorder in patients with schizophrenia or schizoaffective disorder. *Am J Psychiatry* 154(2):271-273, 1997 9016282
- Ellinger LK, Ipema HJ, Stachnik JM: Efficacy of metformin and topiramate in prevention and treatment of second-generation antipsychotic-induced weight gain. *Ann Pharmacother* 44(4):668-679, 2010 20233913
- Elvevåg B, Goldberg TE: Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol* 14(1):1-21, 2000 11253953
- Emsley RA, Raniwalla J, Bailey PJ, Jones AM; PRIZE Study Group: A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. *Int Clin Psychopharmacol* 15(3):121-131, 2000 10870870



- Essock SM, Covell NH, Davis SM, et al: Effectiveness of switching antipsychotic medications. *Am J Psychiatry* 163(12):2090-2095, 2006 17151159
- Essock SM, Schooler NR, Stroup TS, et al; Schizophrenia Trials Network: Effectiveness of switching from antipsychotic polypharmacy to monotherapy. *Am J Psychiatry* 168(7):702-708, 2011 21536693
- Evins AE, Cather C, Deckersbach T, et al: A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *J Clin Psychopharmacol* 25(3):218-225, 2005 15876899
- Evins AE, Cather C, Pratt SA, et al: Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA* 311(2):145-154, 2014 24399553
- Falloon IR, Boyd JL, McGill CW, et al: Family management in the prevention of exacerbations of schizophrenia: a controlled study. *N Engl J Med* 306(24):1437-1440, 1982 6123079
- Faraone SV, Chen WJ, Goldstein JM, et al: Gender differences in age at onset of schizophrenia. *Br J Psychiatry* 164(5):625-629, 1994 7921712
- Fenton WS: Comorbid conditions in schizophrenia. *Current Opinion in Psychiatry* 14(1):17-23, 2001
- Fenton WS, McGlashan TH: The prognostic significance of obsessive-compulsive symptoms in schizophrenia. *Am J Psychiatry* 143(4):437-441, 1986 3953886
- Fenton WS, McGlashan TH, Victor BJ, et al: Symptoms, subtype, and suicidality in patients with schizophrenia spectrum disorders. *Am J Psychiatry* 154(2):199-204, 1997 9016268
- Fenton WS, Stover EL, Insel TR: Breaking the log-jam in treatment development for cognition in schizophrenia: NIMH perspective. *Psychopharmacology (Berl)* 169(3-4):365-366, 2003 12955292
- Ferron JC, Alterman AI, McHugo GJ, et al: A review of research on smoking cessation interventions for adults with schizophrenia spectrum disorders. *Mental Health and Substance Use* 2(1):64-79, 2009
- Fisher M, Holland C, Merzenich MM, et al: Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *Am J Psychiatry* 166(7):805-811, 2009 19448187
- Freedman B, Chapman LJ: Early subjective experience in schizophrenic episodes. *J Abnorm Psychol* 82(1):46-54, 1973 4730655
- Fu DJ, Bossie CA, Kern Sliwa J, et al: Paliperidone palmitate versus risperidone long-acting injection in markedly to severely ill schizophrenia subjects: onset of efficacy with recommended initiation regimens. *Clin Schizophr Relat Psychoses* 8(2):101-109, 109A, 2014a 23446197
- Fu DJ, Bossie CA, Sliwa JK, et al: Paliperidone palmitate versus oral risperidone and risperidone long-acting injection in patients with recently diagnosed schizophrenia: a tolerability and efficacy comparison. *Int Clin Psychopharmacol* 29(1):45-55, 2014b 24113628
- Geddes JR, Lawrie SM: Obstetric complications and schizophrenia: a meta-analysis. *Br J Psychiatry* 167(6):786-793, 1995 8829748
- George TP, Ziedonis DM, Feingold A, et al: Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* 157(11):1835-1842, 2000 11058482

- George TP, Vessicchio JC, Termine A, et al: A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry* 52(1):53-61, 2002 12079730
- Ghadirian AM, Chouinard G, Annable L: Sexual dysfunction and plasma prolactin levels in neuroleptic-treated schizophrenic outpatients. *J Nerv Ment Dis* 170(8):463-467, 1982 6124580
- Gianfrancesco FD, Grogg AL, Mahmoud RA, et al: Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry* 63(10):920-930, 2002 12416602
- Gitlin M, Nuechterlein K, Subotnik KL, et al: Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry* 158(11):1835-1842, 2001 11691689
- Glazer WM: Expected incidence of tardive dyskinesia associated with atypical antipsychotics. *J Clin Psychiatry* 61 (suppl 4): 21-26, 2000a 10739327
- Glazer WM: Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. *J Clin Psychiatry* 61 (suppl 3):16-21, 2000b 10724129
- Glazer WM: Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. *J Clin Psychiatry* 61 (suppl 4):15-20, 2000c 10739326
- Glynn SM, Marder SR, Liberman RP, et al: Supplementing clinic-based skills training with manual-based community support sessions: effects on social adjustment of patients with schizophrenia. *Am J Psychiatry* 159(5):829-837, 2002 11986138
- Goff DC, Sullivan LM, McEvoy JP, et al: A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res* 80(1):45-53, 2005 16198088
- Goldberg TE, Hyde TM, Kleinman JE, et al: Course of schizophrenia: neuropsychological evidence for a static encephalopathy. *Schizophr Bull* 19(4):797-804, 1993 8303228
- Goldstein G, Haas GL, Pakrashi M, et al: The cycle of schizoaffective disorder, cognitive ability, alcoholism, and suicidality. *Suicide Life Threat Behav* 36(1):35-43, 2006 16676623
- Goldstein MJ, Rodnick EH, Evans JR, et al: Drug and family therapy in the aftercare of acute schizophrenics. *Arch Gen Psychiatry* 35(10):1169-1177, 1978 211983
- Gottlieb JD, Romeo KH, Penn DL, et al: Web-based cognitive-behavioral therapy for auditory hallucinations in persons with psychosis: a pilot study. *Schizophr Res* 145(1-3):82-87, 2013 23410709
- Granholm E, McQuaid JR, McClure FS, et al: A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. *Am J Psychiatry* 162(3):520-529, 2005 15741469
- Grech A, Van Os J, Murray RM: Influence of cannabis on the outcome of psychosis. *Schizophr Res* 36(1-3):41, 1999
- Green AI, Burgess ES, Dawson R, et al: Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. *Schizophr Res* 60(1):81-85, 2003 12505141

- Green AI, Drake RE, Brunette MF, et al: Schizophrenia and co-occurring substance use disorder. *Am J Psychiatry* 164(3):402-408, 2007 17329463
- Green AI, Noordsy DL, Brunette MF, et al: Substance abuse and schizophrenia: pharmacotherapeutic intervention. *J Subst Abuse Treat* 34(1):61-71, 2008 17574793
- Green MF: What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 153(3): 321-330, 1996 8610818
- Green MF: Recent studies on the neurocognitive effects of second-generation antipsychotic medications. *Current Opinion in Psychiatry* 15(1):25-29, 2002
- Green MF, Kern RS, Braff DL, et al: Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* 26(1):119-136, 2000 10755673
- Häfner H, Riecher-Rössler A, Maurer K, et al: First onset and early symptomatology of schizophrenia. A chapter of epidemiological and neurobiological research into age and sex differences. *Eur Arch Psychiatry Clin Neurosci* 242(2-3):109-118, 1992 1486099
- Häfner H, Maurer K, Löffler W, et al: The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry* 162:80-86, 1993 8425144
- Häfner H, Maurer K, Löffler W, et al: The epidemiology of early schizophrenia: influence of age and gender on onset and early course. *Br J Psychiatry Suppl* (23):29-38, 1994 8037899
- Hagen K, Solem S, Hansen B: Cognitive behavioural therapy for obsessive-compulsive disorder with comorbid schizophrenia: a case report with repetitive measurements. *Behav Cogn Psychother* 42(3):374-378, 2014 23899371
- Hambrecht M, Maurer K, Häfner H, et al: Transnational stability of gender differences in schizophrenia? An analysis based on the WHO study on determinants of outcome of severe mental disorders. *Eur Arch Psychiatry Clin Neurosci* 242(1):6-12, 1992 1390958
- Hamoui N, Kingsbury S, Anthone GJ, et al: Surgical treatment of morbid obesity in schizophrenic patients. *Obes Surg* 14(3): 349-352, 2004 15072656
- Harkavy-Friedman JM, Nelson E: Management of the suicidal patient with schizophrenia.. *Psychiatr Clin North Am* 20(3): 625-640, 1997 9323317
- Harkavy-Friedman JM, Nelson EA, Venarde DF, et al: Suicidal behavior in schizophrenia and schizoaffective disorder: examining the role of depression. *Suicide Life Threat Behav* 34(1):66-76, 2004 15106889
- Harris MG, Henry LP, Harrigan SM, et al: The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. *Schizophr Res* 79(1):85-93, 2005 16005612
- Harvey PD, Keefe RE: Cognition and the new antipsychotics. *Journal of Advances in Schizophrenia and Brain Research* 1:2-8, 1998
- Hasan A, Falkai P, Wobrock T, et al; WFSBP Task Force on Treatment Guidelines for Schizophrenia: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 3: update 2015 management of special circumstances: depression, suicidality, substance use disorders and pregnancy and lactation. *World J Biol Psychiatry* 16(3):142-170, 2015 25822804

- Hasan S, Buckley P: Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. *Am J Psychiatry* 155(8):1113-1116, 1998 9699705
- Hawton K, Sutton L, Haw C, et al: Schizophrenia and suicide: systematic review of risk factors. *Br J Psychiatry* 187:9-20, 2005 15994566
- Heilä H, Isometsä ET, Henriksson MM, et al: Suicide and schizophrenia: a nationwide psychological autopsy study on age- and sex-specific clinical characteristics of 92 suicide victims with schizophrenia. *Am J Psychiatry* 154(9):1235-1242, 1997 9286182
- Heilä H, Isometsä ET, Henriksson MM, et al: Suicide victims with schizophrenia in different treatment phases and adequacy of antipsychotic medication. *J Clin Psychiatry* 60(3):200-208, 1999 10192600
- Henderson DC, Cagliero E, Gray C, et al: Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 157(6):975-981, 2000 10831479
- Ho BC, Andreasen NC, Flaum M, et al: Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *Am J Psychiatry* 157(5):808-815, 2000 10784476
- Hodel B, Brenner HD: Cognitive therapy with schizophrenic patients: conceptual basis, present state, future directions. *Acta Psychiatr Scand Suppl* 384:108-115, 1994 7879632
- Hogarty GE, Anderson CM, Reiss DJ, et al: Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia, I: one-year effects of a controlled study on relapse and expressed emotion. *Arch Gen Psychiatry* 43(7):633-642, 1986 2872870
- Hogarty GE, McEvoy JP, Ulrich RF, et al: Pharmacotherapy of impaired affect in recovering schizophrenic patients. *Arch Gen Psychiatry* 52(1):29, 1995 7811160
- Hogarty GE, Greenwald D, Ulrich RF, et al: Three-year trials of personal therapy among schizophrenic patients living with or independent of family, II: effects on adjustment of patients. *Am J Psychiatry* 154(11):1514-1524, 1997a 9356558
- Hogarty GE, Kornblith SJ, Greenwald D, et al: Three-year trials of personal therapy among schizophrenic patients living with or independent of family, I: description of study and effects on relapse rates. *Am J Psychiatry* 154(11):1504-1513, 1997b 9356557
- Hogarty GE, Greenwald DP, Eack SM: Durability and mechanism of effects of cognitive enhancement therapy. *Psychiatr Serv* 57(12):1751-1757, 2006 17158490
- Horiguchi M, Huang M, Meltzer HY: The role of 5-hydroxytryptamine 7 receptors in the phencyclidine-induced novel object recognition deficit in rats. *J Pharmacol Exp Ther* 338(2):605-614, 2011 21558435
- Horisawa T, Ishibashi T, Nishikawa H, et al: The effects of selective antagonists of serotonin 5-HT<sub>7</sub> and 5-HT<sub>1A</sub> receptors on MK-801-induced impairment of learning and memory in the passive avoidance and Morris water maze tests in rats: mechanistic implications for the beneficial effects of the novel atypical antipsychotic lurasidone. *Behav Brain Res* 220(1): 83-90, 2011 21277905

- Huber G, Gross G, Schüttler R, et al: Longitudinal studies of schizophrenic patients. *Schizophr Bull* 6(4):592-605, 1980 7444391
- Hummer M, Malik P, Gasser RW, et al: Osteoporosis in patients with schizophrenia. *Am J Psychiatry* 162(1):162-167, 2005 15625215
- Hunt IM, Kapur N, Windfuhr K, et al; National Confidential Inquiry into Suicide and Homicide by People with Mental Illness: Suicide in schizophrenia: findings from a national clinical survey. *J Psychiatr Pract* 12(3):139-147, 2006 16732132
- Hurlburt MS, Hough RL, Wood PA: Effects of substance abuse on housing stability of homeless mentally ill persons in supported housing. *Psychiatr Serv* 47(7):731-736, 1996a 8807687
- Hurlburt MS, Wood PA, Hough RL: Providing independent housing for the homeless mentally ill: a novel approach to evaluating long-term longitudinal housing patterns. *J Community Psychol* 24(3):291-310, 1996b
- Hwang MY, Morgan JE, Losconzcy MF: Clinical and neuropsychological profiles of obsessive-compulsive schizophrenia: a pilot study. *J Neuropsychiatry Clin Neurosci* 12(1):91-94, 2000 10678519
- Hyman SE, Fenton WS: Medicine. What are the right targets for psychopharmacology? *Science* 299(5605):350-351, 2003 12532001
- Insel TR: Rethinking schizophrenia. *Nature* 468(7321):187-193, 2010 21068826
- Iqbal Z, Birchwood M, Chadwick P, et al: Cognitive approach to depression and suicidal thinking in psychosis. 2. Testing the validity of a social ranking model. *Br J Psychiatry* 177:522-528, 2000 11102327
- Jablensky A, Sartorius N, Ernberg G, et al: Schizophrenia: manifestations, incidence and course in different cultures: a World Health Organization ten-country study. *Psychol Med Monogr Suppl* 20:1-97, 1992 1565705
- Jeste DV, Lacro JP, Bailey A: Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. Presented at the 21st Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, Scotland, July 12-16, 1998
- Jin H, Meyer JM, Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res* 71(2-3):195-212, 2004 15474892
- Joffe G, Takala P, Tchoukhine E, et al: Orlistat in clozapine- or olanzapine-treated patients with overweight or obesity: a 16-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 69(5):706-711, 2008 18426261
- Johnson DA: Antipsychotic medication: clinical guidelines for maintenance therapy. *J Clin Psychiatry* 46(5 pt 2):6-15, 1985 2859281
- Jones PB, Barnes TR, Davies L, et al: Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 63(10):1079-1087, 2006 17015810
- Kampman O, Lehtinen K: Compliance in psychoses. *Acta Psychiatr Scand* 100(3):167-175, 1999 10493082
- Kane JM: Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. *J Clin Psychiatry* 65 (suppl 9):16-20, 2004

15189107

- Kane JM, Rifkin A, Quitkin F, et al: Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiatry* 39(1):70-73, 1982 6275811
- Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45(9): 789-796, 1988 3046553
- Kane JM, Woerner MG, Pollack S, et al: Does clozapine cause tardive dyskinesia? *J Clin Psychiatry* 54(9):327-330, 1993 8104929
- Kane JM, Handan G, Malhotra AK: Clozapine, in *Current Issues in the Psychopharmacology of Schizophrenia*. Edited by Breier A, Tran PV, Herrea JM, et al. Philadelphia, PA, Lippincott Williams & Wilkins, 2001, pp 209-223
- Kane JM, Khanna S, Rajadhyaksha S, et al: Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. *Int Clin Psychopharmacol* 21(1):21-28, 2006 16317313
- Kane JM, Meltzer HY, Carson WH Jr, et al; Aripiprazole Study Group: Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. *J Clin Psychiatry* 68(2):213-223, 2007 17335319
- Kane JM, Lauriello J, Laska E, et al: Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol* 28 (2 suppl 1):S29-S35, 2008 18334910
- Kane JM, Fleischhacker WW, Hansen L, et al: Akathisia: an updated review focusing on second-generation antipsychotics. *J Clin Psychiatry* 70(5):627-643, 2009 19389331
- Kane JM, Kishimoto T, Correll CU: Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. *J Clin Epidemiol* 66 (8 suppl):S37-S41, 2013 23849151
- Kane JM, Robinson DG, Schooler NR, et al: Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE Early Treatment Program. *Am J Psychiatry* 173(4):362-372, 2016 26481174
- Kaplan KJ, Harrow M: Positive and negative symptoms as risk factors for later suicidal activity in schizophrenics versus depressives. *Suicide Life Threat Behav* 26(2):105-121, 1996 8840415
- Kapur S, Remington G: Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry* 153(4):466-476, 1996 8599393
- Kapur S, Remington G: Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry* 50(11): 873-883, 2001 11743942
- Kasai K, Shenton ME, Salisbury DF, et al: Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 60(8):766-775, 2003a 12912760
- Kasai K, Shenton ME, Salisbury DF, et al: Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode

- schizophrenia. *Am J Psychiatry* 160(1):156-164, 2003b 12505815
- Keefe RS: The longitudinal course of cognitive impairment in schizophrenia: an examination of data from premorbid through posttreatment phases of illness. *J Clin Psychiatry* 75 (suppl 2):8-13, 2014 24919165
- Keefe RS, Bilder RM, Davis SM, et al; CATIE Investigators; Neurocognitive Working Group: Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry* 64(6):633-647, 2007 17548746
- Kehler J, Nielsen J: PDE10A inhibitors: novel therapeutic drugs for schizophrenia. *Curr Pharm Des* 17(2):137-150, 2011 21355834
- Kelly DL, Shim JC, Feldman SM, et al: Lifetime psychiatric symptoms in persons with schizophrenia who died by suicide compared to other means of death. *J Psychiatr Res* 38(5):531-536, 2004 15380404
- Kessing LV, Thomsen AF, Mogensen UB, et al: Treatment with antipsychotics and the risk of diabetes in clinical practice. *Br J Psychiatry* 197(4):266-271, 2010 20884948
- Kim CH, Jayathilake K, Meltzer HY: Hopelessness, neurocognitive function, and insight in schizophrenia: relationship to suicidal behavior. *Schizophr Res* 60(1): 71-80, 2003 12505140
- Kingdon D, Rathod S, Weiden P, et al: Cognitive therapy for schizophrenia. *J Psychiatr Pract* 14(1):55-57, 2008 18212603
- Kingsbury SJ, Fayek M, Trufasiu D, et al: The apparent effects of ziprasidone on plasma lipids and glucose. *J Clin Psychiatry* 62(5):347-349, 2001 11411816
- Kinon BJ, Ahl J, Liu-Seifert H, et al: Improvement in hyperprolactinemia and reproductive comorbidities in patients with schizophrenia switched from conventional antipsychotics or risperidone to olanzapine. *Psychoneuroendocrinology* 31(5):577-588, 2006 16488084
- Kinon BJ, Zhang L, Millen BA, et al: A multicenter, inpatient, phase 2, double-blind, placebo-controlled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia. *J Clin Psychopharmacol* 31(3):349-355, 2011 21508856
- Kinoshita Y, Furukawa TA, Kinoshita K, et al: Supported employment for adults with severe mental illness. *Cochrane Database Syst Rev* 9:CD008297, 2013 24030739
- Kirli S, Caliskan M: A comparative study of sertraline versus imipramine in postpsychotic depressive disorder of schizophrenia. *Schizophr Res* 33(1-2):103-111, 1998 9783350
- Kishimoto T, Robenzadeh A, Leucht C, et al: Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull* 40(1):192-213, 2014 23256986
- Kleinberg DL, Davis JM, de Coster R, et al: Prolactin levels and adverse events in patients treated with risperidone. *J Clin Psychopharmacol* 19(1):57-61, 1999 9934944
- Kofoed L, Kania J, Walsh T, et al: Outpatient treatment of patients with substance abuse and coexisting psychiatric disorders. *Am J Psychiatry* 143(7):867-872, 1986 3087222

- Kopelowicz A, Liberman RP, Zarate R: Recent advances in social skills training for schizophrenia. *Schizophr Bull* 32 (suppl 1):S12-S23, 2006 16885207
- Koppel BS: Neuroleptic malignant syndrome, in *Principles and Practices of Emergency Medicine*, 4th Edition. Edited by Schwartz GR, Hanke BK, Mayer TA. Baltimore, MD, Williams & Wilkins, 1998, pp 1155-1605
- Koreen AR, Siris SG, Chakos M, et al: Depression in first-episode schizophrenia. *Am J Psychiatry* 150(11):1643-1648, 1993 8105706
- Kraepelin E: *Dementia Praecox and Paraphrenia* (1919). New York, Robert E Krieger, 1971
- Kuo CJ, Tsai SY, Lo CH, et al: Risk factors for completed suicide in schizophrenia. *J Clin Psychiatry* 66(5):579-585, 2005 15889943
- Lauriello J, Bustillo J, Keith SJ: A critical review of research on psychosocial treatment of schizophrenia. *Biol Psychiatry* 46(10):1409-1417, 1999 10578455
- Lee ML, Dickson RA, Campbell M, et al: Clozapine and substance abuse in patients with schizophrenia. *Can J Psychiatry* 43(8):855-856, 1998 9806095
- Lehmann HE, Hanrahan GE: Chlorpromazine; new inhibiting agent for psychomotor excitement and manic states. *AMA Arch Neurol Psychiatry* 71(2):227-237, 1954 13123588
- Leslie DL, Rosenheck RA: Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. *Am J Psychiatry* 161(9):1709-1711, 2004 15337666
- Leucht S, Wahlbeck K, Hamann J, et al: New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 361(9369):1581-1589, 2003 12747876
- Leucht S, Cipriani A, Spineli L, et al: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382(9896):951-962, 2013 23810019
- Levinson DF, Umapathy C, Musthaq M: Treatment of schizoaffective disorder and schizophrenia with mood symptoms. *Am J Psychiatry* 156(8):1138-1148, 1999 10450252
- Lewandowski KE, Cohen BM, Ongur D: Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychol Med* 41(2):225-241, 2011 20836900
- Lewis DA, Gonzalez-Burgos G: Pathophysiologically based treatment interventions in schizophrenia. *Nat Med* 12(9):1016-1022, 2006 16960576
- Lewis DA, Levitt P: Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci* 25:409-432, 2002 12052915
- Lewis DA, Lieberman JA: Catching up on schizophrenia: natural history and neurobiology. *Neuron* 28(2):325-334, 2000 11144342
- Lewis SW, Davies L, Jones PB, et al: Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technol Assess* 10(17):iii-iv, ix-xi, 1-165, 2006 16707074
- Liberman RP, Wallace CJ, Blackwell G, et al: Skills training versus psychosocial occupational therapy for persons with persistent schizophrenia. *Am J*



- Psychiatry 155(8):1087-1091, 1998 9699698
- Liddle PF, Barnes TR, Morris D, et al: Three syndromes in chronic schizophrenia. Br J Psychiatry Suppl (7):119-122, 1989 2695133
- Lieberman JA: Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biol Psychiatry 46(6):729-739, 1999 10494440
- Lieberman JA: Neurobiology and the natural history of schizophrenia. J Clin Psychiatry 67(10):e14, 2006 17107237
- Lieberman JA, Saltz BL, Johns CA, et al: The effects of clozapine on tardive dyskinesia. Br J Psychiatry 158:503-510, 1991 1675900
- Lieberman J, Jody D, Geisler S, et al: Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry 50(5):369-376, 1993 8098203
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353(12):1209-1223, 2005 16172203
- Lindenmayer JP, McGurk SR, Mueser KT, et al: A randomized controlled trial of cognitive remediation among inpatients with persistent mental illness. Psychiatr Serv 59(3):241-247, 2008 18308903
- Lindenmayer JP, McGurk SR, Khan A, et al: Improving social cognition in schizophrenia: a pilot intervention combining computerized social cognition training with cognitive remediation. Schizophr Bull 39(3):507-517, 2013 23125396
- Littrell KH, Petty RG, Hilligoss NM, et al: Olanzapine treatment for patients with schizophrenia and substance abuse. J Subst Abuse Treat 21(4):217-221, 2001 11777671
- Loebel AD, Lieberman JA, Alvir JM, et al: Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 149(9):1183-1188, 1992 1503130
- Malaspina D, Owen MJ, Heckers S, et al: Schizoaffective disorder in the DSM-5. Schizophr Res 150(1):21-25, 2013 23707642
- Malchow B, Keller K, Hasan A, et al: Effects of endurance training combined with cognitive remediation on everyday functioning, symptoms, and cognition in multiepisode schizophrenia patients. Schizophr Bull 41(4):847-858, 2015 25782770
- Marder SR: Integrating pharmacological and psychosocial treatments for schizophrenia. Acta Psychiatr Scand Suppl (407):87-90, 2000 11261649
- Marder SR: Drug initiatives to improve cognitive function. J Clin Psychiatry 67 (suppl 9):31-35, discussion 36-42, 2006 16965187
- Marder SR, Wirshing WC, Mintz J, et al: Two-year outcome of social skills training and group psychotherapy for outpatients with schizophrenia. Am J Psychiatry 153(12):1585-1592, 1996 8942455
- Marder SR, Davis JM, Chouinard G: The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 58(12): 538-546, 1997 9448657
- Marder SR, Essock SM, Miller AL, et al: The Mount Sinai conference on the pharmacotherapy of schizophrenia. Schizophr Bull 28(1):5-16, 2002

12047022

- Marder SR, Essock SM, Miller AL, et al: Physical health monitoring of patients with schizophrenia. *Am J Psychiatry* 161(8): 1334-1349, 2004 15285957
- Margolese HC, Chouinard G, Kolivakis TT, et al: Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 2: Incidence and management strategies in patients with schizophrenia. *Can J Psychiatry* 50(11):703-714, 2005 16363464
- Marshall M, Lewis S, Lockwood A, et al: Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 62(9):975-983, 2005 16143729
- McClave AK, McKnight-Eily LR, Davis SP, et al: Smoking characteristics of adults with selected lifetime mental illnesses: results from the 2007 National Health Interview Survey. *Am J Public Health* 100(12):2464-2472, 2010 20966369
- McEvoy JP, Meyer JM, Goff DC, et al: Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res* 80(1):19-32, 2005 16137860
- McEvoy JP, Lieberman JA, Stroup TS, et al; CATIE Investigators: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 163(4):600-610, 2006 16585434
- McFarlane WR, Levin B, Travis L, et al: Clinical and functional outcomes after 2 years in the early detection and intervention for the prevention of psychosis multisite effectiveness trial. *Schizophr Bull* 41(1):30-43, 2015 25065017
- McGlashan TH: The profiles of clinical deterioration in schizophrenia. *J Psychiatr Res* 32(3-4):133-141, 1998 9793866
- McGlashan TH, Carpenter WT Jr: Postpsychotic depression in schizophrenia. *Arch Gen Psychiatry* 33(2):231-239, 1976 766720
- McGlashan TH, Zipursky RB, Perkins D, et al: Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry* 163(5):790-799, 2006 16648318
- McGorry PD, Yung AR, Phillips LJ, et al: Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry* 59(10):921-928, 2002 12365879
- McGuire AB, Kukla M, Green A, et al: Illness management and recovery: a review of the literature. *Psychiatr Serv* 65(2):171-179, 2014 24178191
- McGurk SR, Twamley EW, Sitzer DI, et al: A meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiatry* 164(12): 1791-1802, 2007 18056233
- Meltzer HY: Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. *Psychopharmacology (Berl)* 99 (suppl):S18-S27, 1989 2682729
- Meltzer HY, Alphs L, Green AI, et al; International Suicide Prevention Trial Study Group: Clozapine treatment for suicidality in schizophrenia:

- International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 60(1):82-91, 2003 12511175
- Meyer JM, Koro CE: The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res* 70(1):1-17, 2004 15246458
- Minkoff K: An integrated treatment model for dual diagnosis of psychosis and addiction. *Hosp Community Psychiatry* 40(10):1031-1036, 1989 2807203
- Mishara AL, Goldberg TE: A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biol Psychiatry* 55(10):1013-1022, 2004 15121486
- Mizuno Y, Suzuki T, Nakagawa A, et al: Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull* 40(6):1385-1403, 2014 24636967
- Montross LP, Zisook S, Kasckow J: Suicide among patients with schizophrenia: a consideration of risk and protective factors. *Ann Clin Psychiatry* 17(3):173-182, 2005 16433060
- Moorhead TW, Stanfield AC, McKechnie AG, et al: Longitudinal gray matter change in young people who are at enhanced risk of schizophrenia due to intellectual impairment. *Biol Psychiatry* 73(10):985-992, 2013 23332356
- Morrison AP, French P, Walford L, et al: Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. *Br J Psychiatry* 185:291-297, 2004 15458988
- Mueser KT, Bennett M, Kushner MG: Epidemiology of substance use disorders among persons with chronic mental illnesses, in *Double Jeopardy: Chronic Mental Illness and Substance Abuse*. Edited by Lehman AF, Dixon L. New York, Harwood Academic Publishers, 1995, pp 9-25
- Mueser KT, Bond GR, Drake RE, et al: Models of community care for severe mental illness: a review of research on case management. *Schizophr Bull* 24(1):37-74, 1998 9502546
- Mueser KT, Noordsy DL, Fox L, et al: Disulfiram treatment for alcoholism in severe mental illness. *Am J Addict* 12(3):242-252, 2003 12851020
- Mueser KT, Meyer PS, Penn DL, et al: The Illness Management and Recovery program: rationale, development, and preliminary findings. *Schizophr Bull* 32 (suppl 1):S32-S43, 2006 16899534
- Mueser KT, Deavers F, Penn DL, et al: Psychosocial treatments for schizophrenia. *Annu Rev Clin Psychol* 9:465-497, 2013 23330939
- Mueser KT, Penn DL, Addington J, et al: The NAVIGATE program for first-episode psychosis: rationale, overview, and description of psychosocial components. *Psychiatr Serv* 66(7):680-690, 2015 25772766
- Mukherjee S, Decina P, Bocola V, et al: Diabetes mellitus in schizophrenic patients. *Compr Psychiatry* 37(1):68-73, 1996 8770530
- Murray RM: Neurodevelopmental schizophrenia: the rediscovery of dementia praecox. *Br J Psychiatry Suppl* (25):6-12, 1994 7865195
- Negrete JC, Knapp WP, Douglas DE, et al: Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. *Psychol Med* 16(3):515-520, 1986 3489951

- Nelson HE, Pantelis C, Carruthers K, et al: Cognitive functioning and symptomatology in chronic schizophrenia. *Psychol Med* 20(2):357-365, 1990 2356261
- Newcomer JW, Weiden PJ, Buchanan RW: Switching antipsychotic medications to reduce adverse event burden in schizophrenia: establishing evidence-based practice. *J Clin Psychiatry* 74(11):1108-1120, 2013 24330898
- Nikiforuk A, Kos T, Fijał K, et al: Effects of the selective 5-HT<sub>7</sub> receptor antagonist SB-269970 and amisulpride on ketamine-induced schizophrenia-like deficits in rats. *PLoS One* 8(6):e66695, 2013 23776692
- Nino-Gomez J, Carlini S, Nemani K, et al: Safety and efficacy of varenicline in schizophrenia and schizoaffective disorder: preliminary data. Presented at Massachusetts General Hospital Clinical Research Day, Boston, MA, May 2010
- Noordsy DL, O'Keefe C, Mueser KT, Xie H: Six-month outcomes for patients who switched to olanzapine treatment. *Psychiatr Serv* 52(4):501-507, 2001 11274497
- Nordentoft M, Madsen T, Fedyszyn I: Suicidal behavior and mortality in first-episode psychosis. *J Nerv Ment Dis* 203(5):387-392, 2015 25919385
- O'Donoghue B, Schäfer MR, Becker J, et al: Metabolic changes in first-episode early onset schizophrenia with second-generation antipsychotics. *Early Interv Psychiatry* 8(3):276-280, 2014 23968390
- O'Keane V, Meaney AM: Antipsychotic drugs: a new risk factor for osteoporosis in young women with schizophrenia? *J Clin Psychopharmacol* 25(1):26-31, 2005 15643097
- Ongür D, Goff DC: Obsessive-compulsive symptoms in schizophrenia: associated clinical features, cognitive function and medication status. *Schizophr Res* 75(2-3):349-362, 2005 15885526
- Osher FC, Kofoed LL: Treatment of patients with psychiatric and psychoactive substance abuse disorders. *Hosp Community Psychiatry* 40(10):1025-1030, 1989 2807202
- Osser DN: Neuroleptic-induced pseudoparkinsonism, in *Movement Disorders in Neurology and Neuropsychiatry*. Edited by Joseph AB, Young RR. Malden, MA, Blackwell Science, 1999, pp 61-68
- Osser DN, Najarian DM, Dufresne RL: Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry* 60(11):767-770, 1999 10584766
- Pantelis C, Velakoulis D, McGorry PD, et al: Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 361(9354):281-288, 2003 12559861
- Patil ST, Zhang L, Martenyi F, et al: Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nat Med* 13(9):1102-1107, 2007 17767166
- Penn DL, Mueser KT: Research update on the psychosocial treatment of schizophrenia. *Am J Psychiatry* 153(5):607-617, 1996 8615405
- Penn DL, Addington J, Pinkham A: Social cognitive impairments, in *Textbook of Schizophrenia*. Edited by Lieberman JA, Stroup TS, Perkins DO. Washington, DC, American Psychiatric Publishing, 2006, pp 261-274

- Penttilä M, Jääskeläinen E, Hirvonen N, et al: Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 205(2):88-94, 2014 25252316
- Perälä J, Suvisaari J, Saarni SI, et al: Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 64(1):19-28, 2007 17199051
- Perkins DO, Gu H, Boteva K, Lieberman JA: Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 162(10):1785-1804, 2005 16199825
- Petrakis IL, O'Malley S, Rounsaville B, et al; VA Naltrexone Study Collaboration Group: Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. *Psychopharmacology (Berl)* 172(3):291-297, 2004 14634716
- Petrakis IL, Poling J, Levinson C, et al; VA New England VISN I MIRECC Study Group: Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. *Biol Psychiatry* 57(10):1128-1137, 2005 15866552
- Petrakis IL, Leslie D, Finney JW, et al: Atypical antipsychotic medication and substance use-related outcomes in the treatment of schizophrenia. *Am J Addict* 15(1):44-49, 2006 16449092
- Phillips SD, Burns BJ, Edgar ER, et al: Moving assertive community treatment into standard practice. *Psychiatr Serv* 52(6):771-779, 2001 11376224
- Pilling S, Bebbington P, Kuipers E, et al: Psychological treatments in schizophrenia, II: meta-analyses of randomized controlled trials of social skills training and cognitive remediation. *Psychol Med* 32(5):783-791, 2002 12171373
- Pilowsky LS, Kerwin RW, Murray RM: Schizophrenia: a neurodevelopmental perspective. *Neuropsychopharmacology* 9(1):83-91, 1993 8397727
- Pitschel-Walz G, Leucht S, Bäuml J, et al: The effect of family interventions on relapse and rehospitalization in schizophrenia—a meta-analysis. *Schizophr Bull* 27(1):73-92, 2001 11215551
- Pompili M, Lester D, Dominici G, et al: Indications for electroconvulsive treatment in schizophrenia: a systematic review. *Schizophr Res* 146(1-3):1-9, 2013 23499244
- Potkin SG, Alphs L, Hsu C, et al; InterSePT Study Group: Predicting suicidal risk in schizophrenic and schizoaffective patients in a prospective two-year trial. *Biol Psychiatry* 54(4):444-452, 2003 12915289
- Potkin SG, Cohen M, Panagides J: Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 68(10):1492-1500, 2007 17960962
- Potvin S, Stip E, Lipp O, et al: Quetiapine in patients with comorbid schizophrenia-spectrum and substance use disorders: an open-label trial. *Curr Med Res Opin* 22(7):1277-1285, 2006 16834826
- Poyurovsky M, Dorfman-Etrog P, Hermesh H, et al: Beneficial effect of olanzapine in schizophrenic patients with obsessive-compulsive symptoms. *Int Clin Psychopharmacol* 15(3):169-173, 2000 10870875

- Praharaj SK, Jana AK, Goyal N, et al: Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. *Br J Clin Pharmacol* 71(3):377-382, 2011 21284696
- Qin P, Nordentoft M: Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. *Arch Gen Psychiatry* 62(4):427-432, 2005 15809410
- Radomsky ED, Haas GL, Mann JJ, et al: Suicidal behavior in patients with schizophrenia and other psychotic disorders. *Am J Psychiatry* 156(10):1590-1595, 1999 10518171
- Rapp CA, Goscha RJ: The principles of effective case management of mental health services. *Psychiatr Rehabil J* 27(4):319-333, 2004 15222145
- Regier DA, Farmer ME, Rae DS, et al: Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 264(19):2511-2518, 1990 2232018
- Reichenberg A: The assessment of neuropsychological functioning in schizophrenia. *Dialogues Clin Neurosci* 12(3):383-392, 2010 20954432
- Remington G, Kapur S: Neuroleptic-induced extrapyramidal symptoms and the role of combined serotonin/dopamine antagonist, in *Schizophrenia '94: Exploring the Spectrum* (Journal of Clinical Psychiatry Monograph Series, Vol. 14, No. 1). Edited by Jones BD. Memphis, TN, Physicians Postgraduate Press, 1996
- Remington G, Kapur S, Zipursky R; American Psychiatric Association: APA Practice Guideline for schizophrenia: risperidone equivalents. *Am J Psychiatry* 155(9): 1301-1302, 1998 9734565
- Riecher-Rössler A, Häfner H, Stumbaum M, et al: Can estradiol modulate schizophrenic symptomatology? *Schizophr Bull* 20(1):203-214, 1994 8197416
- Robinson DG, Woerner MG, Alvir JM, et al: Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 156(4): 544-549, 1999 10200732
- Roche: Media Release: Roche provides update on the first two of six phase III studies of bitopertin in schizophrenia. Basel, F. Hoffmann-La Roche Ltd, January 21, 2014. Available at: <http://www.roche.com/media/store/releases/med-cor-2014-01-21.htm>. Accessed December 30, 2016.
- Rog DJ: The evidence on supported housing. *Psychiatr Rehabil J* 27(4):334-344, 2004 15222146
- Rolfe TJ, McGory P, Cooks J, et al: Cannabis use in first episode psychosis: incidence and short-term outcome. *Schizophr Res* 36(1-3):313, 1999
- Rosenberg SD, Goodman LA, Osher FC, et al: Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. *Am J Public Health* 91(1):31-37, 2001 11189820
- Rosenheck RA, Leslie DL, Sindelar J, et al; CATIE Study Investigators: Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. *Am J Psychiatry* 163(12):2080-2089, 2006 17151158

- Rosenheck RA, Krystal JH, Lew R, et al; CSP555 Research Group: Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* 364(9):842-851, 2011 21366475
- Rossau CD, Mortensen PB: Risk factors for suicide in patients with schizophrenia: nested case-control study. *Br J Psychiatry* 171:355-359, 1997 9373425
- Roth BL, Hanizavareh SM, Blum AE: Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders. *Psychopharmacology (Berl)* 174(1):17-24, 2004 15205874
- Rotondi AJ, Anderson CM, Haas GL, et al: Web-based psychoeducational intervention for persons with schizophrenia and their supporters: one-year outcomes. *Psychiatr Serv* 61(11):1099-1105, 2010 21041348
- Roy A: Risk factors for suicide in psychiatric patients. *Arch Gen Psychiatry* 39(9):1089-1095, 1982 7115014
- Rubio G, Martínez I, Ponce G, et al: Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. *Can J Psychiatry* 51(8):531-539, 2006 16933590
- Russell AJ, Munro JC, Jones PB, et al: Schizophrenia and the myth of intellectual decline. *Am J Psychiatry* 154(5):635-639, 1997 9137118
- Salisbury DF, Kuroki N, Kasai K, et al: Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Arch Gen Psychiatry* 64(5):521-529, 2007 17485604
- Sax KW, Strakowski SM, Keck PE Jr, et al: Relationships among negative, positive, and depressive symptoms in schizophrenia and psychotic depression. *Br J Psychiatry* 168(1):68-71, 1996 8770431
- Sayers SL, Campbell EC, Kondrich J, et al: Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. *J Nerv Ment Dis* 193(6):379-386, 2005 15920378
- Schoemaker J, Naber D, Vrijland P, et al: Long-term assessment of Asenapine vs. Olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry* 43(4):138-146, 2010 20205074
- Schooler NR: Relapse and rehospitalization: comparing oral and depot antipsychotics. *J Clin Psychiatry* 64 (suppl 16):14-17, 2003 14680414
- Schooler NR: Relapse prevention and recovery in the treatment of schizophrenia. *J Clin Psychiatry* 67 (suppl 5):19-23, 2006 16822093
- Schooler N, Rabinowitz J, Davidson M, et al; Early Psychosis Global Working Group: Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 162(5):947-953, 2005 15863797
- Seeman P: Atypical antipsychotics: mechanism of action. *Can J Psychiatry* 47(1):27-38, 2002 11873706
- Sekar A, Bialas AR, de Rivera H, et al: Schizophrenia risk from complex variation of complement component 4. Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* 530(7589): 177-183, 2016 26814963
- Sellwood W, Barrowclough C, Tarrier N, et al: Needs-based cognitive-behavioural family intervention for carers of patients suffering from

- schizophrenia: 12-month follow-up. *Acta Psychiatr Scand* 104(5):346-355, 2001 11722315
- Selzer JA, Lieberman JA: Schizophrenia and substance abuse. *Psychiatr Clin North Am* 16(2):401-412, 1993 8332568
- Sevy S, Kay SR, Opler LA, et al: Significance of cocaine history in schizophrenia. *J Nerv Ment Dis* 178(10):642-648, 1990 2230749
- Shekhar A, Potter WZ, Lightfoot J, et al: Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychopharmacol* 165(8):1033-1039, 2008 18593778
- Shirzadi AA, Ghaemi SN: Side effects of atypical antipsychotics: extrapyramidal symptoms and the metabolic syndrome. *Harv Rev Psychiatry* 14(3):152-164, 2006 16787887
- Simon AE, Cattapan-Ludewig K, Zmilacher S, et al: Cognitive functioning in the schizophrenia prodrome. *Schizophr Bull* 33(3):761-771, 2007 17412711
- Simpson GM: The treatment of tardive dyskinesia and tardive dystonia. *J Clin Psychiatry* 61 (suppl 4):39-44, 2000 10739330
- Siris SG: Depression in schizophrenia: perspective in the era of "atypical" antipsychotic agents. *Am J Psychiatry* 157(9): 1379-1389, 2000a 10964850
- Siris SG: Management of depression in schizophrenia. *Psychiatric Annals* 30(1):13-19, 2000b
- Siris SG, Morgan V, Fagerstrom R, et al: Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. *Arch Gen Psychiatry* 44(6):533-539, 1987 3555386
- Siris SG, Mason SE, Bermanzohn PC, et al: Adjunctive imipramine in substance-abusing dysphoric schizophrenic patients. *Psychopharmacol Bull* 29(1):127-133, 1993 8378506
- Smelson DA, Williams J, Kaune M, et al: Reduced cue-elicited cocaine craving and relapses following treatment with risperidone. Presented at the 153rd annual meeting of the American Psychiatric Association, Chicago, IL, May 13-18, 2000
- Smelson DA, Ziedonis D, Williams J, et al: The efficacy of olanzapine for decreasing cue-elicited craving in individuals with schizophrenia and cocaine dependence: a preliminary report. *J Clin Psychopharmacol* 26(1):9-12, 2006 16415698
- Soni SD, Brownlee M: Alcohol abuse in chronic schizophrenics: implications for management in the community. *Acta Psychiatr Scand* 84(3):272-276, 1991 1950628
- Spencer T, Biederman J, Wilens T, et al: Is attention-deficit hyperactivity disorder in adults a valid disorder? *Harv Rev Psychiatry* 1(6):326-335, 1994 9384867
- Stein LI, Test MA: Alternative to mental hospital treatment, I: conceptual model, treatment program, and clinical evaluation. *Arch Gen Psychiatry* 37(4):392-397, 1980 7362425
- Steinberg ML, Williams JM, Ziedonis DM: Financial implications of cigarette smoking among individuals with schizophrenia. *Tob Control* 13(2):206, 2004 15175544



- Stip E, Tourjman V: Aripiprazole in schizophrenia and schizoaffective disorder: a review. *Clin Ther* 32 (suppl 1):S3-S20, 2010 20152550
- Stroup TS, Lieberman JA, McEvoy JP, et al; CATIE Investigators: Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 163(4):611-622, 2006 16585435
- Susman VL: Clinical management of neuroleptic malignant syndrome. *Psychiatr Q* 72(4):325-336, 2001 11525080
- Szymanski S, Lieberman JA, Alvir JM, et al: Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. *Am J Psychiatry* 152(5):698-703, 1995 7726309
- Takahashi T, Wood SJ, Yung AR, et al: Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. *Arch Gen Psychiatry* 66(4):366-376, 2009 19349306
- Tamminga CA: Principles of the pharmacotherapy of schizophrenia, in *Neurobiology of Mental Illness*. Edited by Charney DS, Nestler EJ, Bunney BS. New York, Oxford University Press, 1999, pp 272-290
- Tarrier N, Barrowclough C, Vaughn C, et al: The community management of schizophrenia: a controlled trial of a behavioural intervention with families to reduce relapse. *Br J Psychiatry* 153:532-542, 1988 3074860
- Tarrier N, Kinney C, McCarthy E, et al: Two-year follow-up of cognitive-behavioral therapy and supportive counseling in the treatment of persistent symptoms in chronic schizophrenia. *J Consult Clin Psychol* 68(5):917-922, 2000 11068978
- Tarsy D, Baldessarini RJ: Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? *Mov Disord* 21(5):589-598, 2006 16532448
- Tibbo P, Kroetsch M, Chue P, et al: Obsessive-compulsive disorder in schizophrenia. *J Psychiatr Res* 34(2):139-146, 2000 10758256
- Tollefson GD, Beasley CM Jr, Tamura RN, et al: Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *Am J Psychiatry* 154(9):1248-1254, 1997 9286184
- Tollefson GD, Sanger TM, Lu Y, et al: Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry* 55(3):250-258, 1998 9510219
- Tollefson GD, Andersen SW, Tran PV: The course of depressive symptoms in predicting relapse in schizophrenia: a double-blind, randomized comparison of olanzapine and risperidone. *Biol Psychiatry* 46(3):365-373, 1999 10435202
- Tollefson GD, Birkett MA, Kiesler GM, et al; Lilly Resistant Schizophrenia Study Group: Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine. *Biol Psychiatry* 49(1):52-63, 2001 11163780
- Tsuang MT, Fleming JA, Simpson JC: Suicide and schizophrenia, in *The Harvard Medical School Guide to Suicide Assessment and Intervention*. Edited by Jacobs DG. San Francisco, CA, Jossey-Bass, 1999, pp 287-299
- Umbricht D, Alberati D, Martin-Facklam M, et al: Effect of bitopertin, a glycine reuptake inhibitor, on negative symptoms of schizophrenia: a randomized,

- double-blind, proof-of-concept study. *JAMA Psychiatry* 71(6):637-646, 2014 24696094
- van Haren NE, Hulshoff Pol HE, Schnack HG, et al: Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol Psychiatry* 63(1):106-113, 2008 17599810
- Vancampfort D, Guelinkcx H, Probst M, et al: Associations between metabolic and aerobic fitness parameters in patients with schizophrenia. *J Nerv Ment Dis* 203(1):23-27, 2015 25494336
- Varsamis J, Adamson JD: Early schizophrenia. *Can Psychiatr Assoc J* 16(6):487-497, 1971 5143681
- Volavka J, Czobor P, Sheitman B, et al: Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry* 159(2): 255-262, 2002 11823268
- Waddington JL: Schizophrenia: developmental neuroscience and pathobiology. *Lancet* 341(8844):531-536, 1993 8094781
- Weiden PJ, Cutler AJ, Polymeropoulos MH, et al: Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. *J Clin Psychopharmacol* 28 (2 suppl 1):S12-S19, 2008 18334908
- Weinberger DR: Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44(7):660-669, 1987 3606332
- Weinberger DR: On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. *Neuropsychopharmacology* 14 (3 suppl):1S-11S, 1996 8866738
- Weinberger DR, McClure RK: Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? *Arch Gen Psychiatry* 59(6):553-558, 2002 12044198
- Weiner E, Ball MP, Summerfelt A, et al: Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. *Am J Psychiatry* 158(4):635-637, 2001 11282701
- Westermeyer JF, Harrow M, Marengo JT: Risk for suicide in schizophrenia and other psychotic and nonpsychotic disorders. *J Nerv Ment Dis* 179(5):259-266, 1991 2022953
- Wilkins JN: Pharmacotherapy of schizophrenia patients with comorbid substance abuse. *Schizophr Bull* 23(2):215-228, 1997 9165632
- Williams JM, Ziedonis DM, Foulds J: A case series of nicotine nasal spray in the treatment of tobacco dependence among patients with schizophrenia. *Psychiatr Serv* 55(9):1064-1066, 2004 15345771
- Williams JM, Anthenelli RM, Morris CD, et al: A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 73(5):654-660, 2012 22697191
- Windgassen K, Wesselmann U, Schulze Mönking H: Galactorrhea and hyperprolactinemia in schizophrenic patients on neuroleptics: frequency and etiology. *Neuropsychobiology* 33(3):142-146, 1996 8776743
- Wirshing DA, Spellberg BJ, Erhart SM, et al: Novel antipsychotics and new onset diabetes. *Biol Psychiatry* 44(8):778-783, 1998 9798083

- Wirshing DA, Wirshing WC, Kysar L, et al: Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 60(6):358-363, 1999 10401912
- Wirshing DA, Erhart SM, Pierre JM, Boyd JA: Nonextrapyramidal side effects of novel antipsychotics. *Current Opinion in Psychiatry* 13(1):45-50, 2000
- Wirshing DA, Boyd JA, Meng LR, et al: The effects of novel antipsychotics on glucose and lipid levels. *J Clin Psychiatry* 63(10):856-865, 2002 12416594
- Wirshing DA, Pierre JM, Erhart SM, Boyd JA: Understanding the new and evolving profile of adverse drug effects in schizophrenia. *Psychiatr Clin North Am* 26(1): 165-190, 2003 12683265
- Witthaus H, Kaufmann C, Böhner G, et al: Gray matter abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. *Psychiatry Res* 173(3):163-169, 2009 19616415
- Woodward ND, Purdon SE, Meltzer HY, Zald DH: A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int J Neuropsychopharmacol* 8(3):457-472, 2005 15784157
- Wyatt RJ: Neuroleptics and the natural course of schizophrenia. *Schizophr Bull* 17(2):325-351, 1991 1679255
- Wyatt RJ: Early intervention for schizophrenia: can the course of the illness be altered? *Biol Psychiatry* 38(1):1-3, 1995 7548467
- Wyatt RJ, Damiani LM, Henter ID: First-episode schizophrenia: early intervention and medication discontinuation in the context of course and treatment. *Br J Psychiatry Suppl* 172(33):77-83, 1998 9764131
- Wykes T, Reeder C, Corner J, et al: The effects of neurocognitive remediation on executive processing in patients with schizophrenia. *Schizophr Bull* 25(2):291-307, 1999 10416732
- Wykes T, Steel C, Everitt B, et al: Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. *Schizophr Bull* 34(3):523-537, 2008 17962231
- Yazigi RA, Quintero CH, Salameh WA: Prolactin disorders. *Fertil Steril* 67(2):215-225, 1997 9022592
- Yood MU, DeLorenze G, Quesenberry CP Jr, et al: The incidence of diabetes in atypical antipsychotic users differs according to agent—results from a multisite epidemiologic study. *Pharmacoepidemiol Drug Saf* 18(9):791-799, 2009 19526626
- Young JW, Geyer MA: Developing treatments for cognitive deficits in schizophrenia: the challenge of translation. *J Psychopharmacol* 29(2):178-196, 2015 25516372
- Yung AR, McGorry PD: The initial prodrome in psychosis: descriptive and qualitative aspects. *Aust N Z J Psychiatry* 30(5):587-599, 1996a 8902166
- Yung AR, McGorry PD: The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull* 22(2):353-370, 1996b 8782291
- Yung AR, Phillips LJ, Nelson B, et al: Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. *J Clin Psychiatry* 72(4):430-440, 2011 21034687

- Ziedonis D, Richardson T, Lee E, et al: Adjunctive desipramine in the treatment of cocaine abusing schizophrenics. *Psychopharmacol Bull* 28(3):309-314, 1992 1480735
- Ziedonis D, Williams JM, Smelson D: Serious mental illness and tobacco addiction: a model program to address this common but neglected issue. *Am J Med Sci* 326(4): 223-230, 2003 14557739
- Zimmet SV, Strous RD, Burgess ES, et al: Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. *J Clin Psychopharmacol* 20(1):94-98, 2000 10653215
- Zipursky RB, Lim KO, Sullivan EV, et al: Widespread cerebral gray matter volume deficits in schizophrenia. *Arch Gen Psychiatry* 49(3):195-205, 1992 1567274

---

The authors would like to acknowledge the contribution of Holly L.L. Pierce in the preparation of this chapter.

## CHAPTER 50

# Treatment of Substance-Related Disorders

Brian J. Sherman, Ph.D.

Karen J. Hartwell, M.D.

Aimee L. McRae-Clark, Pharm.D.

Kathleen T. Brady, M.D., Ph.D.

Substance use disorders are common in the United States, with data from 2014 indicating that approximately 27 million individuals reported illicit drug use in the past month, 17 million had an alcohol use disorder, and 55.2 million were current cigarette smokers ([Center for Behavioral Health Statistics and Quality 2015](#)). Therefore, many Americans are directly affected by substance use disorders, and millions more are affected through family or friends or through the societal costs associated with substance use disorders. The cost to society is great, exacting more than \$700 billion annually in costs

related to crime, lost productivity, and health care ([U.S. Department of Health and Human Services 2014](#)).

Fortunately, there have been major advances in psychotherapeutic and pharmacotherapeutic treatments for substance use disorders. Recent advances in neurobiology have helped to identify major brain circuitry and neurotransmitter systems involved in substance-related disorders, allowing for the development of treatments that more specifically target systems and regions involved in addictive processes. Unfortunately, in spite of new developments in medication treatments, medications are often underused in the treatment of substance use disorders. For example, even though three medications have been approved by the U.S. Food and Drug Administration (FDA) for relapse prevention in DSM-IV ([American Psychiatric Association 1994](#)) alcohol dependence, a study conducted in the Veterans Administration Medical Center (VAMC) system in 2008–2009 found that only 3.4% of the individuals treated for alcohol dependence were prescribed a medication targeting relapse prevention ([Harris et al. 2012](#)). There are many potential reasons for this, including the fact that much of the addiction treatment system has “grown up” outside of traditional medicine, so medications are sometimes not considered in treatment planning. In addition, many treatment programs still do not have the necessary medical personnel to evaluate patients for appropriateness of medication treatment and prescribe as needed. Many insurance plans provide little coverage for medications to treat substance use disorders. However, the Harris et al. study took place in a VAMC, where cost and access to medical personnel should not have been an issue. Broader education of physicians concerning recognition

and pharmacological treatment of substance use disorders is clearly needed.

In this chapter we focus on pharmacotherapeutic treatments for substance-related disorders, but important advances also have been made in psychotherapeutic and behavioral treatments for these disorders. Although pharmacotherapeutic treatments are an important and sometimes neglected part of the treatment armamentarium, medications alone are rarely sufficient for the treatment of substance use disorders and should be accompanied by comprehensive treatment planning and psychosocial treatment.

A meta-analysis of 34 well-controlled trials of psychosocial therapies included studies of contingency management, relapse prevention, cognitive-behavioral therapy (CBT), and combinations of CBT and contingency management. Contingency management treatments had the lowest dropout rates, at fewer than 30%, followed by CBT and combined psychosocial treatments. Treatment involving relapse prevention techniques led to the highest rate of abstinence, at 39%, and greater time in treatment was related to positive outcomes ([Dutra et al. 2008](#)). Another study found that CBT, 12-step facilitation, and brief motivational therapy were all efficacious in the treatment of DSM-IV alcohol dependence ([Project MATCH Research Group 1997](#)). In addition, substance-related disorders are truly complex disorders that are influenced by biological and psychological factors as well as environmental circumstances. One study comparing standard methadone services with methadone services enhanced by on-site access to medical-psychiatric, employment, and family therapy found that individuals receiving enhanced services

showed significantly better outcomes across several functional domains ([McLellan et al. 1993](#)).

---

## Alcohol-Related Disorders

---

In the United States in 2014, approximately 139.7 million people ages 12 years and older reported past-month alcohol use, and 17.0 million people met criteria for alcohol use disorder ([Center for Behavioral Health Statistics and Quality 2015](#)). From 2006 to 2010, excessive alcohol consumption was responsible for 1 in 10 deaths annually among working-age adults ([Stahre et al. 2014](#)), yet only a fraction (1.4 million in 2013) received any formal treatment ([Substance Abuse and Mental Health Services Administration 2014](#)).

Pharmacotherapy for alcohol use disorder involves a two-stage approach. Detoxification from alcohol is the first step and can be inpatient or outpatient, depending on the severity of dependence and other risk factors such as chronic medical conditions. Following detoxification, pharmacotherapeutic agents may be used to prevent relapse or reduce alcohol intake by targeting different neurotransmitter systems associated with alcohol dependence. The FDA has approved disulfiram, naltrexone, and acamprosate for the treatment of alcohol use disorder.

## Alcohol Withdrawal and Detoxification



Alcohol withdrawal syndrome occurs in approximately 50% of alcohol-dependent individuals on reduction or abstinence following a period of prolonged or heavy alcohol use ([Kosten and O'Connor 2003](#)). Most people presenting with alcohol withdrawal syndrome experience mild symptoms, which may include hand tremor, anxiety, headache, insomnia, nausea or vomiting, diaphoresis, and irritability and can be treated on an outpatient basis. However, approximately 5% experience severe symptoms, including seizures and delirium tremens (DTs), which can be fatal and must be treated on an inpatient basis ([Schuckit 1991, 2014](#)).

Benzodiazepines remain the gold standard for treating alcohol withdrawal ([Mayo-Smith 1997](#); [Schmidt et al. 2016](#)). Benzodiazepines exert sedative, hypnotic, and anticonvulsant effects through positive modulation of the  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptor, reducing central nervous system (CNS) hyperactivity associated with alcohol withdrawal ([Brunton et al. 2011](#)). They have been shown to reduce withdrawal severity, seizures, and DTs ([Mayo-Smith 1997](#)). Diazepam and chlordiazepoxide are commonly used and a good choice because of their long half-life, which reduces the risk of rebound symptoms (i.e., seizures) that generally occur a few days into withdrawal. However, they are contraindicated in patients with hepatic or renal dysfunction, the elderly, and/or those at high risk of medical complications associated with the presence of active metabolites and renal excretion. Lorazepam and oxazepam are optimal in such cases, but their short half-life increases the risk for rebound symptoms and requires carefully monitored tapering.

The three most commonly used benzodiazepine detoxification regimens are the symptom-triggered, the

fixed-tapering-dose, and the loading-dose regimens. The symptom-triggered regimen requires frequent clinical assessment with the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar; [Sullivan et al. 1989](#)) and is most often used in the hospital setting. Dosing is based on CIWA-Ar scores, which can range from 0 to 67 (a score of 20 or greater indicates severe withdrawal). This regimen is advantageous because it involves a relatively short duration of treatment and a smaller total quantity of administered medication ([Daepfen et al. 2002](#)). The fixed-tapering-dose regimen involves administering benzodiazepines at scheduled intervals, with initial dosing determined by symptom severity at presentation. This method is often preferred for outpatient detoxification when frequent assessment and monitoring are impractical. The loading dose regimen involves administering a larger dose of a long-acting benzodiazepine every 2 hours under close monitoring. In all regimens, taper occurs over 5–7 days, depending on initial severity, withdrawal history, and other potential medical complications.

Anticonvulsant medications have shown efficacy in treating mild to moderate withdrawal symptoms or as an adjunct to benzodiazepine pharmacotherapy for more severe withdrawal. Evidence suggests that gabapentin and carbamazepine are the most effective agents and carry additional advantages including absence of abuse liability, reduced probability of rebound seizures, and reduced cravings (for a review, see [Hammond et al. 2015](#)). With any detoxification regimen, vitamin and electrolyte replenishment is an important component.

## Relapse Prevention

## Alcohol-Sensitizing Agents

**Disulfiram.** In 1951, disulfiram became the first medication to be approved by the FDA for alcohol use disorder. Disulfiram inhibits the enzyme aldehyde dehydrogenase, resulting in excess blood levels of the toxic metabolite acetaldehyde. Excess acetaldehyde produces a reaction that may include flushing, nausea, tachycardia, and hypotension. The behavioral pairing of this reaction with alcohol consumption acts as a deterrent for individuals with alcohol use disorder. The reaction can last from 30 minutes to several hours, depending on the dose of disulfiram and the amount of alcohol consumed, and severe reactions may require hospitalization. Because side effects may include hepatic dysfunction, liver function tests should be conducted prior to initiation and subsequently as indicated. The initial dosage and standard maintenance dosage is 250 mg/day, but dosing may range from 125 to 500 mg/day.

Evidence on the efficacy of disulfiram is limited and controversial. The largest placebo-controlled study to date, the Veterans Administration (VA) Cooperative Study of Disulfiram Treatment of Alcoholism ([Fuller et al. 1986](#)), found no group differences in abstinence rates or time to first drink; however, the adherence rate in individuals receiving disulfiram was only 20%. Among more recent studies, some have shown disulfiram to be associated with higher abstinence rates and longer times to relapse ([De Sousa and De Sousa 2004, 2005](#)), whereas others have found no significant effects of disulfiram on drinking outcomes ([Ulrichsen et al. 2010](#)).

An important meta-analysis by [Skinner et al. \(2014\)](#) compared blinded with unblinded clinical trials involving

disulfiram and found it to be efficacious only in the unblinded studies, suggesting that its efficacy may depend on the psychological expectancy of an aversive reaction. Subgroup analysis (unblinded randomized controlled trials [RCTs] only) determined that disulfiram was superior to naltrexone, acamprosate, and placebo. Because of low adherence rates ([Fuller and Gordis 2004](#)), guidelines strongly recommend supervised administration, which results in significantly greater efficacy compared with unsupervised administration ([Skinner et al. 2014](#)).

In summary, disulfiram is efficacious and safe under the proper circumstances. It is recommended for patients who are highly motivated to maintain abstinence, have available supervision, comprehend the consequences of drinking while taking disulfiram, and are medically appropriate ([Substance Abuse and Mental Health Services Administration 2015](#)).

## Opioid Antagonists

**Naltrexone.** The opioid antagonist naltrexone was approved in 1994 for the treatment of alcohol use disorder. Although naltrexone's exact mechanism of action in reducing alcohol use is unknown, preclinical trials suggest that it reduces craving by modulating dopamine activity in the nucleus accumbens and ventral tegmental area and by blocking the effects of endogenous opioids following consumption of alcohol (for a review, see [Johnson 2008](#)).

*Oral naltrexone.* Oral naltrexone has shown significant, although modest, efficacy in improving alcohol outcomes. Early clinical trials found reductions in relapse rates over 12 weeks among participants randomly assigned to

naltrexone 50 mg compared with placebo ([O'Malley et al. 1992](#); [Volpicelli et al. 1992](#)). However, 5 months posttreatment, relapse rates did not differ from those with placebo. Similarly, [Anton et al. \(2001, 2006\)](#) found gradually increasing rates of relapse, number of drinking days, and number of heavy drinking days following termination of up to 16 weeks of naltrexone. The VA Cooperative Study ([Krystal et al. 2001](#)) compared oral naltrexone with placebo over treatment periods of 12 and 52 weeks and found no group differences. However, a systematic Cochrane review of 50 RCTs found a 17% reduction in risk for heavy drinking among participants taking naltrexone compared with placebo ([Rösner et al. 2010](#)).

Poor medication adherence has been problematic and limits the efficacy of naltrexone. [Volpicelli et al. \(1997\)](#) found naltrexone to be superior to placebo only when adherence rates were higher than 90%. One large multisite trial (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence [COMBINE] study;  $N=1,383$ ) sought to address poor adherence by adding a medication management component ([Anton et al. 2006](#)). The adherence rate was 85%, and compared with placebo, participants receiving naltrexone plus medication management showed a significantly reduced risk for heavy drinking.

Some studies suggest that a variant of the gene encoding the  $\mu$  opioid receptor (*OPRM1*) is associated with greater naltrexone efficacy ([Anton et al. 2008](#); [Oslin et al. 2003](#)), but other studies have found no difference in naltrexone efficacy among participants with any *OPRM1* variants ([Gelernter et al. 2007](#)). Clinical characteristics including family history of alcohol use disorder and strong alcohol craving on presentation have been associated with good

clinical response to naltrexone ([King et al. 2002](#); [Monterosso et al. 2001](#)).

*Extended-release injectable naltrexone.* Extended-release injectable naltrexone (XR-NTX) was developed to address problems with adherence and was approved by the FDA in 2006. Depot naltrexone 380 mg can provide protective blood plasma levels for up to 30 days, thus eliminating the need for daily oral administration. The seminal trial of depot naltrexone compared six monthly doses of naltrexone 380 mg, naltrexone 190 mg, and placebo in 600 alcohol-dependent individuals ([Garbutt et al. 2005](#)). The 380-mg group showed the greatest reduction in the number of heavy drinking days compared with placebo. Of note, a treatment effect of depot naltrexone was found only in males. In addition, the dropout rate of 14.1% in the high-dose group was comparable to that in studies of oral naltrexone. In summary, depot naltrexone appears to be effective in reducing heavy drinking days for men, but not for women, and its effect on adherence appears to be limited.

**Nalmefene.** Nalmefene, another opioid antagonist, also has been examined in the treatment of alcohol use disorder. In initial trials, [Mason et al. \(1994, 1999\)](#) found nalmefene to be efficacious in preventing relapse to heavy drinking. However, a later 12-week trial of recently abstinent individuals with alcohol use disorder found no differences between nalmefene and placebo on number of heavy drinking days ([Anton et al. 2004](#)). Recent multisite placebo-controlled trials in Europe have found significant reductions in number of heavy drinking days per month and total alcohol consumption with nalmefene (18 mg) compared

with placebo ([Gual et al. 2013](#); [Mann et al. 2013a](#); [van den Brink et al. 2014](#)).

## Anticraving Agents

**Acamprosate.** Acamprosate, an *N*-methyl-D-aspartate receptor modulator, was approved by the FDA in 2004 for the treatment of alcohol use disorder. Although its exact mechanism of action is unclear, acamprosate appears to reduce craving by promoting a balance between inhibitory (GABA) and excitatory (glutamate) neurotransmitters ([Mason and Heyser 2010](#)). Acamprosate offers some advantages over the other two FDA-approved medications for alcohol use disorder (disulfiram and naltrexone), because it is not metabolized by the liver and therefore not affected by alcohol consumption.

A systematic Cochrane review evaluated the efficacy of acamprosate in 24 randomized, double-blind, controlled trials of 6,894 individuals with alcohol use disorder ([Rösner et al. 2010](#)). Compared with placebo, acamprosate reduced the relapse risk by 14% and increased the cumulative abstinence duration by 11%. Secondary outcomes of return to heavy drinking and  $\gamma$ -glutamyltransferase (GGT) levels did not differ by group. The large randomized, placebo-controlled multisite COMBINE study ([Anton et al. 2006](#)) did not find acamprosate to be superior to placebo on alcohol outcomes, and other large-scale RCTs have reported similar nonsignificant results ([Mann et al. 2013b](#); [Mason et al. 2006](#); [Morley et al. 2006](#)). Acamprosate has shown inferiority to disulfiram and naltrexone on drinking outcomes in open-label clinical trials ([De Sousa and De Sousa 2005](#); [Laaksonen et al. 2008](#)). Some studies have suggested that response to acamprosate may be influenced



by genetic factors, including interactions with GATA binding protein 4 (*GATA4*; [Kiefer et al. 2011](#)) and polymorphisms of the GABA<sub>A</sub> receptor  $\alpha_6$  subunit (*GABRA6*) and D<sub>2</sub> dopamine receptor *DRD2* genotypes ([Ooteman et al. 2009](#)), although replication of these findings is needed.

## Anticonvulsants

**Topiramate.** Several anticonvulsant medications have been investigated for off-label use in treating alcohol use disorder, and topiramate appears the most promising. The mechanism of action in regard to alcohol use is unclear, but it may reduce craving as a result of neurobiological action on GABAergic and glutamatergic signaling in corticomesolimbic regions. [Johnson et al. \(2003\)](#) first examined topiramate 300 mg/day compared with placebo among 150 alcohol-dependent participants and found significant reductions in self-reported alcohol consumption and GGT levels with topiramate compared with placebo. A subsequent multisite trial ( $N=371$ ) found flexible dosing with topiramate (up to 300 mg/day) efficacious in reducing alcohol consumption and GGT levels over the 14-week study period ([Johnson et al. 2007](#)). Numerous adverse side effects were reported in the larger trial, including cognitive impairment (memory, concentration), paresthesias, taste disturbances, and anorexia.

Topiramate has shown mixed results compared with other medications approved for the treatment of alcohol use disorder. Topiramate fared worse than disulfiram, engendering shorter time to relapse ([De Sousa et al. 2008](#)), but showed noninferiority ([Baltieri et al. 2008](#)) and superiority on drinking outcomes, including reduced craving, when compared with naltrexone ([Flórez et al.](#)



2011). Although topiramate can be an effective treatment for alcohol use disorder, poor tolerability may limit its utility.

## Serotonergic Agents

**Ondansetron.** Ondansetron, a serotonin type 3 (5-HT<sub>3</sub>) receptor antagonist, has shown promise in the treatment of alcohol use disorder. An RCT in 71 males with nonsevere alcohol dependency found that low-dose ondansetron (0.25 mg twice a day) was associated with greater reductions in drinking compared with placebo or high-dose ondansetron (2.0 mg twice a day) among participants drinking fewer than 10 drinks per drinking day ([Sellers et al. 1994](#)). The first large-scale RCT ([Johnson et al. 2000](#)) found that for adults with early-onset alcohol use disorder (prior to age 25 years), ondansetron 4 µg/kg twice a day was associated with greater percentages of days abstinent and total days abstinent compared with placebo. Investigations of the clinical utility of ondansetron and other serotonergic agents are ongoing.

---

## Opioid-Related Disorders

---

Opioid use disorder is a serious and increasing public health concern. In the United States in 2014, approximately 2.5 million people ages 12 years and older had an opioid use disorder in the past year ([Center for Behavioral Health Statistics and Quality 2015](#)). Opioids (primarily prescription pain relievers and heroin) were involved in 28,647 deaths in 2014, and the rate of opioid overdose has tripled since 2000 ([Rudd et al. 2016](#)). Opioid use has been associated

with mortality, criminality, violence, HIV, hepatitis C, and poor quality of life ([Hulse et al. 1999](#))

The FDA has approved three medications for the treatment of opioid use disorder: methadone, buprenorphine, and naltrexone. All three agents bind to  $\mu$  opioid receptors, but they differ in their pharmacokinetic and pharmacodynamic properties, intrinsic activity at the receptor, and mechanism of relapse prevention. Of importance, most studies have been conducted in individuals who are primarily intravenous heroin users rather than individuals who use prescription opioids. There may be important differences between these two groups, and more systematic treatment studies of individuals with prescription opioid use disorders are needed.

## FDA-Approved Medications

### **Methadone**

Methadone is a full opioid agonist with high affinity for the  $\mu$  opioid receptor, a long terminal half-life, and delayed steady-state efficacy, which contributes to its risk of fatal overdose during induction. Initial dosing should begin with 10–20 mg. If withdrawal symptoms are not adequately suppressed within 1 hour, additional medication may be required but should not exceed 30 mg in the first day and 40 mg in the first 3 days. Once withdrawal symptoms are stabilized, dosing can be increased to 100 mg or higher for tolerant individuals.

With appropriate administration and adherence, methadone is generally safe. However, methadone-associated risks of respiratory depression, QTc interval prolongation, and sudden death require acute monitoring

and led to a 2006 physician safety alert from the FDA. Methadone may be used for detoxification or maintenance therapy.

## **Buprenorphine**

Buprenorphine is a partial opioid agonist with high affinity for the  $\mu$  opioid receptor and slow dissociation, enabling protection for more than 24 hours in many cases. Given its high affinity and slow dissociation, buprenorphine may induce acute withdrawal if receptors are bound by a full agonist at the time of administration. To avoid precipitating withdrawal, physicians should wait until the patient is experiencing withdrawal symptoms to begin induction. Initial dosing usually begins with 2–4 mg, which, if well tolerated, can be followed by an additional 2–4 mg approximately 8 hours later. Some patients will require a 24- to 32-mg maintenance dose, but most patients can be adequately maintained with 16 mg or less once stabilized.

As a partial opioid receptor agonist, buprenorphine confers a ceiling effect, thus reducing overdose potential and euphoria from illicit opioid use. The safety profile of buprenorphine is therefore more favorable than that of full agonists, and it is not associated with QTc interval prolongation, respiratory depression, or other drug interactions. Buprenorphine may be used for detoxification or in combination with naloxone (discussed further in the “Buprenorphine–Naloxone” subsection later in this chapter) for maintenance therapy.

## **Naltrexone**

Naltrexone is an opioid receptor antagonist with high affinity for the  $\mu$  opioid receptor. Through competitive

antagonism at the  $\mu$  opioid receptor, naltrexone blocks the euphoric effects of opioids and reduces overdose risk. Naltrexone is long acting and may be given every 2–3 days; however, daily administration is recommended. Naltrexone is most effective in highly motivated individuals, because noncompliance is common, and relapse to previous levels of opioid use is potentially fatal for individuals who have lost opioid tolerance while taking naltrexone.

Naltrexone may be used for relapse prevention once abstinence is achieved. Extended-release depot and implant formulations have been developed to improve adherence; these formulations are discussed in the “Extended-Release Injectable Naltrexone” subsection under “Relapse Prevention” later in this chapter.

## Detoxification and Withdrawal

Opioid detoxification traditionally has been achieved via short-term substitution therapy followed by abstinence. Opioid withdrawal can begin within 8–12 hours of last use and generally peaks at 24–72 hours, with acute withdrawal symptoms resolving within 5–7 days; however, the time course is dependent on the half-life of the agent being used. A protracted abstinence syndrome may continue for an additional 6–8 months and includes dysphoria, fatigue, insomnia, and irritability ([Martin and Jasinski 1969](#)). Full (methadone) and partial (buprenorphine) opioid agonist medications have been used for detoxification. Over the course of 1–4 weeks, opioid-dependent individuals are tapered off medication and encouraged to remain abstinent with continued psychosocial treatment.

A recent study compared taper regimens of 1, 2, and 4 weeks in 70 prescription opioid-dependent adults attending an outpatient clinic ([Sigmon et al. 2013](#)). On all outcome measures, the 4-week taper condition fared better, showing greater abstinence rates at week 5 compared with the 2-week and 1-week taper groups (63% vs. 29% vs. 29%) and also at week 12 (50% vs. 16% vs. 20%); the 4-week group also had more responders, better retention, and greater posttaper naltrexone ingestion. In a multisite trial, [Woody et al. \(2008\)](#) examined longer taper durations in 152 opioid-dependent youths (ages 15–21 years) randomly assigned to 12 weeks of buprenorphine–naloxone treatment or a 14-day detoxification protocol. Compared with youths receiving the 14-day detoxification regimen, those receiving the 12-week treatment had significantly fewer positive opioid urine test results and higher retention over the 12-week study. However, participants did not differ on any outcome measures at 6, 9, and 12 months posttreatment.

Across studies, longer taper durations are associated with higher abstinence rates during treatment ([Dunn et al. 2011](#)). Furthermore, a systematic Cochrane review found that across studies, heroin-dependent adults who received methadone only for detoxification showed greater illicit heroin use and worse retention compared with those who received methadone for both detoxification and maintenance ([Mattick et al. 2009](#)).

Attempts to augment detoxification with clonidine, an  $\alpha$ -adrenergic agonist, have been investigated. Some studies have been unsuccessful or have shown no advantage for clonidine over agonist detoxification ([Gold et al. 1978, 1980](#); [Ling et al. 2005](#)), and a systematic review found side effects to be a significant issue ([Gowing et al. 2003](#)). A multisite clinical trial across inpatient ( $N=113$ ) and

outpatient ( $N=231$ ) treatment settings compared buprenorphine-naloxone with clonidine in a 13-day opioid detoxification regimen. Buprenorphine-naloxone was more effective in achieving treatment success (retention and negative screen on last day) than clonidine among both inpatients (77% vs. 22%) and outpatients (29% vs. 5%; [Ling et al. 2005](#)). When used in conjunction with buprenorphine, however, clonidine was associated with a longer duration of opioid abstinence in one 14-week placebo-controlled trial ([Kowalczyk et al. 2015](#)).

Rapid detoxification procedures also have been developed, including 1) rapid withdrawal induction with naltrexone (followed by high doses of clonidine and benzodiazepines to attenuate associated symptoms) and 2) rapid withdrawal under general anesthesia (with administration of numerous and varied medications to manage symptoms). These methods generally are not recommended; the latter in particular has been associated with multiple deaths within 72 hours of the procedure ([Whittington et al. 2000](#)). Although detoxification is important, rapidity should not be emphasized. Given the chronic, relapsing nature of opioid use disorders, first-line treatment has shifted toward lengthier taper durations and maintenance therapy followed by relapse prevention.

## Maintenance Therapy

### **Methadone**

Methadone maintenance treatment (MMT) is the most common form of maintenance therapy and involves closely monitored daily administration by licensed physicians at federally regulated treatment centers. Patients must attend

clinic daily unless they earn take-home privileges for meeting clinic criteria such as employment and long-term abstinence (2 years or more). Patients must be at least 18 years old and must have had an opioid use disorder for at least 1 year. Since its introduction in 1964, MMT has been the focus of numerous clinical trials that collectively indicate that MMT clearly reduces illicit opioid use and improves treatment retention ([Fullerton et al. 2014](#); [Mattick et al. 2009](#)). MMT also has been associated with decreased mortality ([Gunne and Grönbladh 1981](#); [Kinlock et al. 2007](#)), reduced nonopioid drug use ([Faggiano et al. 2003](#)), and decreased drug-related HIV risk behaviors ([Sees et al. 2000](#)). Psychosocial counseling focusing on lifestyle changes significantly improves outcomes ([McLellan et al. 1993](#)), and studies have found that interventions such as contingency contracting and voucher incentives are also efficacious ([Brooner et al. 2007](#)).

Because of the recently discovered association between MMT and QTc interval prolongation, which can be fatal, the FDA issued a black box warning in 2006. The Substance Abuse and Mental Health Services Administration (SAMHSA) also issued recommendations for physicians who provide MMT, which included notifying patients of potential cardiac complications, screening patients for cardiac conditions, and, when indicated, conducting a pretreatment and 1-month electrocardiogram ([Center for Substance Abuse Treatment 2005](#)).

## **Buprenorphine**

Buprenorphine was approved by the FDA for the office-based treatment of opioid use disorder in 2002. In order to prescribe buprenorphine, physicians must undergo an 8-hour training and be granted approval from the U.S.

Department of Health and Human Services, after which they may see 30 patients in the first year and 100 per year thereafter.

Early trials of buprenorphine established its efficacy in treating opioid use disorders. A 25-week RCT compared buprenorphine with methadone and found the two medications to be equally effective in reducing opioid use and maintaining participants in treatment (R.E. [Johnson et al. 1992](#)). A systematic Cochrane review evaluated evidence comparing buprenorphine maintenance with placebo and methadone maintenance ([Mattick et al. 2014](#)). Fixed-dose results suggested that compared with placebo, buprenorphine improved treatment retention at any dose but suppressed illicit opioid use only at doses of 16 mg or higher. Compared with methadone, buprenorphine did not differ in treatment retention or suppression of opiate use at medium or high doses (methadone: medium = 40–85 mg, high  $\geq$  85 mg; buprenorphine: medium=7–15 mg, high $\geq$ 16 mg), although low-dose methadone ( $\leq$ 40 mg) was associated with better retention than low-dose buprenorphine (2–6 mg). Studies that used flexible dosing found that compared with methadone maintenance, buprenorphine retained fewer participants, but among those retained in treatment, no difference was seen in suppression of opioid use. In summary, whereas methadone at low or flexible doses appears to be more effective than buprenorphine in retaining patients in treatment, methadone at medium to high fixed doses is no different from buprenorphine in treatment retention or opioid use suppression.

## **Buprenorphine-Naloxone**



Buprenorphine-naloxone was introduced to address the risks of diversion and injection overdose associated with buprenorphine alone. Naloxone is a high-affinity  $\mu$  opioid receptor antagonist. It has high bioavailability when injected and therefore prevents abuse and overdose by immediately counteracting the agonist properties of buprenorphine, resulting in acute withdrawal. However, sublingually, naloxone has low bioavailability; therefore, when the combination is administered sublingually, as is customary, the individual experiences the intended agonist effect of buprenorphine without experiencing withdrawal. A buprenorphine-to-naloxone ratio of 4:1 has been established.

[Fudala et al. \(2003\)](#) conducted the seminal efficacy study of office-based treatment of opioid use disorders using combination buprenorphine-naloxone compared with buprenorphine alone or placebo. The 4-week double-blind, randomized trial ( $N=326$ ) found buprenorphine alone and buprenorphine-naloxone to have greater efficacy than placebo, as measured by percentage of negative opioid drug screens (20.7% vs. 17.8 vs. 5.8) and reductions in opioid craving. The open-label phase ( $N=461$ ) demonstrated that both the buprenorphine-naloxone combination and buprenorphine alone can be safely administered in an outpatient office-based setting. The study authors concluded that buprenorphine-naloxone is at least as good as buprenorphine alone and better than placebo.

[Weiss et al. \(2011\)](#) conducted a multisite, randomized, two-phase adaptive treatment design examining brief and extended buprenorphine-naloxone treatment for prescription opioid dependence ( $N=653$ ). Brief treatment included a 2-week stabilization phase, followed by a 2-week

taper and an 8-week postmedication follow-up assessment (12-week treatment), whereas the extended treatment condition included 12 weeks of buprenorphine-naloxone treatment, followed by a 4-week taper and an 8-week postmedication follow-up (24-week treatment). Extended treatment produced more successful outcomes compared with brief treatment, but only while subjects were maintained on buprenorphine-naloxone; at 8-week postmedication follow-up, there were significant reductions in treatment success rates.

## **Buprenorphine Implants**

Further efforts to reduce diversion, improve adherence, and enhance outcomes include the development of subcutaneous buprenorphine implants, which were approved by the FDA in 2016. A randomized, placebo-controlled 6-month multisite trial ([Ling et al. 2010](#)) found buprenorphine implants to be efficacious as evidenced by greater mean percentage of negative opioid drug screens from weeks 1 to 16 compared with placebo (40.4% vs. 28.3%) and for the entire 24-week period (36.6% vs. 22.4%). The implant group also had higher retention rates (65.7% vs. 30.9%) and fewer clinician- and patient-rated withdrawal symptoms. A subsequent study confirmed the safety and efficacy of buprenorphine implants in reducing opioid use, improving retention, reducing craving and withdrawal ratings, and increasing global ratings of improvement compared with placebo ([Rosenthal et al. 2013](#)). Importantly, the authors reported that buprenorphine implants were noninferior to the commonly used sublingual buprenorphine formulation on percentage of negative urine drug screens during the 24-week study.

## Maintenance Treatment During Pregnancy

Opioid-dependent pregnant women warrant special consideration. MMT during pregnancy has been considered the gold standard of care and is associated with reduced fetal and maternal morbidity, greater prenatal treatment attendance, and improved fetal outcomes overall ([Jones et al. 2008](#); [Kaltenbach et al. 1998](#)). However, these studies were conducted in patients dependent on illicit opioids, and there have been no systematic investigations of the management of opioid use disorders in pregnant women taking prescription opioids.

Neonatal abstinence syndrome involves dysfunction of respiratory, gastrointestinal, and autonomic nervous systems; is common among prenatally exposed neonates, with incidence rates ranging from 45% to 97% ([Cleary et al. 2010](#)); and often requires inpatient detoxification. Although longitudinal studies have suggested that MMT during pregnancy does not impair offspring cognitive performance at age 4 years, performance across groups was significantly lower than in normative samples ([Kaltenbach and Finnegan 1984](#)). Buprenorphine monotherapy is a viable and perhaps desirable alternative that produces less fetal heart rate suppression and less severe neonatal abstinence syndrome compared with methadone ([Jones et al. 2012](#)). Studies of maintenance treatment and detoxification in pregnant women with prescription opioid use disorders are clearly needed.

## Relapse Prevention

### Oral Naltrexone

Naltrexone has been approved by the FDA for the treatment of opioid use disorders since 1984. It acts by blocking the  $\mu$  opioid receptor for 24–72 hours (depending on dose), preventing the individual from experiencing drug-induced euphoria. Continued abstinence through relapse prevention allows recovery of the endogenous opioid system and relief of protracted abstinence symptoms. Naltrexone was introduced in addiction treatment in the 1970s as an orally administered nonaddictive medication with hopes of wide acceptance and effectiveness. However, numerous clinical trials have reported poor outcomes compared with placebo, no treatment, or other pharmacological treatment ([Minozzi et al. 2011](#); [Schottenfeld et al. 2008](#)). Moreover, adherence rates are generally low, and overdose due to relapse in previously tolerant opioid-dependent individuals poses a serious risk for oral naltrexone use. To address poor adherence and associated overdose risk of relapse, XR-NTX was developed and approved by the FDA in 2010.

### **Extended-Release Injectable Naltrexone**

The seminal study of XR-NTX was conducted at 13 clinical sites in Russia ([Krupitsky et al. 2011](#)), where opioid agonist treatment is illegal. In this 24-week double-blind, placebo-controlled, randomized trial ( $N=250$ ), participants receiving XR-NTX had a significantly greater median proportion of confirmed weeks abstinent compared with placebo (90% vs. 35%), higher median numbers of opioid-free days (99.2% vs. 60.4%), longer treatment retention (>168 days vs. 96 days), and greater reductions in craving scores. Among those who entered the open-label phase of the study ( $n=114$ ), 62.3% completed the phase and 50.9%

were abstinent at the end of the trial ([Krupitsky et al. 2013](#)).

XR-NTX has been examined in high-risk populations, including incarcerated individuals and health care professionals. In an open-label pilot study of XR-NTX in 27 prerelease prisoners with a history of opioid use disorders during the year before incarceration ([Gordon et al. 2015](#)), participants received one prerelease injection of XR-NTX followed by six injections after release to the community. Compared with participants who completed fewer than six community injections, those who completed all six were less likely to test positive for opioids at any point during the study (0% vs. 62.5%). Health care professionals with opioid use disorders also showed favorable responses to XR-NTX in a prospective noncomparison study ([Gastfriend et al. 2014](#)). After a 2-week detoxification period, all participants ( $N=38$ ) were offered XR-NTX for up to 24 months; 39.5% remained on XR-NTX at 24 months, and 90% remained abstinent while maintained on the medication.

According to a SAMHSA advisory, subgroups most likely to benefit from XR-NTX include patients unsuccessful with methadone or buprenorphine, those who prefer a less stigmatizing and more convenient alternative, those opposed to agonist therapy, highly motivated individuals, and adolescents or young adults for whom access to treatment facilities is often restricted by governmental regulations ([Substance Abuse and Mental Health Services Administration 2012](#)).

## Overdose Prevention

Recently, overdose education and naloxone rescue kits have been developed and used in various settings to address the growing opioid overdose epidemic. Naloxone is an opioid antagonist that is capable of reversing opioid overdose by decoupling opioids from the opioid receptor and inducing acute withdrawal. It can be administered via injection or nasal spray. Access has increased in the past 5 years, with 44 states plus the District of Columbia passing immunity laws that enable physicians to prescribe the drug or civilians and first responders to administer the drug without fear of civil, criminal, or professional liability ([National Conference of State Legislatures 2017](#)). Thirty-four states plus the District of Columbia also have passed various types of Good Samaritan laws that encourage individuals witnessing or experiencing an overdose to call 911 or seek emergency medical assistance by protecting help-seeking individuals from prosecution for minor drug-related crimes.

---

## **Tobacco-Related Disorders**

---

According to the 2014 National Survey on Drug Use and Health, 66.9 million people, or 25% of the population ages 12 years and older, were current users of a tobacco product, with 21% being current cigarette smokers ([Center for Behavioral Health Statistics and Quality 2015](#)). Approximately 4.5% were current cigar smokers, 1% were current pipe tobacco smokers, and 3% used smokeless tobacco. Few tobacco users are successful in permanently quitting in their initial attempt. Most tobacco users consume tobacco for many years and cycle through periods

of abstinence and relapse. Failure to grasp the chronic nature of tobacco use disorders can lead to discouragement in health care providers and impede the treatment of tobacco use over time. According to data from the 2001–2010 National Health Interview Surveys, in 2010 more than 70% of U.S. smokers reported that they wanted to quit, and 52% reported having tried to quit in the past year ([Centers for Disease Control and Prevention 2011](#)). Unfortunately, most of these quit attempts are unaided, and most smokers return to regular smoking within a few weeks ([Ward et al. 1997](#)).

## Counseling Strategies

Behavioral strategies, including in-person counseling, telephone quitlines, and self-help materials, provide a small but important effect in achieving smoking cessation. Telephone counseling is readily available in the United States through the publicly funded quitline 1-800-QUIT-NOW (1-800-784-8669). A pooled estimate of 47 trials indicated that increasing the amount of behavioral support increased the chance of successful smoking cessation by 10%–25% ([Stead et al. 2015](#)).

## Pharmacotherapy

Current practice guidelines recommend the use of an effective medication at every quit attempt unless medically contraindicated or within special populations, such as pregnant women and adolescents, for which there is limited evidence of effectiveness ([Fiore et al. 2008](#)). Seven first-line medications are safe, effective, and FDA approved for

smoking cessation; these include nicotine replacement therapies (NRTs; patch, gum, lozenge, nasal spray, inhaler), bupropion sustained release (SR), and varenicline. Generally, cessation medications double the quit rate relative to placebo (20% vs. 10%; [Cahill et al. 2013](#)).

## **Nicotine Replacement Therapies**

NRTs partially replace the nicotine obtained from cigarettes and are intended to aid in quitting by reducing the severity of nicotine withdrawal. A recent Cochrane review ([Stead et al. 2012](#)) of 150 studies found that NRT increased cessation rates to 17%, compared with 10% with placebo (number needed to treat [NNT]=15). Nicotine patches, gum, and lozenges are available over the counter. The nicotine inhaler and nasal spray are prescription medications. Nicotine from the gum and lozenge is absorbed through the buccal mucosa. Nicotine from the inhaler and nasal spray is absorbed through the oropharynx and nasal mucosa, respectively. The nicotine patch, which is designed for skin absorption, has the advantage of once-a-day application and as result has higher adherence rates.

The nicotine gum is available in 2- and 4-mg doses, with the 4-mg nicotine gum recommended for individuals who smoke 25 or more cigarettes a day. Smokers should be instructed to use one piece of gum every 1-2 hours (maximum of 24 pieces per day) for the first weeks and to taper the frequency over the next 6 weeks. The gum should be slowly chewed until a “peppery” taste emerges, and then “parked” between the cheek and the gum to facilitate absorption. The gum should be intermittently slowly chewed and parked until the taste dissipates, typically in about 30 minutes. Common side effects include hiccups, dyspepsia, and jaw discomfort.



The lozenge is available in 2- and 4-mg doses, with the 4-mg dose recommended for individuals who smoke their first cigarette within 30 minutes of awakening. In general, at least 9 lozenges per day should be used for the first 6 weeks, with a maximum of 20 lozenges per day. Common adverse effects include hiccups, nausea, and heartburn.

The patch has the advantage of daily dosing, thus enhancing compliance. For patients who smoke more than 10 cigarettes a day, a standard course would include 21 mg for 6 weeks followed by 14 mg for 2 weeks and then 7 mg for 2 weeks. About 50% of patients will experience a mild local skin reaction ([Fiore et al. 2008](#)), which requires discontinuation in about 5% of patients. Rotating the site on a daily basis can help prevent skin reactions. Insomnia and vivid dreams also may occur; removing the patch before bedtime can reduce the disruption in sleep.

The nicotine inhaler delivers 4 mg of nicotine over 80 inhalations. Recommended dosing is 6-16 cartridges a day for 3 months, followed by tapering over the subsequent 3 months. Coughing and rhinitis are common side effects. Exacerbation of reactive airway disease can occur.

The nicotine nasal spray produces the highest nicotine level compared with other forms of NRT. The initial dose is 0.5 mg to each nostril (total 1 mg) per hour as needed, with a minimum of 8 doses and a maximum of 40 doses per day. The recommended duration of therapy is 3-6 months. Most patients experience varying degrees of nasal irritation. Other common side effects include transient changes in taste and smell. Severe reactive airway disease is a contraindication.

Of note, the use of NRT is not an independent risk factor for an acute myocardial infarction. However, NRT should be used with caution in patients who have unstable angina

pectoris or severe arrhythmias and who have experienced a myocardial infarction within the past 2 weeks. Some smokers may benefit from a longer course of NRT treatment. [Schnoll et al. \(2015\)](#) compared 8 weeks (standard), 24 weeks (extended), and 52 weeks (maintenance) of nicotine patch treatment in combination with 12 weeks of smoking cessation counseling. At 6 months, 22% of the participants in the standard treatment group were abstinent, compared with 27% in the extended and maintenance groups.

## **Bupropion SR**

In the late 1990s, the SR formulation of bupropion was approved by the FDA for smoking cessation and marketed under the trade name Zyban. Bupropion SR is an antidepressant with noradrenergic and dopaminergic effects and antagonist action at the nicotinic acetylcholine receptor. In a recent systematic review ([Hughes et al. 2014](#)), bupropion was associated with a significantly higher rate of smoking abstinence at 6 months compared with placebo (19.7% vs. 11.5%). Bupropion may work by blocking nicotine effects, relieving withdrawal, or decreasing depressed mood. A standard bupropion SR course begins with one 150-mg tablet taken by mouth once a day for 3 days, at which point the dosage is increased to one tablet taken by mouth twice a day (separated by at least 8 hours) for 7–12 weeks. The tobacco quit date is 1 week after starting medication. If the treatment is successful, some patients benefit from continued treatment for up to 6 months to prevent relapse.

Bupropion SR is generally well tolerated. Bupropion reduces seizure threshold, and seizures are estimated to occur in 1 out of 1,000 treated patients ([Hughes et al.](#)

2014). Contraindications include seizure disorders, eating disorders, and monoamine oxidase inhibitor use within 14 days.

## Varenicline

Varenicline is a partial agonist at the  $\alpha_4\beta_2$  nicotinic receptor that relieves symptoms of nicotine withdrawal and blocks nicotine from attaching to the receptor, thus reducing the rewarding properties of smoking (Coe et al. 2005). Numerous controlled studies support the efficacy of varenicline for smoking cessation. Two early studies that included more than 2,000 participants (Gonzales et al. 2006; Jorenby et al. 2006) were 12-week RCTs comparing varenicline, bupropion, and placebo. Rates of continuous abstinence for the last month of the treatment phase were 44% for varenicline, 30% for bupropion, and 18% for placebo. Continuous abstinence rates for 1 year for varenicline, bupropion, and placebo were 23%, 14.6%, and 10.3%, respectively, in one study (Jorenby et al. 2006). A standard course is typically 0.5 mg every day for 3 days, then 0.5 mg twice a day for 4 days, and then 1 mg twice a day with food. The target quit date is 1 week after starting varenicline. If clinically warranted, the initial total 12-week course can be continued for an additional 12 weeks if initial treatment is successful.

## Black Box Warnings

In 2009, a black box warning was added to the packaging information for both varenicline and bupropion after an FDA review of postmarketing data concluded that these medications could potentially increase the risk of depression, suicidality, agitation, worsening of preexisting

psychiatric illnesses, and changes in behavior in treated individuals ([U.S. Food and Drug Administration 2009](#)). These warnings call for close monitoring for symptoms or changes in behavior. A 2015 meta-analysis of 39 RCTs with almost 11,000 participants found no evidence of an increased risk of suicide, suicide attempts, suicidal thoughts, depression, aggression, or death in participants taking varenicline compared with placebo ([Thomas et al. 2015](#)), confirming results of an earlier meta-analysis by [Gibbons and Mann \(2013\)](#) that included 17 RCTs conducted by Pfizer and a large data set from the U.S. Department of Defense.

## Combination Therapies

Previous research has indicated that combination NRT—patch and lozenge—increased quit rates compared with either placebo or monotherapy ([Piper et al. 2009](#)).

Varenicline combined with bupropion has been investigated in several RCTs. Of the prospective trials, one showed a greater 4-week smoking abstinence for weeks 8–11 with combination therapy (39.8%) than with monotherapy (25.9%) (odds ratio [OR]=1.89; 95% confidence interval [CI]=1.07–3.35). [Ebbert et al. \(2014\)](#) found greater prolonged abstinence (53% vs. 43% at 12 weeks and 37% vs. 28% at 26 weeks) in the combination group compared with varenicline plus placebo, although results were not significant at 52 weeks. In a study by [Rose and Behm \(2014\)](#), smokers who used the nicotine patch and did not reduce smoking were randomly assigned to 12 weeks of varenicline and bupropion SR or varenicline plus placebo. Participants receiving the combination had significantly higher abstinence rates compared with the varenicline plus placebo group (40% vs. 26%). The

combination treatment was significantly more effective in males and highly dependent smokers ([Rose and Behm 2014](#)).

## **Second-Line Medications**

Second-line medications should be considered on a case-by-case basis if first-line medications (alone or in combination) are ineffective or contraindicated. Several medications are effective but have a more limited role because of potential side effects and lack of FDA approval for smoking cessation. Medications in this category include clonidine and nortriptyline ([Fiore et al. 2008](#)).

## **Special Populations**

### **Women Who Are Pregnant or Who Are Trying to Conceive**

The harmful effects of smoking during pregnancy are well known and include small-for-gestational-age neonates, stillbirth, preterm birth, and placenta previa ([Jauniaux and Burton 2007](#)). Current guidelines recommend the use of in-person psychosocial strategies that exceed minimal advice to quit smoking. Although quitting smoking during the first trimester will produce the greatest benefit, quitting at any time can be beneficial. In a recent meta-analysis that excluded potentially biased, non-placebo-controlled RCTs, NRT was no more effective than placebo ([Coleman et al. 2015](#)). Evidence is insufficient to recommend the use of bupropion or varenicline during pregnancy.

### **Children and Adolescents**

Tobacco use is typically initiated and established during adolescence ([U.S. Department of Health and Human Services 2012](#)). In the 2014 National Youth Tobacco Survey, about 25% of high school students reported current use of a tobacco product, and 13% reported use of two or more tobacco products ([Rudd et al. 2016](#)). E-cigarettes (13%) were the most commonly used tobacco product. Current treatment guidelines recommend that clinicians assess for tobacco use and strongly recommend abstinence in children and adolescents. Psychosocial interventions, especially those that contain cognitive-behavioral components, have been found to be efficacious in the short term for the treatment of adolescent smokers ([Simon et al. 2015](#)). Contingency management and motivational interviewing have shown some effectiveness as stand-alone treatments, and strategies that include elements of the transtheoretical model of change also have shown promise.

## **Individuals With Comorbid Psychiatric Disorders**

Despite the significant decline in smoking rates in the general population, comparable declines in smoking rates among smokers with psychiatric disorders have not been realized. According to combined data from the 2009-2011 National Survey on Drug Use and Health, approximately 20% of adults had some form of a mental illness in the past year, of whom 36% were current smokers, compared with 21% of adults with no mental illness ([Centers for Disease Control and Prevention 2013](#)). In a recent study examining prevalence of cigarette smoking among adults with and without psychiatric disorders, 64% of participants with schizophrenia and 44% of those with bipolar disorder

reported that they smoked regularly, compared with 19% of control participants without psychiatric illness ([Dickerson et al. 2013](#)). Unfortunately, individuals with mental illnesses are frequently excluded from clinical studies focused on the treatment of nicotine dependence, and smoking cessation therapies are not routinely offered to patients with severe mental illness. Mental health professionals commonly have permissive attitudes toward smoking and mistakenly assume that patients with comorbid psychiatric and substance use disorders are not interested in quitting ([Sheals et al. 2016](#)). These attitudes and misconceptions undermine the provision of smoking cessation interventions in these populations.

Evidence shows that smoking cessation therapies are both effective and well tolerated in populations with severe mental illness. In a recently completed meta-analysis, [Roberts et al. \(2016\)](#) examined RCTs in which NRT, bupropion, or varenicline (as monotherapy or in combination) was compared with placebo or another FDA-approved medication in motivated smokers with severe mental illness (including bipolar disorder, depressive psychoses, delusional disorder, schizophrenia, and schizoaffective disorder). Bupropion and varenicline were both found to be more efficacious than placebo (ORs=4.51 and 5.17, respectively). A significant difference was not detected between bupropion plus NRT and placebo plus NRT. Both bupropion and varenicline were well tolerated, with no significant differences in dropouts resulting from adverse events, including change in mental status and suicidal ideation. Clinical practice guidelines recommend a treatment duration of 12 weeks, but more recent evidence indicates that maintenance pharmacotherapy for 1 year

may improve sustained abstinence rates in individuals with schizophrenia spectrum disorders ([Evins and Cather 2015](#)).

Both NRT and bupropion have been found to be efficacious in patients with current or past depression ([Gierisch et al. 2012](#)). Varenicline has been found to be effective in patients with stably treated depression or past depression without causing an exacerbation in symptoms ([Anthenelli et al. 2013](#)).

Admission to a smoke-free psychiatric hospital is a natural opportunity to provide smoking cessation treatment. Daily smokers with and without an intention to quit were recruited from several locked psychiatric units and randomly assigned to interventions that included tailored counseling with an emphasis on readiness to quit and NRT availability after discharge ([Schuck et al. 2016](#)). An impressive 76% of eligible smokers enrolled, of whom 88% requested study-provided NRT. Those with more severe psychiatric symptoms were more likely to request NRT posthospitalization ( $P<0.01$ ). Participants who requested NRT at discharge were more likely to make a 24-hour quit attempt and to self-report abstinence at the 1-week follow-up (54% quit attempt, 14% abstinent) compared with participants who did not request NRT at discharge (25% quit attempt, 4% abstinent) ( $P<0.05$ ).

## **Individuals With Comorbid Substance Use Disorders**

Individuals who are receiving treatment for a substance use disorder have smoking rates two to four times higher than those in the general population ([Guydish et al. 2016](#)) and are more likely to die from smoking-related illnesses than from complications from drug use ([Baca and Yahne 2009](#)).



However, many individuals receiving substance use disorder treatment continue to smoke despite achieving abstinence from alcohol and drugs ([McClure et al. 2015](#)). Current treatment guidelines recommend that patients with substance use disorders should be offered smoking cessation treatment ([Fiore et al. 2008](#)). It has been suggested that varenicline may be the most effective treatment for alcohol use disorders and comorbid alcohol and tobacco use disorders because alcohol produces activation in the mesolimbic pathway through its effects on nicotinic acetylcholine receptors ([Söderpalm et al. 2000](#)). Varenicline has been reported to decrease alcohol craving and consumption in smoking cessation trials ([Fucito et al. 2011](#); [Mitchell et al. 2012](#)).

In a recent review of smoking cessation interventions during substance use disorder treatment, a variety of pharmacotherapy and behavioral treatment options significantly improved smoking outcomes ([Thurgood et al. 2015](#)). Opioid-dependent smokers may present a particular challenge. Smoking prevalence rates among opioid-dependent individuals are fourfold higher than in the general population, and current pharmacotherapy outcomes have been disappointing and typically worse than those seen in the general population of smokers ([Miller and Sigmon 2015](#)). Clearly, additional research to understand the relation between tobacco and substance use disorders is warranted, given that smoking cessation has the potential to improve the morbidity and mortality associated with these common disorders.

---

## Stimulant-Related Disorders

---

The search for a pharmacotherapeutic treatment for cocaine and amphetamine use disorders has been extremely active over the last 20 years, with controlled trials of antidepressants, anticonvulsants, dopamine agonists and antagonists, and many other agents. Unfortunately, many medications that show promise in animal models of stimulant dependence and/or positive outcomes in small uncontrolled trials fail to decrease drug use by objective measures in larger controlled trials. In addition, many clinical trials in stimulant-dependent individuals are flawed by high dropout rates and medication noncompliance. To date, no medications have clearly shown efficacy in the treatment of cocaine or amphetamine dependence; however, the medications discussed in this section have shown promise, often in subgroups of individuals studied.

## Agonist Replacement Strategies

The focus of numerous studies has been agonist replacement in which a pharmacologically similar agent is substituted for the stimulant of abuse. As discussed in other sections of this chapter, agonist replacement therapies are effective in both nicotine and opioid dependence. An ideal agonist replacement therapy for stimulant dependence should share some pharmacological and behavioral effects with cocaine or amphetamine but have less abuse potential. Unfortunately, many of the agents that have shown promise do not meet these criteria.

Methylphenidate, a piperidine derivative that produces effects similar to those of cocaine at the dopamine transporter and is approved for the treatment of attention-

deficit/hyperactivity disorder (ADHD), has been tested in cocaine- and amphetamine-dependent individuals with and without ADHD. Although the results of methylphenidate treatment in individuals with cocaine and amphetamine dependence generally have been negative ([Stoops and Rush 2013](#)), findings have been mixed in individuals with ADHD, with positive results seen in cocaine- and amphetamine-dependent individuals taking 60 mg/day ([Konstenius et al. 2010](#); [Levin et al. 2007](#)) and negative results seen in cocaine-dependent individuals taking 80–90 mg/day ([Levin et al. 2006](#); [Schubiner et al. 2002](#)).

Several trials have indicated that D-amphetamine and methamphetamine can decrease cocaine use in cocaine-dependent individuals ([Grabowski et al. 2001, 2004](#); [Mooney et al. 2009](#); [Shearer et al. 2003](#)). However, trials of D-amphetamine in amphetamine dependence have been negative ([Galloway et al. 2011](#); [Longo et al. 2010](#)).

These studies suggest that stimulant replacement warrants further investigation, but it must be noted that the abuse and diversion potential of methylphenidate and amphetamines limits the potential widespread utility of this approach ([Stoops et al. 2004](#)).

## Other Pharmacotherapeutic Agents

### **Bupropion**

Bupropion, an antidepressant with dopaminergic activity, has been tested in multiple clinical trials in both cocaine and methamphetamine dependence. The results were largely mixed, but bupropion appears to have some efficacy when combined with consistent behavioral treatment in

cocaine dependence ([Poling et al. 2006](#)) and in methamphetamine-dependent users who had lighter use ([Elkashef et al. 2008](#); [Shoptaw et al. 2008](#)).

## **Disulfiram**

In addition to its effects on alcohol metabolism, disulfiram blocks the enzymatic degradation of both cocaine and dopamine. Investigators have hypothesized that increased dopamine levels may help improve hedonic tone (i.e., sense of well-being, pleasure, or contentment) in cocaine-dependent individuals, and the increased cocaine levels have been shown to increase cocaine-related anxiety and dysphoria in individuals pretreated with disulfiram ([Hameedi et al. 1995](#)). Regardless of the mechanism, four clinical trials to date have reported that disulfiram reduces cocaine use in cocaine-dependent patients ([Carroll et al. 2004](#); [George et al. 2000](#)). Given these results, disulfiram definitely should be considered in the treatment of cocaine dependence as long as the individual is willing to remain alcohol-free and understands the potential for increased toxicity with cocaine use.

## **Modafinil**

Modafinil, a novel stimulant and glutamatergic agent that is FDA approved for narcolepsy, has been tested in both cocaine and amphetamine dependence. Although initial trials were positive ([Dackis et al. 2005](#)), subsequent trials found that efficacy was limited to individuals who did not have a history of alcohol dependence and to men ([Anderson et al. 2009](#); [Dackis et al. 2012](#)). Trials of modafinil are ongoing, but the medication is well tolerated and may be useful in reducing cocaine withdrawal symptoms and

helping some individuals attain abstinence ([Malcolm et al. 2002](#)).

## Topiramate

There have also been several promising studies with topiramate, an anticonvulsant agent that has shown promise in alcohol dependence (see “Topiramate” subsection earlier in this chapter). In one placebo-controlled trial of cocaine dependence, topiramate-treated subjects were more likely than placebo-treated subjects to achieve 3 weeks of continuous abstinence and to be rated as clinically improved ([Kampman et al. 2004](#)).

## GABAergic and Glutamatergic Modulators

Several other promising agents that modulate GABAergic and glutamatergic systems are under investigation for the treatment of stimulant use disorders. Both vigabatrin and *N*-acetylcysteine had strong effects in animal models of cocaine dependence but showed less promise in clinical trials.

Vigabatrin ( $\gamma$ -vinyl-GABA), an anticonvulsant that increases GABA neurotransmission by inhibiting GABA transaminase, showed promise in several open-label trials of both cocaine and methamphetamine dependence. One placebo-controlled trial reported higher rates of abstinence (as assessed by both self-report and urine drug screening) in the vigabatrin-treated group with cocaine dependence ([Brodie et al. 2009](#)), whereas a multisite trial ([Somoza et al. 2013](#)) found no difference in any outcomes in cocaine-

dependent individuals taking vigabatrin compared with placebo. However, compliance with vigabatrin was low in this trial, calling the negative results into question.

*N*-acetylcysteine is a glutamatergic agent that also has shown consistent effects in animal models of cocaine dependence ([Baker et al. 2003](#)). Although an initial pilot study with a crossover design showed promise in cocaine dependence ([LaRowe et al. 2006](#)), a follow-up double-blind, placebo-controlled trial ([LaRowe et al. 2013](#)) found no difference between two doses of *N*-acetylcysteine and placebo in any outcome measures. However, a reduction in cocaine-positive urine drug screens was seen in a small subset of individuals who were abstinent at initiation of study drug, suggesting that *N*-acetylcysteine may be more efficacious in relapse prevention than in initiating abstinence. Further studies are required to assess this possibility.

---

## Conclusion

---

Effective pharmacological treatments are available for alcohol, opioid, and tobacco use disorders, but studies suggest that these treatments are underused. The search for a medication treatment for stimulant use disorders remains an active area of research, with a wide range of agents being tested across hundreds of clinical trials. Given the devastating personal and societal effects of substance-related disorders, pharmacotherapy should be considered when appropriate as part of a comprehensive treatment plan.

---

# References

---

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- Anderson AL, Reid MS, Li SH, et al: Modafinil for the treatment of cocaine dependence. *Drug Alcohol Depend* 104(1-2): 133-139, 2009 19560290
- Anthenelli RM, Morris C, Ramey TS, et al: Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. *Ann Intern Med* 159(6):390-400, 2013 24042367
- Anton RF, Moak DH, Latham PK, et al: Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. *J Clin Psychopharmacol* 21(1):72-77, 2001 11199951
- Anton RF, Pettinati H, Zweben A, et al: A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* 24(4):421-428, 2004 15232334
- Anton RF, O'Malley SS, Ciraulo DA, et al; COMBINE Study Research Group: Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA* 295(17):2003-2017, 2006 16670409
- Anton RF, Oroszi G, O'Malley S, et al: An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. *Arch Gen Psychiatry* 65(2):135-144, 2008 18250251
- Baca CT, Yahne CE: Smoking cessation during substance abuse treatment: what you need to know. *J Subst Abuse Treat* 36(2):205-219, 2009 18715746

- Baker DA, McFarland K, Lake RW, et al: N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. *Ann N Y Acad Sci* 1003:349–351, 2003 14684458
- Baltieri DA, Daró FR, Ribeiro PL, et al: Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction* 103(12):2035–2044, 2008 18855810
- Brodie JD, Case BG, Figueroa E, et al: Randomized, double-blind, placebo-controlled trial of vigabatrin for the treatment of cocaine dependence in Mexican parolees. *Am J Psychiatry* 166(11):1269–1277, 2009 19651710
- Brooner RK, Kidorf MS, King VL, et al: Comparing adaptive stepped care and monetary-based voucher interventions for opioid dependence. *Drug Alcohol Depend* 88 (suppl 2):S14–S23, 2007 17257782
- Brunton L, Chabner B, Knollman B (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 12th Edition. New York, McGraw-Hill, 2011
- Cahill K, Stevens S, Perera R, et al: Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* (5):CD009329, 2013 23728690
- Carroll KM, Fenton LR, Ball SA, et al: Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 61(3):264–272, 2004 14993114
- Center for Behavioral Health Statistics and Quality: Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health (HHS Publ No SMA 15-4927, NSDUH Series H-50). September 2015. Available at: <http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf>. Accessed May 17, 2016.
- Center for Substance Abuse Treatment: Medication-Assisted Treatment for Opioid Addiction in Opioid



Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD, Substance Abuse and Mental Health Services Administration, 2005. Available at: <http://store.samhsa.gov/shin/content//SMA12-4214/SMA12-4214.pdf>.

Center for Substance Abuse Treatment: Incorporating Alcohol Pharmacotherapies Into Medical Practice: Treatment Improvement Protocol (TIP) Series, No 49 (HHS Publ No SMA 12-4389). Rockville, MD, Substance Abuse and Mental Health Services Administration, 2009

Centers for Disease Control and Prevention (CDC): Quitting smoking among adults—United States, 2001–2010. MMWR Morb Mortal Wkly Rep 60(44):1513–1519, 2011 22071589

Centers for Disease Control and Prevention (CDC): Vital signs: current cigarette smoking among adults aged  $\geq 18$  years with mental illness—United States, 2009–2011. MMWR Morb Mortal Wkly Rep 62(5):81–87, 2013 23388551

Cleary BJ, Donnelly J, Strawbridge J, et al: Methadone dose and neonatal abstinence syndrome-systematic review and meta-analysis. Addiction 105(12):2071–2084, 2010 20840198

Coe JW, Brooks PR, Vetelino MG, et al: Varenicline: an  $\alpha 4 \beta 2$  nicotinic receptor partial agonist for smoking cessation. J Med Chem 48(10):3474–3477, 2005 15887955

Coleman T, Chamberlain C, Davey MA, et al: Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev (12): CD010078, 2015 26690977

Dackis CA, Kampman KM, Lynch KG, et al: A double-blind, placebo-controlled trial of modafinil for cocaine dependence. Neuropsychopharmacology 30(1):205–211, 2005 15525998

- Dackis CA, Kampman KM, Lynch KG, et al: A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *J Subst Abuse Treat* 43(3):303-312, 2012 22377391
- Daepfen JB, Gache P, Landry U, et al: Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. *Arch Intern Med* 162(10):1117-1121, 2002 12020181
- De Sousa A, De Sousa A: A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. *Alcohol Alcohol* 39(6):528-531, 2004 15525790
- De Sousa A, De Sousa A: An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. *Alcohol Alcohol* 40(6):545-548, 2005 16043433
- De Sousa AA, De Sousa J, Kapoor H: An open randomized trial comparing disulfiram and topiramate in the treatment of alcohol dependence. *J Subst Abuse Treat* 34(4):460-463, 2008 17629442
- Dickerson F, Stallings CR, Origoni AE, et al: Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999-2011. *Psychiatr Serv* 64(1):44-50, 2013 23280457
- Dunn KE, Sigmon SC, Strain EC, et al: The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. *Drug Alcohol Depend* 119(1-2):1-9, 2011 21741781
- Dutra L, Stathopoulou G, Basden SL, et al: A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry* 165(2):179-187, 2008 18198270
- Ebbert JO, Hatsukami DK, Croghan IT, et al: Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA* 311(2):155-163, 2014 24399554

- Elkashef AM, Rawson RA, Anderson AL, et al: Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology* 33(5):1162-1170, 2008 17581531
- Evins AE, Cather C: Effective cessation strategies for smokers with schizophrenia. *Int Rev Neurobiol* 124:133-147, 2015 26472528
- Faggiano F, Vigna-Taglianti F, Versino E, et al: Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev* (3):CD002208, 2003 12917925
- Fiore MC, Jaen CR, Baker TB: Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update. May 2008. Available at: [http://www.aafp.org/dam/AAFP/documents/patient\\_care/clinical\\_recommendations/TreatingTobaccoUseandDependence-2008Update.pdf](http://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/TreatingTobaccoUseandDependence-2008Update.pdf). Accessed May 17, 2016.
- Flórez G, Saiz PA, García-Portilla P, et al: Topiramate for the treatment of alcohol dependence: comparison with naltrexone. *Eur Addict Res* 17(1):29-36, 2011 20975274
- Fucito LM, Toll BA, Wu R, et al: A preliminary investigation of varenicline for heavy drinking smokers. *Psychopharmacology (Berl)* 215(4):655-663, 2011 21221531
- Fudala PJ, Bridge TP, Herbert S, et al; Buprenorphine/Naloxone Collaborative Study Group: Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 349(10):949-958, 2003 12954743
- Fuller RK, Gordis E: Does disulfiram have a role in alcoholism treatment today? *Addiction* 99(1):21-24, 2004 14678055
- Fuller RK, Branchey L, Brightwell DR, et al: Disulfiram treatment of alcoholism: a Veterans Administration

- cooperative study. JAMA 256(11):1449-1455, 1986 3528541
- Fullerton CA, Kim M, Thomas CP, et al: Medication-assisted treatment with methadone: assessing the evidence. Psychiatr Serv 65(2):146-157, 2014 24248468
- Galloway GP, Buscemi R, Coyle JR, et al: A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. Clin Pharmacol Ther 89(2):276-282, 2011 21178989
- Garbutt JC, Kranzler HR, O'Malley SS, et al; Vivitrex Study Group: Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA 293(13):1617-1625, 2005 15811981
- Gastfriend D, Earley PH, Silverman B, Memisoglu A: Open-label 24-month study of injectable extended-release naltrexone (XR-NTX) in healthcare professionals with opioid dependence. Drug Alcohol Depend 140(1):e67-e68, 2014
- Gelernter J, Gueorguieva R, Kranzler HR, et al; VA Cooperative Study #425 Study Group: Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. Alcohol Clin Exp Res 31(4):555-563, 2007 17374034
- George TP, Chawarski MC, Pakes J, et al: Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. Biol Psychiatry 47(12):1080-1086, 2000 10862808
- Gibbons RD, Mann JJ: Varenicline, smoking cessation, and neuropsychiatric adverse events. Am J Psychiatry 170(12):1460-1467, 2013 24030388
- Gierisch JM, Bastian LA, Calhoun PS, et al: Smoking cessation interventions for patients with depression: a

- systematic review and meta-analysis. *J Gen Intern Med* 27(3):351-360, 2012 22038468
- Gold MS, Redmond DE Jr, Kleber HD: Clonidine blocks acute opiate-withdrawal symptoms. *Lancet* 2(8090):599-602, 1978 80526
- Gold MS, Pottash AL, Sweeney DR, et al: Efficacy of clonidine in opiate withdrawal: a study of thirty patients. *Drug Alcohol Depend* 6(4):201-208, 1980 7023893
- Gonzales D, Rennard SI, Nides M, et al; Varenicline Phase 3 Study Group: Varenicline, an  $\alpha_4\beta_2$  nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 296(1):47-55, 2006 16820546
- Gordon MS, Kinlock TW, Vocci FJ, et al: A phase 4, pilot, open-label study of VIVITROL® (Extended-Release Naltrexone XR-NTX) for prisoners. *J Subst Abuse Treat* 59:52-58, 2015 26299956
- Gowing L, Farrell M, Ali R, White J: Alpha2 adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev* (2):CD002024, 2003 12804419
- Grabowski J, Rhoades H, Schmitz J, et al: Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J Clin Psychopharmacol* 21(5):522-526, 2001 11593078
- Grabowski J, Rhoades H, Stotts A, et al: Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: two double-blind randomized clinical trials. *Neuropsychopharmacology* 29(5):969-981, 2004 15039761
- Gual A, He Y, Torup L, et al; ESENSE 2 Study Group: A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *Eur Neuropsychopharmacol* 23(11):1432-1442, 2013 23562264

- Gunne LM, Grönbladh L: The Swedish methadone maintenance program: a controlled study. *Drug Alcohol Depend* 7(3):249–256, 1981 7261900
- Guydish J, Passalacqua E, Pagano A, et al: An international systematic review of smoking prevalence in addiction treatment. *Addiction* 111(2):220–230, 2016 26392127
- Hameedi FA, Rosen MI, McCance-Katz EF, et al: Behavioral, physiological, and pharmacological interaction of cocaine and disulfiram in humans. *Biol Psychiatry* 37(8):560–563, 1995 7619981
- Hammond CJ, Niciu MJ, Drew S, et al: Anticonvulsants for the treatment of alcohol withdrawal syndrome and alcohol use disorders. *CNS Drugs* 29(4):293–311, 2015 25895020
- Harris AH, Oliva E, Bowe T, et al: Pharmacotherapy of alcohol use disorders by the Veterans Health Administration: patterns of receipt and persistence. *Psychiatr Serv* 63(7):679–685, 2012 22549276
- Hughes JR, Stead LF, Hartmann-Boyce J, et al: Antidepressants for smoking cessation. *Cochrane Database Syst Rev* (1): CD000031, 2014 24402784
- Hulse GK, English DR, Milne E, et al: The quantification of mortality resulting from the regular use of illicit opiates. *Addiction* 94(2):221–229, 1999 10396790
- Jauniaux E, Burton GJ: Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. *Early Hum Dev* 83(11):699–706, 2007 17900829
- Johnson BA: Update on neuropharmacological treatments for alcoholism: scientific basis and clinical findings. *Biochem Pharmacol* 75(1):34–56, 2008 17880925
- Johnson BA, Roache JD, Javors MA, et al: Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. *JAMA* 284(8):963–971, 2000 10944641

- Johnson BA, Ait-Daoud N, Bowden CL, et al: Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 361(9370):1677-1685, 2003 12767733
- Johnson BA, Rosenthal N, Capece JA, et al; Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group: Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 298(14):1641-1651, 2007 17925516
- Johnson RE, Jaffe JH, Fudala PJ: A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 267(20):2750-2755, 1992 1578593
- Jones HE, O'Grady KE, Malfi D, et al: Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. *Am J Addict* 17(5):372-386, 2008 18770079
- Jones HE, Heil SH, Baewert A, et al: Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. *Addiction* 107 (suppl 1):5-27, 2012 23106923
- Jorenby DE, Hays JT, Rigotti NA, et al; Varenicline Phase 3 Study Group: Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 296(1):56-63, 2006 16820547
- Kaltenbach K, Finnegan LP: Developmental outcome of children born to methadone maintained women: a review of longitudinal studies. *Neurobehav Toxicol Teratol* 6(4):271-275, 1984 6392916
- Kaltenbach K, Berghella V, Finnegan L: Opioid dependence during pregnancy: effects and management. *Obstet Gynecol Clin North Am* 25(1):139-151, 1998 9547764
- Kampman KM, Pettinati H, Lynch KG, et al: A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend* 75(3):233-240, 2004 15283944

- Kiefer F, Witt SH, Frank J, et al: Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk and treatment response to acamprosate. *Pharmacogenomics J* 11(5):368–374, 2011 20585342
- King AC, Schluger J, Gunduz M, et al: Hypothalamic-pituitary-adrenocortical (HPA) axis response and biotransformation of oral naltrexone: preliminary examination of relationship to family history of alcoholism. *Neuropsychopharmacology* 26(6):778–788, 2002 12007748
- Kinlock TW, Gordon MS, Schwartz RP, et al: A randomized clinical trial of methadone maintenance for prisoners: results at 1-month post-release. *Drug Alcohol Depend* 91(2-3):220–227, 2007 17628351
- Konstenius M, Jayaram-Lindström N, Beck O, et al: Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: a pilot study. *Drug Alcohol Depend* 108(1-2):130–133, 2010 20015599
- Kosten TR, O'Connor PG: Management of drug and alcohol withdrawal. *N Engl J Med* 348(18):1786–1795, 2003 12724485
- Kowalczyk WJ, Phillips KA, Jobes ML, et al: Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessment. *Am J Psychiatry* 172(8):760–767, 2015 25783757
- Krupitsky E, Nunes EV, Ling W, et al: Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 377(9776):1506–1513, 2011 21529928
- Krupitsky E, Nunes EV, Ling W, et al: Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. *Addiction* 108(9):1628–1637, 2013 23701526



- Krystal JH, Cramer JA, Krol WF, et al; Veterans Affairs Naltrexone Cooperative Study 425 Group: Naltrexone in the treatment of alcohol dependence. *N Engl J Med* 345(24):1734-1739, 2001 11742047
- Laaksonen E, Koski-Jännes A, Salaspuro M, et al: A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. *Alcohol Alcohol* 43(1):53-61, 2008 17965444
- LaRowe SD, Mardikian P, Malcolm R, et al: Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. *Am J Addict* 15(1):105-110, 2006 16449100
- LaRowe SD, Kalivas PW, Nicholas JS, et al: A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. *Am J Addict* 22(5):443-452, 2013 23952889
- Levin FR, Evans SM, Brooks DJ, et al: Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. *Drug Alcohol Depend* 81(2):137-148, 2006 16102908
- Levin FR, Evans SM, Brooks DJ, et al: Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. *Drug Alcohol Depend* 87(1):20-29, 2007 16930863
- Ling W, Amass L, Shoptaw S, et al; Buprenorphine Study Protocol Group: A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction* 100(8):1090-1100, 2005 16042639
- Ling W, Casadonte P, Bigelow G, et al: Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. *JAMA* 304(14):1576-1583, 2010 20940383

- Longo M, Wickes W, Smout M, et al: Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. *Addiction* 105(1):146–154, 2010 19839966
- Malcolm R, Book SW, Moak D, et al: Clinical applications of modafinil in stimulant abusers: low abuse potential. *Am J Addict* 11(3):247–249, 2002 12202017
- Mann K, Bladström A, Torup L, et al: Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. *Biol Psychiatry* 73(8):706–713, 2013a 23237314
- Mann K, Lemenager T, Hoffmann S, et al: Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. *Addict Biol* 18(6):937–946, 2013b 23231446
- Martin WR, Jasinski DR: Physiological parameters of morphine dependence in man—tolerance, early abstinence, protracted abstinence. *J Psychiatr Res* 7(1):9–17, 1969 5352850
- Mason BJ, Heyser CJ: The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence. *Expert Opin Drug Saf* 9(1):177–188, 2010 20021295
- Mason BJ, Ritvo EC, Morgan RO, et al: A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp Res* 18(5):1162–1167, 1994 7847600
- Mason BJ, Salvato FR, Williams LD, et al: A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 56(8):719–724, 1999 10435606
- Mason BJ, Goodman AM, Chabac S, Leher P: Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial:

- the role of patient motivation. *J Psychiatr Res* 40(5):383-393, 2006 16546214
- Mattick RP, Breen C, Kimber J, et al: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* (3):CD002209, 2009 19588333
- Mattick RP, Breen C, Kimber J, et al: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* (2):CD002207, 2014 24500948
- Mayo-Smith MF; American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal: Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 278(2):144-151, 1997 9214531
- McClure EA, Campbell AN, Pavlicova M, et al: Cigarette smoking during substance use disorder treatment: secondary outcomes from a National Drug Abuse Treatment Clinical Trials Network study. *J Subst Abuse Treat* 53:39-46, 2015 25595301
- McLellan AT, Arndt IO, Metzger DS, et al: The effects of psychosocial services in substance abuse treatment. *JAMA* 269(15): 1953-1959, 1993 8385230
- Miller ME, Sigmon SC: Are pharmacotherapies ineffective in opioid-dependent smokers? Reflections on scientific literature and future directions. *Nicotine Tob Res* 17(8):955-959, 2015 26180219
- Minozzi S, Amato L, Vecchi S, et al: Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* (4):CD001333, 2011 21491383
- Mitchell JM, Teague CH, Kayser AS, et al: Varenicline decreases alcohol consumption in heavy-drinking smokers. *Psychopharmacology (Berl)* 223(3):299-306, 2012 22547331

- Monterosso JR, Flannery BA, Pettinati HM, et al: Predicting treatment response to naltrexone: the influence of craving and family history. *Am J Addict* 10(3):258-268, 2001 11579624
- Mooney ME, Herin DV, Schmitz JM, et al: Effects of oral methamphetamine on cocaine use: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend* 101(1-2):34-41, 2009 19058926
- Morley KC, Teesson M, Reid SC, et al: Naltrexone versus acamprosate in the treatment of alcohol dependence: a multi-centre, randomized, double-blind, placebo-controlled trial. *Addiction* 101(10):1451-1462, 2006 16968347
- National Conference of State Legislatures: Drug Overdose Immunity and Good Samaritan Laws. January 20, 2017. Available at: <http://www.ncsl.org/research/civil-and-criminal-justice/drug-overdose-immunity-good-samaritan-laws.aspx>. Accessed January 23, 2017.
- O'Malley SS, Jaffe AJ, Chang G, et al: Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Arch Gen Psychiatry* 49(11):881-887, 1992 1444726
- Ooteman W, Naassila M, Koeter MWJ, et al: Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using genetic indicators. *Addict Biol* 14(3):328-337, 2009 19523047
- Oslin DW, Berrettini W, Kranzler HR, et al: A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology* 28(8):1546-1552, 2003 12813472
- Piper ME, Smith SS, Schlam TR, et al: A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch Gen Psychiatry* 66(11):1253-1262, 2009 19884613
- Poling J, Oliveto A, Petry N, et al: Six-month trial of bupropion with contingency management for cocaine

- dependence in a methadone-maintained population. *Arch Gen Psychiatry* 63(2):219–228, 2006 16461866
- Project MATCH Research Group: Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. *J Stud Alcohol* 58(1): 7–29, 1997 8979210
- Roberts E, Eden Evins A, McNeill A, et al: Efficacy and tolerability of pharmacotherapy for smoking cessation in adults with serious mental illness: a systematic review and network meta-analysis. *Addiction* 111(4):599–612, 2016 26594837
- Rose JE, Behm FM: Combination treatment with varenicline and bupropion in an adaptive smoking cessation paradigm. *Am J Psychiatry* 171(11):1199–1205, 2014 24934962
- Rosenthal RN, Ling W, Casadonte P, et al: Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction* 108(12):2141–2149, 2013 23919595
- Rösner S, Hackl-Herrwerth A, Leucht S, et al: Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* (9):CD004332, 2010 20824837
- Rudd RA, Aleshire N, Zibbell JE, et al: Increases in drug and opioid overdose deaths—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep* 64(50–51):1378–1382, 2016 26720857
- Schmidt KJ, Doshi MR, Holzhausen JM, et al: A review of the treatment of severe alcohol withdrawal. *Ann Pharmacother* 50(5):389–401, 2016 26861990
- Schnoll RA, Goelz PM, Veluz-Wilkins A, et al: Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med* 175(4):504–511, 2015 25705872
- Schottenfeld RS, Chawarski MC, Mazlan M: Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind,

- placebo-controlled trial. *Lancet* 371(9631):2192-2200, 2008 18586174
- Schubiner H, Saules KK, Arfken CL, et al: Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. *Exp Clin Psychopharmacol* 10(3):286-294, 2002 12233989
- Schuck RK, Dahl A, Hall SM, et al: Smokers with serious mental illness and requests for nicotine replacement therapy post-hospitalisation. *Tob Control* 25(1):27-32, 2016 25209524
- Schuckit MA: Alcohol and alcoholism, in *Harrison's Principles of Internal Medicine*. Edited by Wilson JD, Braunwald E, Isselbacher KJ, et al. New York, McGraw-Hill, 1991, pp 2149-2151
- Schuckit MA: Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med* 371(22):2109-2113, 2014 25427113
- Sees KL, Delucchi KL, Masson C, et al: Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA* 283(10):1303-1310, 2000 10714729
- Sellers EM, Toneatto T, Romach MK, et al: Clinical efficacy of the 5-HT<sub>3</sub> antagonist ondansetron in alcohol abuse and dependence. *Alcohol Clin Exp Res* 18(4):879-885, 1994 7978099
- Sheals K, Tombor I, McNeill A, Shahab L: A mixed-method systematic review and meta-analysis of mental health professionals' attitudes toward smoking and smoking cessation amongst people with mental illnesses. *Addiction* 111(9):1536-1553, 2016 27003925
- Shearer J, Wodak A, van Beek I, et al: Pilot randomized double blind placebo-controlled study of dexamphetamine for cocaine dependence. *Addiction* 98(8):1137-1141, 2003 12873248

- Shoptaw S, Heinzerling KG, Rotheram-Fuller E, et al: Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug Alcohol Depend* 96(3):222-232, 2008 18468815
- Sigmon SC, Dunn KE, Saulsgiver K, et al: A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry* 70(12):1347-1354, 2013 24153411
- Simon P, Kong G, Cavallo DA, et al: Update of adolescent smoking cessation interventions: 2009-2014. *Curr Addict Rep* 2(1):15-23, 2015 26295017
- Skinner MD, Lahmek P, Pham H, et al: Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. *PLoS One* 9(2):e87366, 2014 24520330
- Söderpalm B, Ericson M, Olausson P, et al: Nicotinic mechanisms involved in the dopamine activating and reinforcing properties of ethanol. *Behav Brain Res* 113(1-2):85-96, 2000 10942035
- Somoza EC, Winship D, Gorodetzky CW, et al: A multisite, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of vigabatrin for treating cocaine dependence. *JAMA Psychiatry* 70(6):630-637, 2013 23575810
- Stahre M, Roeber J, Kanny D, et al: Contribution of excessive alcohol consumption to deaths and years of potential life lost in the United States. *Prev Chronic Dis* 11:E109, 2014 24967831
- Stead LF, Perera R, Bullen C, et al: Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* (11): CD000146, 2012 23152200
- Stead LF, Koilpillai P, Lancaster T: Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev* (10): CD009670, 2015 26457723
- Stoops WW, Rush CR: Agonist replacement for stimulant dependence: a review of clinical research. *Curr Pharm*

Des 19(40): 7026–7035, 2013 23574440

Stoops WW, Glaser PE, Fillmore MT, et al: Reinforcing, subject-rated, performance and physiological effects of methylphenidate and d-amphetamine in stimulant abusing humans. *J Psychopharmacol* 18(4):534–543, 2004 15582920

Substance Abuse and Mental Health Services Administration: An Introduction to Extended-Release Injectable Naltrexone for the Treatment of People With Opioid Dependence. 2012. Available at: <https://store.samhsa.gov/shin/content/SMA12-4682/SMA12-4682.pdf>. Accessed May 18, 2016.

Substance Abuse and Mental Health Services Administration: Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. September 2014. Available at: <http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf>. Accessed May 18, 2016.

Substance Abuse and Mental Health Services Administration and National Institute on Alcohol Abuse and Alcoholism: Medication for the Treatment of Alcohol Use Disorder: A Brief Guide (HHS Publ No SMA 15-4907). 2015. Available at: <http://store.samhsa.gov/shin/content/SMA15-4907/SMA15-4907.pdf>. Accessed May 18, 2016.

Sullivan JT, Sykora K, Schneiderman J, et al: Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict* 84(11):1353–1357, 1989 2597811

Thomas KH, Martin RM, Knipe DW, et al: Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. *BMJ* 350:h1109, 2015 25767129

Thurgood SL, McNeill A, Clark-Carter D, et al: A systematic review of smoking cessation interventions for adults in



- substance abuse treatment or recovery. *Nicotine Tob Res* 18(5):993–1001, 2015 26069036
- Ulrichsen J, Nielsen MK, Ulrichsen M: Disulfiram in severe alcoholism—an open controlled study. *Nord J Psychiatry* 64(6): 356–362, 2010 20297945
- U.S. Department of Health and Human Services: Preventing tobacco use among youth and young adults: a report of the Surgeon General. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012
- U.S. Department of Health and Human Services: The Health Consequence of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014
- U.S. Food and Drug Administration: Information for Healthcare Professionals: Varenicline (Marketed as Chantix) and Bupropion (Marketed as Zyban, Wellbutrin, and Generics). July 1, 2009. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169986.htm>. Accessed May 18, 2016.
- van den Brink W, Sørensen P, Torup L, et al; SENSE Study Group: Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: a 1-year, randomised controlled study. *J Psychopharmacol* 28(8):733–744, 2014 24671340
- Volpicelli JR, Alterman AI, Hayashida M, et al: Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 49(11):876–880, 1992 1345133

- Volpicelli JR, Rhines KC, Rhines JS, et al: Naltrexone and alcohol dependence: role of subject compliance. Arch Gen Psychiatry 54(8):737-742, 1997 9283509
- Ward KD, Klesges RC, Zbikowski SM, et al: Gender differences in the outcome of an unaided smoking cessation attempt. Addict Behav 22(4):521-533, 1997 9290861
- Weiss RD, Potter JS, Fiellin DA, et al: Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry 68(12):1238-1246, 2011 22065255
- Whittington RA, Collins ED, Kleber HD: Rapid opioid detoxification during general anesthesia: is death not a significant outcome? Anesthesiology 93(5):1363-1364, 2000 11046233
- Woody GE, Poole SA, Subramaniam G, et al: Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA 300(17):2003-2011, 2008 18984887

# CHAPTER 51

## Treatment of Personality Disorders

Marissa Miyazaki, M.D.

Daphne Simeon, M.D.

Eric Hollander, M.D.

**Personality disorders** are among the most challenging conditions faced by clinicians. The two main approaches to the treatment of personality disorders are psychosocial treatment and medications. Psychotherapy continues to be the treatment foundation for all personality disorders, and psychotherapy studies on the whole have shown improvement with treatment—two to four times greater than the improvement seen in the control conditions ([Perry and Bond 2000](#)).

The main indications for using medications in treating personality disorders are periods of decompensation, crises, and hospitalizations; the longer-term management of symptom clusters that are maladaptive and may be responsive to medication; and the reappearance or worsening of comorbid conditions. The underlying rationale for medication use is that associated behavioral traits might have neurobiological and psychological correlates ([Oquendo et al. 2005](#); [Simeon et al. 1992](#)).

In this chapter we summarize the literature to date on the pharmacological treatment of personality disorders. We begin with a brief overview of current conceptualizations of personality and what constitutes a “personality disorder,” followed by a discussion of the treatment of Cluster B disorders (which has the largest evidence base), Cluster A disorders, and Cluster C disorders. Findings from neuroimaging, neuroendocrine and cognitive-behavioral studies pertinent to the understanding of personality disorders are summarized. The chapter concludes with a brief overview of emerging areas of research and their implications for our understanding of the pathophysiology and treatment of personality disorders.

---

### Models of Personality

---

Whereas nobody doubts the existence of personality, what constitutes its disordered form has been controversial. There is little disagreement on the limitations of the current categorical classification of personality disorders, but consensus on a unified model has been lacking. Much of the debate has centered on dimensional versus categorical models of personality disorders. The alternative dimensional model for personality disorders in Section III of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition

(DSM-5; [American Psychiatric Association 2013](#)), has two main criteria: impairment in personality functioning and one or more pathological personality traits.

The founder of personality psychology, [Allport \(1937\)](#), in one of the earliest conceptualizations of personality disorders, theorized that “personality ‘is’ something and personality ‘does’ something” (p. 48). In the nearly 80 years since then, research into what personality “is” (i.e., trait structural models) has dominated the field ([Ro et al. 2013](#)). Recently there has been increased attention on what personality “does”—that is, the functional aspects of personality and how it serves to adapt individuals’ behaviors to their situations ([Ro and Clark 2009](#)). Distinguishing personality functioning from traits is important conceptually, because simply having extreme traits is not necessarily pathological. From an evolutionary perspective, [Livesley and Jang \(2000\)](#) theorized that severe personality pathology reflects a failure of three adaptive systems: a “self-system” (i.e., development of a stable concept of self and, correspondingly, of others) and two “other-systems” (i.e., the capacity for close personal relations and intimacy, and the ability to function effectively at a societal level). The consequence of this system failure is an inability to handle major life tasks—in effect, Freud’s *lieben und arbeiten* (to love and to work).

The heterogeneity and absence of evidence to support treatment of individual personality disorders led researchers to largely ignore specific DSM Axis II personality disorder categories and adopt a more parsimonious approach to treatment, focusing instead on dimensions of psychopathology that cut across various personality disorders. The limitations of categorical models led to the development of a trait-based algorithm initially proposed by [Siever and Davis \(1991\)](#) and further developed by [Soloff \(1998\)](#). This new algorithm posited that four dimensions cutting across all personality disorder categories— affective instability, anxiety-inhibition, cognitive-perceptual disturbances and impulsivity-aggression—should be studied rather than individual symptom clusters or diagnoses. This model has served as a dominant framework for understanding the evidence regarding medication effects on personality disorders ([Bateman et al. 2015](#)).

The diagnosis and classification of personality disorders are shifting toward a more dimensional model of classification ([Widiger and Simonsen 2005](#)). Although several models were proposed in DSM-IV-TR ([American Psychiatric Association 2000](#)), the model included in Section III of the recently published DSM-5 as an alternative to current categorical classifications is based on the empirically supported Five-Factor Model (FFM), which includes the following broad domains: negative affectivity (vs. emotional stability), detachment (vs. extraversion), antagonism (vs. agreeableness), disinhibition (vs. conscientiousness), and psychoticism (vs. lucidity) ([Widiger and Costa 1994](#)). This model, in contrast to other models, was felt to adequately cover the full range of personality disorder symptomatology and has amassed the most empirical support ([Widiger and Costa 1994](#)). Compared with other models, it was felt to more accurately reflect normal as well as abnormal personality functioning and to better account for the symptoms and traits of DSM-IV-TR personality disorders ([Clark 2007](#)). The aspects of personality functioning considered to be most important to people across all cultures and languages when they describe themselves and others pertain to interpersonal relatedness, a domain thought to form the core of personality disorders ([Pincus 2005](#)) and captured by the two factors of extraversion and agreeableness.

Despite the formidable challenges in understanding what constitutes “disordered” personality features and their optimal treatment approach, reasons for optimism exist. The traditional view that personality disorders are necessarily chronic, stable over time, and marked by poor outcomes has been challenged in recent years in light of the fact that the

more serious epiphenomena of disorders such as borderline personality disorder, including serious suicide attempts, impulsive behaviors, misuse of services, and aggressive outbursts, all show improvement with treatment. Findings from longitudinal studies of personality disorders such as the Collaborative Longitudinal Personality Disorders Study (CLPS) and the McLean Study of Adult Development (MSAD) have challenged the traditional entrenched pessimism about the poor prognoses of personality disorders such as borderline personality disorder (Gunderson et al. 2011; Zanarini et al. 2010). Such findings have driven the removal from DSM-5 of the separate Axis II category altogether, as well as the introduction of terms such as *remission* and *relapse* to the conceptualization of personality disorders.

---

## Pharmacotherapy for Cluster B Personality Disorders

---

Almost all of the clinical research trials examining medication treatments for personality disorders have studied borderline personality disorder (BPD). The symptom clusters typically targeted in this condition, although varying from trial to trial in how they are defined and assessed, are dysregulated impulsivity and aggression, affective lability and hyperreactivity, cognitive-perceptual disorganization, anxiety, and dissociation. Dysregulation of impulses and affective instability are widely viewed as the hallmark symptoms of BPD. Studies suggest that despite the limitations in our knowledge of treatments for BPD, drugs are very frequently prescribed, and polypharmacy is common (Bridler et al. 2015; Knappich et al. 2014; Zanarini et al. 2004b).

### Conventional Antipsychotics

Abnormalities in dopamine signaling are thought to underlie the cognitive-perceptual symptoms of BPD, which include paranoia, perceptual aberrations, and subtle thought disorder, and this understanding forms the rationale for the use of antipsychotics in the disorder. BPD patients have been found to have higher plasma and cerebrospinal fluid levels of the dopamine metabolite homovanillic acid, and dopamine receptor genetic polymorphisms have been found to interact with traumatic attachment stressors in producing the attachment insecurity and disorganization thought to be integral to BPD (Steele and Siever 2010). On the whole, studies with conventional antipsychotics suggest significant improvements in anger with haloperidol and in suicidality with flupenthixol decanoate, whereas effects on psychosis, irritability, and affective symptoms have been variable (Table 51-1). Any benefits of older antipsychotic agents must be weighed against these agents' well-established propensity to cause extrapyramidal symptoms (EPS) and tardive dyskinesia.

---

**TABLE 51-1. Summary of medication treatment trials with antipsychotics in bord (BPD)**

---

Study	Subjects	Antipsychotic(s)	Other agent(s)	Duration	Out
Typical antipsychotics					

---

*Note.* SztPD=schizotypal personality disorder.

<b>Study</b>	<b>Subjects</b>	<b>Antipsychotic(s)</b>	<b>Other agent(s)</b>	<b>Duration</b>	<b>Out</b>
Leone 1982	80 BPD	Loxapine	Chlorpromazine	6 weeks	Impr g d h
Montgomery and Montgomery 1982	30 BPD	Depot flupenthixol	Placebo	4-6 months	Dec
Serban and Siegel 1984	16 BPD, 14 SztPD, 16 both	Thiothixene, haloperidol	—	12 weeks	Impr p sc a h
Goldberg et al. 1986	17 BPD, 13 SztPD, 20 both	Thiothixene	Placebo	12 weeks	Dec
Soloff et al. 1986, 1989	35 BPD, 4 SztPD, 51 both	Haloperidol	Amitriptyline, placebo	5 weeks	Impr d g h d o a
Cowdry and Gardner 1988	16 BPD	Trifluoperazine	Alprazolam, carbamazepine, tranylcypromine, placebo	6-week crossover	Impr is g m ir tr se d ci b st
Soloff et al. 1993	42 BPD, 66 BPD and SztPD	Haloperidol	Phenelzine, placebo	5 weeks	Mir h d h
Cornelius et al. 1993	Continuation of above study			16-week extension	Rec w le h ir a p

*Note.* SztPD=schizotypal personality disorder.

Study	Subjects	Antipsychotic(s)	Other agent(s)	Duration	Out
<b>Atypical antipsychotics</b>					
<a href="#">Frankenburg and Zanarini 1993</a>	15 refractory BPD	Clozapine	—	2–9 months	33%
<a href="#">Schulz et al. 1998</a>	BPD	Risperidone	Placebo	8 weeks	Mo th
<a href="#">Schulz et al. 1999</a>	11 BPD (7 also SztPD)	Olanzapine	—	8 weeks	Ger ir
<a href="#">Zanarini and Frankenburg 2001</a>	28 BPD	Olanzapine	Placebo	6 months	Dec a: st
<a href="#">Rocca et al. 2002</a>	15 BPD with marked aggression	Risperidone	—	8 weeks	Dec ir
<a href="#">Bogenschutz and Nurnberg 2004</a>	40 BPD	Olanzapine	Placebo	12 weeks	Gre B
<a href="#">Villeneuve and Lemelin 2005</a>	23 BPD	Quetiapine	—	12 weeks	Imp r fu
<a href="#">Nickel et al. 2006</a>	52 BPD	Aripiprazole	Placebo	12 weeks	Imp r d
<a href="#">Bellino et al. 2006</a>	14 BPD	Quetiapine	—	12 weeks	Imp ir
<a href="#">Perrella et al. 2007</a>	29 BPD	Quetiapine	—	12 weeks	Imp a:
<a href="#">Schulz et al. 2007</a>	314 BPD	Olanzapine	Placebo	12 weeks	No sy b p
<a href="#">Zanarini et al. 2007</a>	451 BPD	Low-dosage olanzapine (2.5 mg/day), moderate-dosage olanzapine (5–10 mg/day)	Placebo	12 weeks	Gre o: ol lc p
<a href="#">Linehan et al. 2008</a>	24 BPD	Olanzapine	Placebo	6 months	Gre ir w

*Note.* SztPD=schizotypal personality disorder.

Study	Subjects	Antipsychotic(s)	Other agent(s)	Duration	Out
<a href="#">Pascual et al. 2008</a>	60 BPD	Ziprasidone	Placebo	12 weeks	No syb
<a href="#">Zanarini et al. 2011</a>	451 BPD	Olanzapine	Placebo	12 weeks	Sig B
<a href="#">Bellino et al. 2011</a>	18 BPD	Paliperidone extended release	—	12 weeks	Sig B
<a href="#">Black et al. 2014</a>	95 BPD	Quetiapine	Placebo	8 weeks	Sig B

*Note.* SztPD=schizotypal personality disorder.

## Atypical Antipsychotics

Atypical antipsychotics have received increased attention in recent years (see [Table 51-1](#)). On the whole, BPD treatment studies using atypical antipsychotics have shown improvements in affective instability, impulsivity, psychosis, and interpersonal dysfunction. In clinical practice, it appears that atypical antipsychotics are prescribed more frequently than conventional agents due to their greater tolerability and lower risks of EPS and tardive dyskinesia. A number of studies have examined olanzapine in the treatment of BPD (see [Table 51-1](#)). The largest study to date was conducted by [Zanarini et al. \(2011\)](#). In this 12-week randomized, double-blind, placebo-controlled trial, 451 outpatients with DSM-IV ([American Psychiatric Association 1994](#)) borderline personality disorder received olanzapine 2.5 mg/day ( $n=150$ ), olanzapine 5–10 mg/day ( $n=148$ ), or placebo ( $n=153$ ). Olanzapine 5–10 mg/day showed a clinically modest advantage over placebo in the treatment of overall borderline psychopathology. Treatment-emergent adverse events included somnolence, fatigue, increased appetite, and weight gain ([Zanarini et al. 2011](#)). A 12-week open-label extension of the study found sustained improvements over longer durations ([Zanarini et al. 2012](#)). Another large-scale placebo-controlled study comparing the efficacy and tolerability of low and moderate dosages of extended-release quetiapine in 95 adults with BPD found that participants in the low-dosage quetiapine (150 mg/day) group had significant improvement on overall BPD severity measures compared with those in the placebo group. Eighty-two percent in the low-dosage quetiapine group were rated as “responders,” compared with 74% in the moderate-dosage (300 mg/day) group and 48% in the placebo group. The most common adverse events with quetiapine (which were more prominent in the high-dosage group) included sedation, changes in appetite, and dry mouth. The overall completion rate for the 8-week double-blind treatment phase was 67% (67% for the low-dosage quetiapine group, 58% for the moderate-dosage quetiapine group, and 79% for the placebo group) ([Black et al. 2014](#)).

## Antidepressants

Although older antidepressants including tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have shown modest efficacy in improving affective symptoms in BPD ([Cornelius et al. 1993](#); [Cowdry and Gardner 1988](#); [Soloff et al. 1993](#)), both TCAs and



MAOIs pose serious risks in overdose and carry the potential for adverse events that are of particular concern in this unstable, impulsive population.

BPD studies with selective serotonin reuptake inhibitors (SSRIs) have yielded mixed findings. Whereas some older studies suggested statistically significant superiority of SSRIs over placebo in BPD (Coccaro and Kavoussi 1997; Markovitz 1995; Salzman et al. 1995), more recent controlled studies with SSRIs showed either no difference from placebo or additional benefit over placebo only when SSRIs were used to augment standard treatments such as dialectical behavior therapy (Simpson et al. 2004). SSRI monotherapy also has demonstrated no statistical benefit over atypical antipsychotic monotherapy for depression and impulsive aggression (Zanarini et al. 2004a).

BPD studies with serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (Markovitz and Wagner 1995) and the newer agent duloxetine (Bellino et al. 2010) also showed modest efficacy in treating affective symptoms (irritability, anger) and impulsive behaviors (self-injury), but these trials were limited by their open-label design and small sample sizes. Studies of antidepressant treatment in BPD are summarized in Table 51-2.

**TABLE 51-2. Summary of medication treatment trials with antidepressants in borderline personality disorder (BPD)**

Study	Subjects	Antidepressant(s)	Other agent(s)	Duration	Outcomes
Soloff et al. 1986, 1989	35 BPD, 4 SztPD, 51 both	Amitriptyline	Haloperidol, placebo	5 weeks	Improvement in depression, work, other symptoms with impulsive hostility, impulsive functional halcyon
Soloff et al. 1993	42 BPD, 66 BPD and SztPD	Phenelzine	Haloperidol, placebo	5 weeks	Improvement in depression, anxiety, hostility, phenelzine, minimum improvement with

*Note.* SztPD=schizotypal personality disorder.

Study	Subjects	Antidepressant(s)	Other agent(s)	Duration	Outco
Cornelius et al. 1993	Continuation of above study			16-week extension	Mode: imp dep irrit phe red irrit wor dep par: halc
Cowdry and Gardner 1988	16 BPD	Tranlycypromine	Alprazolam, carbamazepine, trifluoperazine, placebo	6-week crossover	Great imp moc imp trar dec: of b dysc carl incr beh dysc suic alpr imp tole with trifl
Markovitz et al. 1991	22 BPD or SztPD	Fluoxetine	—	12 weeks	Mark: self- dep anxi inte sens: par:
Markovitz 1995	23 BPD	Sertraline	—	12 weeks	Half o sho imp self- dep suic

*Note.* SztPD=schizotypal personality disorder.

Study	Subjects	Antidepressant(s)	Other agent(s)	Duration	Outco
	Continuation of above study			1 year	Declin dep of s self
Kavoussi et al. 1994	9 personality disorder with impulsive aggression	Sertraline	—	8 weeks	Decre imp agg
Markovitz 1995	17 BPD	Fluoxetine	Placebo	14 weeks	Globa on a
Salzman et al. 1995	27 BPD or BPD traits	Fluoxetine	Placebo	12 weeks	Decre dep
Markovitz and Wagner 1995	45 BPD	Venlafaxine	—	12 weeks	40% c imp self
Coccaro and Kavoussi 1997	40 impulsive- aggressive personality disorder (one-third BPD), no major depression	Fluoxetine	Placebo	12 weeks	Mark agg irrit irre cha anxi
Rinne et al. 2002	38 BPD	Fluvoxamine	Placebo	6 weeks	Imprc rapi but or a
Simpson et al. 2004	20 BPD	Fluoxetine	Placebo	12 weeks	No sig add of a fluo dial beh (DB

*Note.* SztPD=schizotypal personality disorder.

Study	Subjects	Antidepressant(s)	Other agent(s)	Duration	Outco
<a href="#">Zanarini et al. 2004a</a>	45 BPD	Fluoxetine	Olanzapine, fluoxetine + olanzapine	8 weeks	Olanz flu olar sup fluo mor redi dep imp agg effe stat sign
<a href="#">Bellino et al. 2010</a>	18 BPD	Duloxetine	—	12 weeks	Signif on i ang affe dysi

*Note.* SztPD=schizotypal personality disorder.

## Mood Stabilizers

Mood stabilizers are known to calm excitatory neurotransmission, but the various agents differ in terms of their mechanism of action and effects on  $\gamma$ -aminobutyric acid (GABA)-ergic and glutamatergic signaling mechanisms. As a class, mood stabilizers have gained increasing attention as a medication strategy for treatment of BPD symptoms, demonstrating moderate effect sizes on impulsive aggression, affective instability, self-injurious behaviors, and overall functioning.

Early studies supported a role for lithium in BPD ([Rifkin et al. 1972](#)). In a single small controlled study ([Links et al. 1990](#)), 17 subjects with BPD received 6 weeks each of lithium, the TCA desipramine, and placebo in a randomized crossover design, and 10 subjects completed at least two medication trials. Neither medication was better than placebo for depressive symptoms, although lithium led to a significant decrease in anger and suicidality according to clinician but not patient perception.

Anticonvulsants are used more widely than lithium in the treatment of BPD symptoms. Early studies with carbamazepine reported mixed findings, with some showing improvement in behavioral dyscontrol ([Cowdry and Gardner 1988](#)) and others showing no significant improvement with carbamazepine treatment ([de la Fuente and Lotstra 1994](#)) compared with placebo.

More recently, anticonvulsant trials have focused on valproate and newer anticonvulsants. In one placebo-controlled trial, 16 outpatients with BPD were treated for 10 weeks with valproate or placebo ([Hollander et al. 2001](#)). Global improvement was significant by two measures in patients treated with valproate, but the small sample size and high dropout rate precluded statistically significant findings. In another controlled study, valproate's efficacy was examined in 30 women with comorbid BPD and bipolar II disorder over 6 months of treatment ([Frankenburg and Zanarini 2002](#)). Valproate at an

average dosage of 850 mg/day was well tolerated and resulted in significant improvement in interpersonal sensitivity, hostility/anger, and aggression compared with placebo.

A larger placebo-controlled multicenter trial of valproate showed some efficacy for impulsive aggression in Cluster B personality disorders (Hollander et al. 2003). In this study, 91 outpatients selected for the presence of prominent impulsive aggression and the absence of bipolar I disorder or current major depression were randomly assigned to 12 weeks of treatment with placebo or valproate (mean dosage of 1,400 mg/day). Valproate was well tolerated overall, with only 17% of subjects discontinuing because of valproate-related adverse events. The main finding of the study was a significant decrease in impulsive aggression in the last month of treatment, with valproate treatment reducing irritability, impulsive behaviors, and overall aggression, including verbal assault, assault against objects, and assault against others (Hollander et al. 2003).

Controlled studies have focused on lamotrigine (200 mg/day) and topiramate (200-250 mg/day) and suggest that both agents may offer therapeutic benefits in treating affective instability and impulsivity in BPD. Lamotrigine (at a target dosage of 200 mg/day) has demonstrated efficacy in treating impulsivity, affective symptoms, and aggression in BPD (Tritt et al. 2005). Long-term follow-up studies suggest that the benefits of lamotrigine are sustained and that it is an effective and relatively safe agent for longer-term treatment of aggression in women with BPD (Leiberich et al. 2008). Topiramate is another agent that has demonstrated efficacy for certain dimensions of BPD, such as anger (Loew et al. 2006; Nickel et al. 2004, 2005). Follow-up studies of topiramate support its efficacy long-term (Loew and Nickel 2008; Nickel et al. 2006).

BPD treatment trials with mood stabilizers are summarized in Table 51-3.

**TABLE 51-3. Summary of medication treatment trials with mood stabilizers in borderline personality disorder (BPD)**

Study	Subjects	Mood stabilizer(s)	Other agent(s)	Duration	Outcomes
Rifkin et al. 1972	21 emotionally unstable character disorder	Lithium	Placebo	6 weeks	Decreased labile

<b>Study</b>	<b>Subjects</b>	<b>Mood stabilizer(s)</b>	<b>Other agent(s)</b>	<b>Duration</b>	<b>Outco</b>
<a href="#">Cowdry and Gardner 1988</a>	16 BPD	Carbamazepine	Trifluoperazine, tranylcypromine, alprazolam, placebo	6-week crossover	Decre of b dys carl gre imp moe imp trai inci beh dys suic alpr imp but issu trifl
<a href="#">Links et al. 1990</a>	17 BPD	Lithium	Desipramine, placebo	6-week crossover	No siq imp witl des dep trei imp ang suic (litl des clin ove imp (litl des
<a href="#">de la Fuente and Lotstra 1994</a>	20 BPD without depression	Carbamazepine	Placebo	4 weeks	No ef dep beh dys glol
<a href="#">Stein et al. 1995</a>	11 BPD	Valproate	—	8 weeks	Mode half less anx imp reje sen

<b>Study</b>	<b>Subjects</b>	<b>Mood stabilizer(s)</b>	<b>Other agent(s)</b>	<b>Duration</b>	<b>Outcomes</b>
<a href="#">Pinto and Akiskal 1998</a>	8 BPD without depression	Lamotrigine	—	1 year	Two c thro glo res dec imp suic
<a href="#">Frankenburg and Zanarini 2002</a>	30 BPD	Valproate	Placebo	6 months	Signi imp hos agg inte sen
<a href="#">Hollander et al. 2001</a>	16 BPD	Valproate	Placebo	12 weeks	Redu inte pro dep sor imp ang stat sigr
<a href="#">Hollander et al. 2003</a>	91 impulsive-aggressive Cluster B	Valproate	Placebo	12 weeks	Signi dec imp agg
<a href="#">Nickel et al. 2004</a>	29 male BPD	Topiramate	Placebo	8 weeks	Decre sigr wei
<a href="#">Nickel et al. 2005</a>	42 male BPD	Topiramate	Placebo	8 weeks	Decre wei
<a href="#">Tritt et al. 2005</a>	24 female BPD	Lamotrigine	Placebo	8 weeks	Decre no v cha
<a href="#">Loew et al. 2006</a>	56 female BPD	Topiramate	Placebo	10 weeks	Impr inte sen anx of li loss
<a href="#">Simeon et al. 2007</a>	20 BPD	Valproate extended release	—	12 weeks	Overa imp dec irrit agg

## Other Medications and Agents

Despite their widespread use, benzodiazepines on the whole are not recommended in the treatment of BPD due to their risk of worsening impulsivity and suicidality (Cowdry and Gardner 1988). Studies using the  $\alpha_2$ -adrenergic agonist clonidine showed efficacy in treatment of comorbid posttraumatic stress disorder (PTSD) and BPD (Ziegenhorn et al. 2009) and suggest a role for clonidine in the treatment of hyperarousal and sleep disturbances associated with BPD. Finally, several randomized controlled trials support the use of omega-3 fatty acids in reducing aggression and affective symptoms in patients with moderate to severe BPD (Zanarini and Frankenburg 2003).

## Neuropeptides and Other Future Directions for Research

Recent psychopharmacological research in patients with BPD has centered on neuropeptides, including the opioids, oxytocin, vasopressin, and neuropeptide Y, all of which modulate complex networks of neurotransmitter systems and facilitate coordination of affective signaling and behaviors. BPD has been conceptualized as being related to disturbed attachment, and thus oxytocin, vasopressin, and opioids may be of particular relevance for treating BPD, given the developmental role of these neuropeptides in attachment and the relationship between attachment security and stable social cognitive representations of self and other (Fonagy and Luyten 2009; Stanley and Siever 2010).

Although some studies have suggested a role for opiate antagonists in the treatment of dissociative symptoms and flashbacks in BPD (Bohus et al. 1999; Griengl et al. 2001), other trials have not demonstrated any benefit of opioid antagonist treatment on acute symptoms of tension and dissociation in BPD (Philipsen et al. 2004).

Another neuropeptide system that has received increased attention for drug intervention in the treatment of interpersonal dysfunction is the oxytocin system. Oxytocin is associated with empathic processing and affiliative bonding and has been shown to have attenuating effects on the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Oxytocin deficits have been linked to attachment insecurity and separation distress, and oxytocin plays a role in mediation of social cues, trust, and prosocial behavior (Bartz and Hollander 2006). Lower cerebrospinal fluid levels of oxytocin have been found in women with a history of childhood abuse or neglect (Heim et al. 2009), and early experimental studies suggest a role for the oxytocin system in attenuating emotional and hormonal responses to stress in BPD (Simeon et al. 2011).

Individuals with BPD have been found to lack psychophysiological and amygdala indicators of habituation to repeated interpersonal affective stimuli of positive or negative valence (Hazlett et al. 2012). Working through interpersonal experiences may be difficult for BPD patients, and adjunctive medication treatment that targets the capacity for habituation may optimize overall treatment efficacy. Habituation, a process dependent on neuroplasticity and changes in receptor density, is fundamentally affected by glutamatergic *N*-methyl-D-aspartate (NMDA) signaling, suggesting a role for glutamatergic medications in improving the affective, impulsive, interpersonal, and cognitive symptoms of BPD. Enhancement of learning and psychophysiological habituation modulated by NMDA signaling could synergize psychopharmacology and psychotherapy, analogous to strategies proposed for PTSD with respect to enhancement of fear extinction



and interference of traumatic memory consolidation (Grosjean and Tsai 2007; Ripoll 2013).

Endocannabinoid neurotransmission has been implicated in impulsivity (Pattij and Vanderschuren 2008), depression and suicidality (Vinod and Hungund 2006), and psychosis (Parolaro et al. 2010), possibly related to modulation in dopaminergic signaling (Fitzgerald et al. 2012). Both BPD and complex PTSD are powerfully associated with the experience of interpersonal violence during childhood and adolescence. These disorders frequently co-occur and often result in pervasive problems in emotion regulation and pain perception, processes that involve the endocannabinoid system. A recent study investigated serum levels of the endocannabinoids anandamide and 2-arachidonoylglycerol and related fatty acid ethanolamides (FAEs) in BPD patients, PTSD patients, and healthy control subjects. Significant alterations were found for both endocannabinoids in BPD and for the FAE oleoylethanolamide in PTSD, suggesting a respective link to both disorders (Schaefer et al. 2014).

There is evidence that cyclical hormone changes (e.g., higher progesterone levels in the luteal phase; estrogen fluctuations at ovulation and in the luteal phase) may affect the expression of BPD features among at-risk women (Eisenlohr-Moul et al. 2015). Finally, altered levels of inflammatory cytokines such as interleukin-6 (Coccaro et al. 2015), prolactin (Atmaca et al. 2015b), N-acetylaspartate (NAA) (Atmaca et al. 2015a), and cortisol (Rausch et al. 2015) have been linked with BPD and suggest putative neurobiochemical targets for future drug research.

## Conclusions and Treatment Guidelines for Cluster B Personality Disorders

In summary, several open and controlled pharmacological treatment trials of BPD have been conducted. Interpretation of the findings is somewhat complicated by the diversity of patient presentations at treatment entry, including inpatient or outpatient status; overall severity of baseline pathology; presence of comorbid personality disorders; presence or absence of major depressive disorder, including atypical symptoms; emphasis on varying symptomatology, such as psychoticism or impulsive aggression; and use of a wide range of outcome measures. In addition, some of the core features of the disorder, such as identity diffusion, interpersonal vicissitudes, and primitive defensive structure, were never examined, and therefore the assumption that these features are less medication responsive has not been empirically proven. On the basis of the existent algorithms in the literature, modified according to the results of the latest medication trials, we propose a medication treatment approach for BPD (Table 51-4).

**TABLE 51-4. Psychopharmacological treatment guidelines for borderline personality disorder**

**If the most prominent symptoms are depression, interpersonal sensitivity, and impulsivity and aggression:**

1. Start with selective serotonin reuptake inhibitor (SSRI) (or related antidepressant).
2. *If good response*, maintain.  
*If partial response*, add mood stabilizer.  
*If no response*, switch to mood stabilizer.
3. *If significant residual anger, anxiety, or dyscontrol*, add atypical antipsychotic.

**If the most prominent symptoms are mood lability, impulsivity and aggression, and family history of bipolar spectrum:**

1. Start with mood stabilizer (valproate; carbamazepine or lithium as alternatives).
2. *If good response*, maintain.  
*If partial response*, add mood stabilizer.  
*If no response*, switch to mood stabilizer.

3. *If significant residual anger, anxiety, or dyscontrol*, add atypical antipsychotic.

**If the most prominent symptoms are paranoia, psychoticism, hostility, and overwhelming anxiety:**

1. Start with atypical antipsychotic (olanzapine and risperidone most studied).
  2. *If good response*, maintain.  
*If partial response*, add SSRI or mood stabilizer.  
*If no response and minimal mood symptoms*, switch to typical antipsychotic.
- 

In almost all Cluster B personality disorder trials, BPD has been the primary focus. Although some of these trials, as individually mentioned in the overview above, included mixed samples of Cluster B participants, they did not present separate analyses for non-BPD diagnoses. Therefore, the general principle to follow in treating Cluster B disorders other than BPD would be to target symptom clusters with medications as per the guidelines developed for BPD (see [Table 51-4](#)). In general, narcissistic and histrionic personality disorders are not characterized by the severe degree of either mood lability or impulse dyscontrol seen in BPD, but for individuals in whom such features are more prominent or problematic, medication trials can be attempted.

In regard to antisocial personality disorder, the general treatment guideline is that individuals who meet full criteria for the disorder are generally treatment noncompliant and nonresponsive. Very few pharmacological studies have focused on patients with antisocial personality disorder ([Coccaro 1993](#)). Early trials suggested a role for lithium in reducing markers of antisocial behavior, including rule infractions and impulsive-aggressive behavior, among incarcerated males ([Wickham and Reed 1987](#)). Studies with phenytoin 300 mg/day among prisoners and outpatients also showed some benefit for impulsive (but not premeditated) behaviors as well as reduced measures of anxiety and depression ([Stanford et al. 2001](#)). Finally, there is some evidence of benefit from nortriptyline (25-75 mg/day) and bromocriptine (15 mg/day) ([Powell et al. 1995](#)) in reducing alcohol abuse among individuals with antisocial personality disorder, a significant finding in light of the fact that men with antisocial personality disorder have been found to be three to five times more likely than those without the disorder to abuse alcohol and illicit drugs ([Robins and Price 1991](#)).

More recently, a report on four antisocial personality disorder inpatients in a maximum-security facility found decreases in impulsivity, hostility, aggressiveness, irritability, and rage reactions with quetiapine treatment at dosages of 600-800 mg/day ([Walker et al. 2003](#)). Generally, borderline patients who have some antisocial traits are more responsive to medication treatment than are purely antisocial patients. Studies with the mood stabilizer valproate suggested that individuals with antisocial personality disorder were less responsive to the pharmacotherapy than were subjects with other Cluster B personality disorders ([Hollander et al. 2003](#)). It has also been found, however, that borderline patients are significantly more likely than antisocial personality disorder patients to have received adequate medication trials with anxiolytics and antidepressants ([Zanarini et al. 1988](#)).

---

## Pharmacotherapy for Cluster A Personality Disorders

---

The main symptoms of Cluster A personality disorders—cognitive and perceptual distortions—are reminiscent of both the positive and the negative symptoms of schizophrenia, and dopaminergic dysregulation has been postulated to underlie these symptoms ([Siever and Davis 1991](#)). Schizotypal personality disorder is by far the most extensively investigated disorder of the cluster in terms of biological underpinnings ([Siever 1985](#); [Siever et al. 1990](#)), relation to DSM-IV Axis I as a schizophrenia spectrum disorder ([Asarnow et al. 2001](#); [Kendler et al. 1994](#)), and pharmacological treatment trials. Similar to schizophrenia patients, patients with schizotypal personality disorder (SztPD) often demonstrate cognitive processing deficits, structural functioning abnormalities, and other physiological abnormalities ([McClure et al. 2007](#)). Some studies have reported greater preservation of frontal volume in patients with SztPD ([Siever and Davis 2004](#)) compared with patients with schizophrenia. Functional magnetic resonance imaging (fMRI) data point to abnormal caudate volumes in SztPD patients, with associated cognitive deficits in working memory, implicating striatum dysfunction, and associated abnormalities in cortical-subcortical circuits may play a key role in disorders of cognition and behavior such as SztPD ([Levitt et al. 2004](#)).

[Serban and Siegel \(1984\)](#) treated a sample of patients, one-third of whom had SztPD and one-third of whom had SztPD and BPD, with either thiothixene or haloperidol, without placebo, and found marked improvement in psychotic spectrum symptoms. [Goldberg et al. \(1986\)](#) treated a sample of outpatients with BPD and/or SztPD with thiothixene or placebo and found a significant improvement in psychotic symptoms with thiothixene that was more pronounced in the patients with SztPD. [Soloff et al. \(1986, 1989\)](#), in a sample containing a sizable proportion of patients with combined SztPD and BPD, found haloperidol to be superior to placebo in the treatment of schizotypal symptoms but failed to replicate this finding in a later study ([Soloff et al. 1993](#)), possibly due to lower severity of symptoms in the second study.

[Schulz et al. \(1999\)](#) reported improvement in psychotic symptoms in a small group of patients who received olanzapine, most of whom had SztPD that was comorbid with BPD. There is one published randomized, placebo-controlled trial of an atypical antipsychotic (risperidone 0.25–2.0 mg/day) focusing exclusively on SztPD, which found risperidone to be significantly more efficacious than placebo ([Koenigsberg et al. 2003](#)).

The evidence for use of antidepressants in treatment of SztPD symptoms was weak and at times contradictory, with only a few open-label studies demonstrating some improvement in impulsive aggression, self-injurious behaviors, and depressive and psychotic symptoms with the SSRI fluoxetine ([Coccaro and Kavoussi 1997](#); [Markovitz et al. 1991](#)) and other studies showing detrimental effects (worsening of hostility and paranoia) with the TCA amitriptyline ([Soloff et al. 1986, 1989](#)).

Randomized controlled trials have shown improved cognitive performance on neuropsychological tasks with pergolide, a dopaminergic agonist active at both the D<sub>1</sub> and the D<sub>2</sub> receptor ([McClure et al. 2010](#)), and the noradrenergic  $\alpha_{2A}$  agonist guanfacine ([McClure et al. 2007](#)). Research on the neurobiological substrates of social cognitive dysfunction (empathic deficits, relational paranoia, and social isolation in SztPD) may provide future targets for pharmacotherapeutic intervention.

---

## Pharmacotherapy for Cluster C Personality Disorders

---

Anxiety and behavioral inhibition are the main symptoms that characterize individuals with Cluster C personality disorders, although the focus of the anxiety varies across disorders. The anxiety centers on social interaction in avoidant personality disorder, need for control of uncertainty in obsessive-compulsive personality disorder, and conflicts surrounding autonomy in dependent personality disorder.

Limited data suggest a role for the MAOI phenelzine ([Deltito and Perugi 1986](#); [Liebowitz et al. 1988](#)) and the SSRI fluoxetine ([Deltito and Stam 1989](#)) in the treatment of avoidant personality disorder. However, in all of these studies, most, if not all, of the avoidant subjects had comorbid social phobia, and the criteria used to differentiate the two conditions and their medication response were not clearly defined. In a more systematic approach, [Reich et al. \(1989\)](#) openly treated 14 patients with DSM-III-R ([American Psychiatric Association 1984](#)) social phobia with alprazolam for 8 weeks at a mean daily dosage of 3 mg and specifically measured treatment response in nine avoidant personality traits based on the DSM-III-R diagnostic criteria for avoidant personality disorder. Six of the nine avoidant traits showed significant improvement during treatment, correlating with a change in subjective anxiety and disability.

[Greve and Adams \(2002\)](#) reported anecdotal evidence for the anticonvulsant carbamazepine in the treatment of irritability and hostility associated with obsessive-compulsive personality disorder ([Greve and Adams 2002](#)). Although overlap with DSM-IV Axis I obsessive-compulsive disorder was suggested by previous findings of a familial spectrum of obsessive-compulsive disorder and obsessive-compulsive personality disorder ([Samuels et al. 2000](#)) and the clinical observation that both disorders exhibit compulsive behaviors, more recent data are emerging that support separation of the two as distinct clinical entities, differentiable on the basis of obsessions in obsessive-compulsive disorder versus excessive capacity to delay reward in obsessive-compulsive personality disorder ([Pinto et al. 2014](#)).

---

## Conclusion

---

In this chapter we reviewed the pharmacological treatment of personality disorders, providing a conceptual framework, highlighting methodological limitations, and summarizing medication treatment trials to date. Almost all of these trials focused on symptom clusters, such as psychoticism, impulsivity, hostility/aggression, mood instability, and anxiety/inhibition. This focus is consistent with the growing conceptualization of personality disorders as syndromes of overlapping traits arising from a complex interaction between genetic determinants and developmental processes, influenced by adverse life events, with the primary manifestations of the disorder represented as difficulties with interpersonal relationships. Translation of current research into robust clinical recommendations for the treatment of personality disorders has been hampered by a number of methodological limitations, including heterogeneity of study populations, selective attention to BPD, and diversity of outcome measures. Despite these limitations, there is sufficient evidence to suggest a role for medications as an adjunctive treatment for symptom reduction, functional improvement, and overall adaptation for personality disorders. Progress in our understanding of the neurobiological underpinnings of

personality and their component dimensions will help guide development of better models of personality and its disordered forms, thereby providing a basis for rational pharmacotherapy to complement psychosocial interventions.

---

## References

---

- Allport GW: Personality: A Psychological Interpretation. New York, H. Holt, 1937
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1984
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC, American Psychiatric Association, 2013
- Asarnow RF, Nuechterlein KH, Fogelson D, et al: Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. *Arch Gen Psychiatry* 58(6):581-588, 2001 11386988
- Atmaca M, Karakoc T, Mermi O, et al: Neurochemical alterations associated with borderline personality disorder. *Int J Psychiatry Med* 48(4):317-324, 2015a 25817526
- Atmaca M, Korkmaz S, Ustundag B, Ozkan Y: Increased serum prolactin in borderline personality disorder. *Int J Psychiatry Med* 49(3):169-175, 2015b 25930735
- Bartz JA, Hollander E: The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior. *Horm Behav* 50(4):518-528, 2006 16884725
- Bateman AW, Gunderson J, Mulder R: Treatment of personality disorder. *Lancet* 385(9969):735-743, 2015 25706219
- Bellino S, Paradiso E, Bogetto F: Efficacy and tolerability of quetiapine in the treatment of borderline personality disorder: a pilot study. *J Clin Psychiatry* 67(7):1042-1046, 2006 16889446
- Bellino S, Paradiso E, Bozzatello P, et al: Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder: a pilot study. *Depress Res Treat* 24(3):333-339, 2010 18719047
- Bellino S, Bozzatello P, Rinaldi C, Bogetto F: Paliperidone ER in the treatment of borderline personality disorder: a pilot study of efficacy and tolerability. *Depress Res Treat* 2011 2011:680194. doi: 10.1155/2011/680194. Epub 2011 Aug 4 21826264
- Black DW, Zanarini MC, Romine A, et al: Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 171(11):1174-1182, 2014 24968985
- Bogenschutz MP, George Nurnberg H: Olanzapine versus placebo in the treatment of borderline personality disorder. *J Clin Psychiatry* 65(1):104-109, 2004 14744178
- Bohus MJ, Landwehrmeyer GB, Stiglmayr CE, et al: Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder: an open-label trial. *J Clin Psychiatry* 60(9):598-603, 1999 10520978
- Bridler R, Häberle A, Müller ST, et al: Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: a comparison with other psychiatric disorders. *Eur Neuropsychopharmacol* 25(6):763-772, 2015 25907249
- Clark LA: Assessment and diagnosis of personality disorder: perennial issues and an emerging reconceptualization. *Annu Rev Psychol* 58:227-257, 2007 16903806
- Coccaro EF: Psychopharmacological studies in patients with personality disorders: review and perspective. *J Pers Disord* 7 (suppl):181-192, 1993

- Coccaro EF, Kavoussi RJ: Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry* 54(12):1081-1088, 1997 9400343
- Coccaro EF, Lee R, Coussons-Read M: Cerebrospinal fluid inflammatory cytokines and aggression in personality disordered subjects. *Int J Neuropsychopharmacol* 18(7):pyv001, 2015 25650410
- Cornelius JR, Soloff PH, Perel JM, Ulrich RF: Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. *Am J Psychiatry* 150(12):1843-1848, 1993 8238640
- Cowdry RW, Gardner DL: Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranlycypromine. *Arch Gen Psychiatry* 45(2):111-119, 1988 3276280
- de la Fuente JM, Lotstra F: A trial of carbamazepine in borderline personality disorder. *Eur Neuropsychopharmacol* 4(4):479-486, 1994 7894258
- Deltito JA, Perugi G: A case of social phobia with avoidant personality disorder treated with MAOI. *Compr Psychiatry* 27(3):255-258, 1986 3709141
- Deltito JA, Stam M: Psychopharmacological treatment of avoidant personality disorder. *Compr Psychiatry* 30(6):498-504, 1989 2684499
- Eisenlohr-Moul TA, DeWall CN, Girdler SS, Segerstrom SC: Ovarian hormones and borderline personality disorder features: preliminary evidence for interactive effects of estradiol and progesterone. *Biol Psychol* 109:37-52, 2015 25837710
- Fitzgerald ML, Shobin E, Pickel VM: Cannabinoid modulation of the dopaminergic circuitry: implications for limbic and striatal output. *Prog Neuropsychopharmacol Biol Psychiatry* 38(1):21-29, 2012 22265889
- Fonagy P, Luyten P: A developmental, mentalization-based approach to the understanding and treatment of borderline personality disorder. *Dev Psychopathol* 21(4):1355-1381, 2009 19825272
- Frankenburg FR, Zanarini MC: Clozapine treatment of borderline patients: a preliminary study. *Compr Psychiatry* 34(6):402-405, 1993 8131384
- Frankenburg FR, Zanarini MC: Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J Clin Psychiatry* 63(5):442-446, 2002 12019669
- Goldberg SC, Schulz SC, Schulz PM, et al: Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. *Arch Gen Psychiatry* 43(7):680-686, 1986 3521531
- Greve KW, Adams D: Treatment of features of Obsessive-Compulsive Personality Disorder using carbamazepine. *Psychiatry Clin Neurosci* 56(2):207-208, 2002 11952927
- Griengl H, Sendera A, Dantendorfer K: Naltrexone as a treatment of self-injurious behavior—a case report. *Acta Psychiatr Scand* 103(3):234-236, 2001 11240582
- Grosjean B, Tsai GE: NMDA neurotransmission as a critical mediator of borderline personality disorder. *J Psychiatry Neurosci* 32(2):103-115, 2007 17353939
- Gunderson JG, Stout RL, McGlashan TH, et al: Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders study. *Arch Gen Psychiatry* 68(8):827-837, 2011 21464343
- Hazlett EA, Zhang J, New AS, et al: Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. *Biol Psychiatry* 72(6):448-456, 2012 22560044
- Heim C, Young LJ, Newport DJ, et al: Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Mol Psychiatry* 14(10):954-958, 2009 18957940
- Hollander E, Allen A, Lopez RP, et al: A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *J Clin Psychiatry* 62(3):199-203, 2001 11305707
- Hollander E, Tracy KA, Swann AC, et al: Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacology* 28(6):1186-1197, 2003 12700713

- Kavoussi RJ, Liu J, Coccaro EF: An open trial of sertraline in personality disordered patients with impulsive aggression. *J Clin Psychiatry* 55(4):137-141, 1994 8071257
- Kendler KS, Gruenberg AM, Kinney DK: Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. *Arch Gen Psychiatry* 51(6):456-468, 1994 8192548
- Knappich M, Hörz-Sagstetter S, Schwerthöffer D, et al: Pharmacotherapy in the treatment of patients with borderline personality disorder: results of a survey among psychiatrists in private practices. *Int Clin Psychopharmacol* 29(4):224-228, 2014 24896541
- Koenigsberg HW, Reynolds D, Goodman M, et al: Risperidone in the treatment of schizotypal personality disorder. *J Clin Psychiatry* 64(6):628-634, 2003 12823075
- Leiberich P, Nickel MK, Tritt K, Pedrosa Gil F: Lamotrigine treatment of aggression in female borderline patients, Part II: an 18-month follow-up. *J Psychopharmacol* 22(7):805-808, 2008 18308777
- Leone NF: Response of borderline patients to loxapine and chlorpromazine. *J Clin Psychiatry* 43(4):148-150, 1982 7040351
- Levitt JJ, Westin CF, Nestor PG, et al: Shape of caudate nucleus and its cognitive correlates in neuroleptic-naive schizotypal personality disorder. *Biol Psychiatry* 55(2):177-184, 2004 14732598
- Liebowitz MR, Gorman JM, Fyer AJ, et al: Pharmacotherapy of social phobia: an interim report of a placebo-controlled comparison of phenelzine and atenolol. *J Clin Psychiatry* 49(7):252-257, 1988 3292516
- Linehan MM, McDavid JD, Brown MZ, et al: Olanzapine plus dialectical behavior therapy for women with high irritability who meet criteria for borderline personality disorder: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry* 69(6):999-1005, 2008 18466045
- Links PS, Steiner M, Boiago I, Irwin D: Lithium therapy for borderline patients: preliminary findings. *J Pers Disord* 4(2):173-181, 1990
- Livesley WJ, Jang KL: Toward an empirically based classification of personality disorder. *J Pers Disord* 14(2):137-151, 2000 10897464
- Loew TH, Nickel MK: Topiramate treatment of women with borderline personality disorder, part II: an open 18-month follow-up. *J Clin Psychopharmacol* 28(3):355-357, 2008 18480701
- Loew TH, Nickel MK, Muehlbacher M, et al: Topiramate treatment for women with borderline personality disorder: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 26(1):61-66, 2006 16415708
- Markovitz PJ: Pharmacotherapy of impulsivity, aggression, and related disorders, in *Impulsivity and Aggression*. Edited by Hollander E, Stein DJ. New York, Wiley, 1995, pp 263-288
- Markovitz PJ, Wagner SC: Venlafaxine in the treatment of borderline personality disorder. *Psychopharmacol Bull* 31(4):773-777, 1995 8851652
- Markovitz PJ, Calabrese JR, Schulz SC, Meltzer HY: Fluoxetine in the treatment of borderline and schizotypal personality disorders. *Am J Psychiatry* 148(8):1064-1067, 1991 1853957
- McClure MM, Barch DM, Romero MJ, et al: The effects of guanfacine on context processing abnormalities in schizotypal personality disorder. *Biol Psychiatry* 61(10):1157-1160, 2007 16950221
- McClure MM, Harvey PD, Goodman M, et al: Pergolide treatment of cognitive deficits associated with schizotypal personality disorder: continued evidence of the importance of the dopamine system in the schizophrenia spectrum. *Neuropsychopharmacology* 35(6):1356-1362, 2010 20130535
- Montgomery SA, Montgomery D: Pharmacological prevention of suicidal behaviour. *J Affect Disord* 4(4):291-298, 1982 6131083
- Nickel MK, Nickel C, Mitterlehner FO, et al: Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin*



- Psychiatry 65(11):1515-1519, 2004 15554765
- Nickel MK, Nickel C, Kaplan P, et al: Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. *Biol Psychiatry* 57(5):495-499, 2005 15737664
- Nickel MK, Muehlbacher M, Nickel C, et al: Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* 163(5):833-838, 2006 16648324
- Oquendo MA, Kronic A, Parsey RV, et al: Positron emission tomography of regional brain metabolic responses to a serotonergic challenge in major depressive disorder with and without borderline personality disorder. *Neuropsychopharmacology* 30(6):1163-1172, 2005 15770239
- Parolaro D, Realini N, Vigano D, et al: The endocannabinoid system and psychiatric disorders. *Exp Neurol* 224(1):3-14, 2010 20353783
- Pascual JC, Soler J, Puigdemont D, et al: Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. *J Clin Psychiatry* 69(4):603-608, 2008 18251623
- Pattij T, Vanderschuren L: The neuropharmacology of impulsive behaviour. *Trends Pharmacol Sci* 29(4):192-199, 2008 18304658
- Perrella C, Carrus D, Costa E, Schifano F: Quetiapine for the treatment of borderline personality disorder; an open-label study. *Prog Neuropsychopharmacol Biol Psychiatry* 31(1):158-163, 2007 17045720
- Perry JC, Bond M: Empirical studies of psychotherapy for personality disorders, in *Psychotherapy for Personality Disorders (Review of Psychiatry Series, Vol 19; Oldham JM and Riba MB, series eds)*. Edited by Gunderson JG, Gabbard GO. Washington, DC, American Psychiatric Press, 2000, pp 1-31
- Philipsen A, Schmahl C, Lieb K: Naloxone in the treatment of acute dissociative states in female patients with borderline personality disorder. *Pharmacopsychiatry* 37(5):196-199, 2004 15470797
- Pincus AL: The interpersonal nexus of personality disorders, in *Handbook of Personality and Psychopathology*. Edited by Strack S. Hoboken, NJ, Wiley, 2005, pp 120-139
- Pinto OC, Akiskal HS: Lamotrigine as a promising approach to borderline personality: an open case series without concurrent DSM-IV major mood disorder. *J Affect Disord* 51(3):333-343, 1998 10333987
- Pinto A, Steinglass JE, Greene AL, et al: Capacity to delay reward differentiates obsessive-compulsive disorder and obsessive-compulsive personality disorder. *Biol Psychiatry* 75(8):653-659, 2014 24199665
- Powell BJ, Campbell JL, Landon JF, et al: A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. *Alcohol Clin Exp Res* 19(2):462-468, 1995 7625583
- Rausch J, Gäbel A, Nagy K, et al: Increased testosterone levels and cortisol awakening responses in patients with borderline personality disorder: gender and trait aggressiveness matter. *Psychoneuroendocrinology* 55:116-127, 2015 25796037
- Reich J, Noyes R Jr, Yates W: Alprazolam treatment of avoidant personality traits in social phobic patients. *J Clin Psychiatry* 50(3):91-95, 1989 2925598
- Rifkin A, Quitkin F, Carrillo C, et al: Lithium carbonate in emotionally unstable character disorder. *Arch Gen Psychiatry* 27(4):519-523, 1972 4561258
- Rinne T, van den Brink W, Wouters L, van Dyck R: SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *Am J Psychiatry* 159(12):2048-2054, 2002 12450955
- Ripoll LH: Psychopharmacologic treatment of borderline personality disorder. *Dialogues Clin Neurosci* 15(2):213-224, 2013 24174895
- Ro E, Clark LA: Psychosocial functioning in the context of diagnosis: assessment and theoretical issues. *Psychol Assess* 21(3): 313-324, 2009 19719344



- Ro E, Stringer D, Clark LA: The schedule for nonadaptive and adaptive personality: a useful tool for diagnosis and classification of personality disorder, in *Oxford Handbook of Personality Disorders*. Edited by Widiger TA. New York, Oxford University Press, 2013, pp 58-59
- Robins LN, Price RK: Adult disorders predicted by childhood conduct problems: results from the NIMH Epidemiologic Catchment Area project. *Psychiatry* 54(2): 116-132, 1991 1852846
- Rocca P, Marchiaro L, Cocuzza E, Bogetto F: Treatment of borderline personality disorder with risperidone. *J Clin Psychiatry* 63(3):241-244, 2002 11926724
- Salzman C, Wolfson AN, Schatzberg A, et al: Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J Clin Psychopharmacol* 15(1):23-29, 1995 7714224
- Samuels J, Nestadt G, Bienvenu OJ, et al: Personality disorders and normal personality dimensions in obsessive-compulsive disorder. *Br J Psychiatry* 177:457-462, 2000 11060001
- Schaefer C, Enning F, Mueller JK, et al: Fatty acid ethanolamide levels are altered in borderline personality and complex posttraumatic stress disorders. *Eur Arch Psychiatry Clin Neurosci* 264(5):459-463, 2014 24253425
- Schulz SC, Camlin KL, Berry SA, et al: A double-blind study of risperidone for BPD (NR270). Poster presented at the 151st annual meeting of the American Psychiatric Association, Toronto, Ontario, Canada, May 30-June 4, 1998
- Schulz SC, Camlin KL, Berry SA, Jesberger JA: Olanzapine safety and efficacy in patients with borderline personality disorder and comorbid dysthymia. *Biol Psychiatry* 46(10):1429-1435, 1999 10578457
- Schulz SC, Zanarini MC, Detke HC, et al: Olanzapine for the treatment of borderline personality disorder: a flexible-dose 12-week randomized double-blind placebo-controlled study. Presented at the 160th Annual Meeting of the American Psychiatric Association, San Diego, CA, May 19-24, 2007 (No. 83)
- Serban G, Siegel S: Response of borderline and schizotypal patients to small doses of thiothixene and haloperidol. *Am J Psychiatry* 141(11):1455-1458, 1984 6388363
- Siever LJ: Biological markers in schizotypal personality disorder. *Schizophr Bull* 11(4):564-575, 1985 4081650
- Siever LJ, Davis KL: A psychobiological perspective on the personality disorders. *Am J Psychiatry* 148(12):1647-1658, 1991 1957926
- Siever LJ, Davis KL: The pathophysiology of schizophrenia disorders: perspectives from the spectrum. *Am J Psychiatry* 161(3):398-413, 2004 14992962
- Siever LJ, Keefe R, Bernstein DP, et al: Eye tracking impairment in clinically identified patients with schizotypal personality disorder. *Am J Psychiatry* 147(6):740-745, 1990 2343917
- Simeon D, Stanley B, Frances A, et al: Self-mutilation in personality disorders: psychological and biological correlates. *Am J Psychiatry* 149(2):221-226, 1992 1734743
- Simeon D, Baker B, Chaplin W, et al: An open-label trial of extended release valproate in the treatment of borderline personality disorder. *CNS Spectr* 12:439-443, 2007 17545954
- Simeon D, Bartz J, Hamilton H, et al: Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. *Psychoneuroendocrinology* 36(9): 1418-1421, 2011 21546164
- Simpson EB, Yen S, Costello E, et al: Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. *J Clin Psychiatry* 65(3):379-385, 2004 15096078
- Soloff PH: Algorithms for pharmacological treatment of personality dimensions: symptom-specific treatments for cognitive-perceptual, affective, and impulsive-behavioral dysregulation. *Bull Menninger Clin* 62(2):195-214, 1998 9604516

- Soloff PH, George A, Nathan RS, et al: Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. *Arch Gen Psychiatry* 43(7):691-697, 1986 3521532
- Soloff PH, George A, Nathan S, et al: Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *J Clin Psychopharmacol* 9(4):238-246, 1989 2768542
- Soloff PH, Cornelius J, George A, et al: Efficacy of phenelzine and haloperidol in borderline personality disorder. *Arch Gen Psychiatry* 50(5):377-385, 1993 8489326
- Stanford MS, Houston RJ, Mathias CW, et al: A double-blind placebo-controlled crossover study of phenytoin in individuals with impulsive aggression. *Psychiatry Res* 103(2-3):193-203, 2001 11549407
- Stanley B, Siever LJ: The interpersonal dimension of borderline personality disorder: toward a neuropeptide model. *Am J Psychiatry* 167(1):24-39, 2010 19952075
- Steele H, Siever L: An attachment perspective on borderline personality disorder: advances in gene-environment considerations. *Curr Psychiatry Rep* 12(1):61-67, 2010 20425312
- Stein DJ, Simeon D, Frenkel M, et al: An open trial of valproate in borderline personality disorder. *J Clin Psychiatry* 56(11):506-510, 1995 7592502
- Tritt K, Nickel C, Lahmann C, et al: Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. *J Psychopharmacol* 19(3):287-291, 2005 15888514
- Villeneuve E, Lemelin S: Open-label study of atypical neuroleptic quetiapine for treatment of borderline personality disorder: impulsivity as main target. *J Clin Psychiatry* 66(10):1298-1303, 2005 16259544
- Vinod KY, Hungund BL: Role of the endocannabinoid system in depression and suicide. *Trends Pharmacol Sci* 27(10):539-545, 2006 16919786
- Walker C, Thomas J, Allen TS: Treating impulsivity, irritability, and aggression of antisocial personality disorder with quetiapine. *Int J Offender Ther Comp Criminol* 47(5):556-567, 2003 14526596
- Wickham EA, Reed JV: Lithium for the control of aggressive and self-mutilating behaviour. *Int Clin Psychopharmacol* 2(3):181-190, 1987 3320183
- Widiger TA, Costa PT Jr: Personality and personality disorders. *J Abnorm Psychol* 103(1):78-91, 1994 8040485
- Widiger TA, Simonsen E: Alternative dimensional models of personality disorder: finding a common ground. *J Pers Disord* 19(2):110-130, 2005 15899712
- Zanarini MC, Frankenburg FR: Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry* 62(11):849-854, 2001 11775043
- Zanarini MC, Frankenburg FR: Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* 160(1):167-169, 2003 12505817
- Zanarini MC, Frankenburg FR, Gunderson JG: Pharmacotherapy of borderline outpatients. *Compr Psychiatry* 29(4):372-378, 1988 3409692
- Zanarini MC, Frankenburg FR, Parachini EA: A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry* 65(7):903-907, 2004a 15291677
- Zanarini MC, Frankenburg FR, Vujanovic AA, et al: Axis II comorbidity of borderline personality disorder: description of 6-year course and prediction to time-to-remission. *Acta Psychiatr Scand* 110(6):416-420, 2004b 15521825
- Zanarini MC, Schulz SC, Detke HC, et al: A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized double-blind placebo-controlled study. Presented at the 160th Annual Meeting of the American Psychiatric Association, San Diego, CA, May 19-24, 2007 (No. 84)

- Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G: Time to attainment of recovery from borderline personality disorder and stability of recovery: a 10-year prospective follow-up study. *Am J Psychiatry* 167(6):663-667, 2010 20395399
- Zanarini MC, Schulz SC, Detke HC, et al: A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 72(10):1353-1362, 2011 21535995
- Zanarini MC, Schulz SC, Detke H, et al: Open-label treatment with olanzapine for patients with borderline personality disorder. *J Clin Psychopharmacol* 32(3):398-402, 2012 22544004
- Ziegenhorn AA, Roepke S, Schommer NC, et al: Clonidine improves hyperarousal in borderline personality disorder with or without comorbid posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 29(2):170-173, 2009 19512980

## CHAPTER 52

# Treatment of Eating Disorders

W. Stewart Agras, M.D.

Eating disorders—anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED)—have a combined prevalence in women of 3%–6%, taking into account the diagnostic changes in DSM-5 ([American Psychiatric Association 2013](#); [Hudson et al. 2007](#); [Mond 2013](#)). About 10% of all cases of AN and BN are in males, with the proportion rising to about 30% for BED in clinical samples. Because much comorbid psychopathology is associated with each of these disorders, including current major depression in about 25% of cases, the treatment plan must take any such disorders into account. Both psychopharmacological and psychotherapeutic treatments are effective for BN and BED. Hence, determining how to sequence or combine treatment modalities is an important issue. Cases of BN (and BED) were rarely seen until their increase throughout the Western world in the late 1970s

([Garner et al. 1985](#)). This increase has been attributed to increasing societal pressures on women to maintain a thin body shape.

Research on the psychopathology and treatment of the eating disorders was relatively slow to develop compared with research in the depressive and anxiety disorders. This delay was likely attributable to the low prevalence of AN and the relatively recent increase in the number of cases of BN. Moreover, BED was not officially recognized as a disorder until DSM-5 ([American Psychiatric Association 2013](#)), although there is now a large body of literature on the condition. Despite this slow start, sufficient controlled treatment trials are now available to provide guidance to the clinician.

---

## **Bulimia Nervosa**

---

BN has its onset in adolescence or early adult life, with a prodromal period characterized by dissatisfaction with body shape and a fear of becoming overweight, followed by dietary restriction and weight loss. Sooner or later, periods of dietary restriction are followed by episodes of binge eating experienced as a loss of control over dietary intake. These, in turn, further aggravate dissatisfaction with body shape and fears of weight gain. Ultimately, the bulimic patient discovers purging, usually in the form of self-induced vomiting, with or without laxative or diuretic use, excessive exercise, or (less commonly) fasting; and in rare cases in the form of chewing food and spitting it out.

Medical complications of BN include potassium depletion, which combined with low weight may lead to cardiovascular

complications and death. Other complications include dental caries, salivary gland enlargement, and exercise injuries ([Mitchell and Crow 2010](#)). Comorbid psychopathology includes major depression; anxiety disorders, social phobia, and panic disorder; obsessive-compulsive disorder; alcoholism; and personality disorders, particularly those in the Cluster B spectrum.

## Pharmacological Treatment

### Antidepressants

The use of antidepressants in the treatment of BN was sparked by the observation that depression is often a comorbid feature of the disorder ([Pope and Hudson 1982](#)). In 1982, two groups of researchers conducted small-scale uncontrolled studies indicating that both tricyclic antidepressants and monoamine oxidase inhibitors reduced binge eating and purging ([Pope and Hudson 1982](#); [Walsh et al. 1982](#)). A wide range of antidepressants have been found effective in double-blind, placebo-controlled studies, including imipramine ([Agras et al. 1987](#); [Mitchell et al. 1990](#); [Pope et al. 1983](#)), desipramine ([Agras et al. 1991](#); [Barlow et al. 1988](#); [Blouin et al. 1989](#); [Hughes et al. 1986](#)), phenelzine ([Walsh et al. 1988](#)), brofaromine ([Kennedy et al. 1993](#)), trazodone ([Pope et al. 1989](#)), fluoxetine ([Fluoxetine Bulimia Nervosa Collaborative Study Group 1992](#)), fluvoxamine ([Milano et al. 2005](#)), and citalopram ([Leombruni et al. 2006](#)). Fluoxetine is the only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of BN. Antidepressants are prescribed for BN at the same dosages used for treating depression, with the exception of fluoxetine, for which a dosage of 60 mg/day

was found more effective than 20 mg/day in reducing binge eating and purging in a placebo-controlled trial involving 387 bulimic women ([Fluoxetine Bulimia Nervosa Collaborative Study Group 1992](#)).

Overall, most antidepressants appear effective for the short-term treatment of BN, with little difference between them ([Hay and Claudino 2010](#)). Less is known about the long-term effectiveness of medication. In an early study ([Fichter et al. 1991](#)), 72 patients with BN successfully treated as inpatients were randomly assigned to receive either fluvoxamine or placebo. Those on the active drug had a higher rate of recovery over a 15-week period. In a second study of this issue, 147 women with BN who had decreased their vomiting by at least 50% while taking 60 mg of fluoxetine over an 8-week period were randomly allocated to continue medication or to be switched to placebo ([Romano et al. 2002](#)). A survival analysis found that the group receiving active medication experienced a longer time to relapse (or dropout) than did the placebo group. However, it should be noted that at the 12-month follow-up, 83% of the fluoxetine group and 92% of the placebo group had relapsed or dropped out. The authors suggest that given these results, a multimodal approach to the treatment of BN, including cognitive-behavioral therapy (CBT), should be considered.

To date, only one study has compared different lengths of antidepressant treatment, in this case with desipramine. Patients with BN treated for 16 weeks relapsed to pretreatment levels of binge eating when medication was withdrawn. On the other hand, those treated for 24 weeks maintained remission after withdrawal and at 1-year follow-up ([Agras et al. 1991, 1994](#)). This study suggests that patients who respond to antidepressant treatment should

be given a minimum trial of 6 months on medication. For the most part, however, controlled studies of antidepressants are of relatively short duration, as is the assessment of bulimic symptoms. Both of these factors may somewhat exaggerate the clinical efficacy of these medications.

In a study involving 77 BN patients ([Walsh et al. 2006b](#)) that examined the rate of decline in bulimic symptoms with desipramine, the authors found that patients unlikely to respond to the antidepressant could be reliably identified after 2 weeks of treatment. This finding was replicated in a combined data set ( $N=785$ ) from two controlled trials ([Sysko et al. 2010](#)). Patients who did not reduce binge eating or vomiting by 60% by week 2 of treatment were unlikely to respond to fluoxetine. Identification of poor responders early in treatment allows for the deployment of different approaches to treatment.

One problem with medication given at times other than bedtime is that a significant amount may be purged through subsequent vomiting. Side effects and reasons for discontinuation of the various medications are similar to those observed in the treatment of depression. However, a study of bupropion found that a higher-than-expected proportion of bulimic patients developed grand mal seizures ([Horne et al. 1988](#)). The authors concluded that bupropion should not be used for the treatment of BN.

## **Antiepileptics**

Although considerable evidence from controlled trials indicates that most antidepressants are useful in the treatment of BN, few controlled studies of other pharmacological agents with a reasonable sample size have appeared in the literature. However, topiramate (an



anticonvulsant drug) has been evaluated in two controlled trials. The reason for considering topiramate was that epileptic patients experienced appetite reduction and weight loss on this medication. In the first study ([Hoopes et al. 2003](#)), patients meeting criteria for DSM-IV-TR ([American Psychiatric Association 2000](#)) bulimia nervosa were allocated at random to treatment with either topiramate at an average dosage of 100 mg/day ( $n=35$ ) or placebo ( $n=34$ ) over a 10-week period. Twenty-two (63%) of those in the topiramate group completed the trial, and topiramate was statistically superior in reducing binge eating and purging, with 22% of completers in remission at the end of treatment. In the second study ([Nickel et al. 2005](#)), 30 patients with BN were randomly allocated to receive either topiramate or placebo. Topiramate was statistically superior to placebo in reducing binge eating and purging; however, no data on remission or recovery were reported. Side effects commonly seen with topiramate are fatigue, cognitive blunting, and flu-like symptoms.

## Combined Treatment

CBT for BN developed in parallel with the use of antidepressants. CBT is considered the first-line treatment for BN because it appears to be more effective than antidepressant medication and other psychotherapies such as interpersonal psychotherapy ([Hay and Claudino 2010](#)). There is also evidence for the effectiveness of guided self-help CBT. The components of CBT include psychoeducation about BN; reduction of dieting and reinstatement of normal eating; exposure to feared foods; reduction of concerns about weight and shape; and reduction of interpersonal

triggers of binge eating. The existence of two different and effective treatments, antidepressant medications and CBT, naturally led to the question of whether the combined treatments would be more effective than either treatment alone.

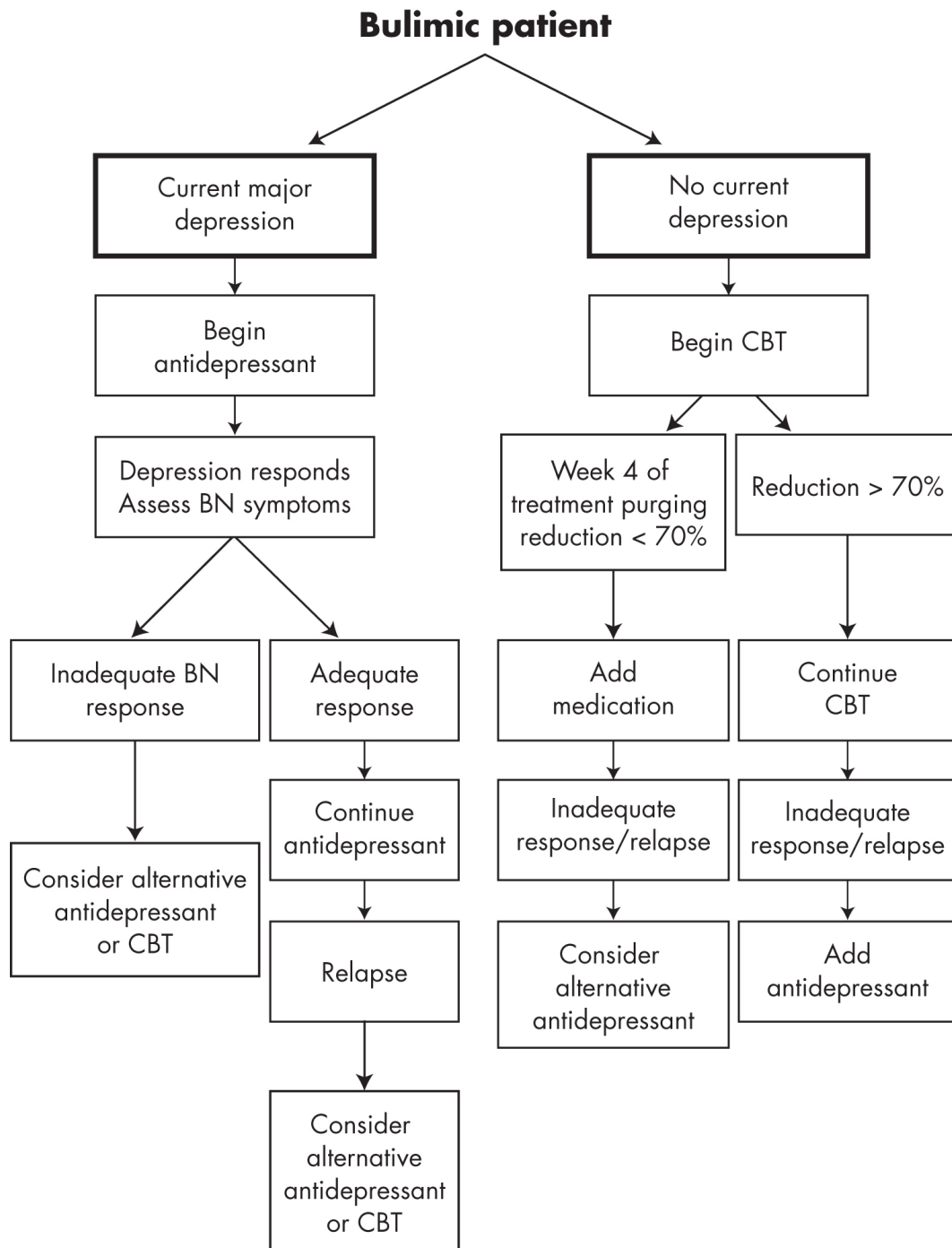
The largest study of combined treatment conducted to date, which involved 120 women with BN, used a medication regimen consisting of desipramine followed by fluoxetine if the first medication was either ineffective or poorly tolerated ([Walsh et al. 1997](#)). It is important to note that the two-medication combination was used by two-thirds of the patients assigned to active medication, suggesting that a two-medication combination is closer to clinical reality than the use of a single medication. The average dosage of desipramine was 188 mg/day, and that of fluoxetine was 55 mg/day. Forty-three percent of the patients receiving medication dropped out of the study, compared with 32% of those receiving psychotherapy. Patients receiving active medication (in combination with CBT) had a significantly greater reduction in binge eating compared with those receiving placebo. Finally, antidepressant medication combined with CBT was superior to medication alone in reducing purging frequency. Among patients receiving CBT plus medication, 50% were in remission at the end of treatment, compared with 25% of those receiving medication alone. These findings suggest that the combination of CBT plus antidepressant medication may be the most effective approach to the treatment of BN.

## Comprehensive Treatment

Patients with BN should be treated as outpatients unless there are medical or psychiatric reasons for hospitalization (e.g., an intercurrent physical illness or a comorbid psychiatric disorder requiring hospitalization, such as major depressive disorder with suicidality). One reason that outpatient treatment is useful for the BN patient is that gains made in the hospital may not carry over to the patient's home environment, where more complex food stimuli and greater stress are present than in the hospital.

The research evidence to date suggests that the combination of antidepressant medication and CBT is likely to be somewhat more effective than either therapy alone. Because CBT is more effective than antidepressant medication and is associated with fewer dropouts than medication, in the ideal case, CBT should be the first therapy offered to the patient. However, CBT is not always available, and in such circumstances, medication will be the only choice. In addition, patient preferences for one or the other treatment should be taken into account.

The flow chart in [Figure 52-1](#) presents an algorithm as guidance to the overall treatment of BN. The first decision to make is whether the patient has current major depression, which is seen in approximately 25% of bulimic patients presenting for treatment. Because depressive symptoms can interfere with the conduct of CBT for BN, antidepressant medication should precede CBT in such patients. When the patient has sufficiently recovered from depression, the eating disorder should be reevaluated. If the patient has not recovered from the eating disorder, then CBT should be added.



**FIGURE 52-1.** Flow chart depicting different treatment sequences for bulimia nervosa (BN). CBT=cognitive-behavioral therapy.

As shown in [Figure 52-1](#), if patients without concurrent depression show less than a 70% reduction in purging with CBT after 4 weeks (six sessions) of therapy, an antidepressant should be added. This algorithm is based on the findings of a multisite study involving 194 women with BN, which found that the initial treatment response to CBT predicted outcome reasonably well ([Agras et al. 2000](#)). Patients experiencing less than a 70% reduction in purging after 4 weeks of treatment were more likely to be nonresponders. If there is inadequate response to antidepressant treatment or a relapse, an alternative antidepressant should be used. For patients who complete CBT with insufficient improvement despite having reduced their purging at session 6, an antidepressant should be advised.

---

## Binge-Eating Disorder

---

Although the association between binge eating and obesity had been noted from time to time, it was not until the upsurge of research into the psychopathology and treatment of BN that systematic attention was paid to BED. The principal features of BED are episodes of binge eating at a frequency of at least 1 day per week for 3 months, marked distress caused by binge eating, and binge eating that does not occur during the course of BN or AN ([American Psychiatric Association 2013](#)). Purging does not occur in this condition, although about 10% of patients with BED have a history of BN.

Between 1% and 3% of women in the general population meet criteria for BED ([Hudson et al. 2007, 2012](#)), a

proportion that is little changed by the new DSM-5 criteria, which—like those for BN—now require an average of one binge episode per week over a 3-month period. In clinical populations, the ratio of women to men with BED is approximately 3:2, the highest rate for men of any eating disorder. Although obesity is not a requirement for the diagnosis of BED, there is a substantial overlap between BED and obesity. Studies have shown that about one-quarter of obese individuals have symptoms that meet criteria for BED, and that the prevalence of binge eating increases as body mass index increases ([Marcus et al. 1985](#); [Spitzer et al. 1993](#); [Telch et al. 1988](#)). Because binge eating often precedes the onset of overweight, binge eating may be a risk factor for obesity. Moreover, BED is associated with comorbid psychopathology similar to that seen in BN and causes much distress; hence, it is an entity deserving of treatment in its own right. A comparison of individuals with BED with weight-matched non-binge-eating obese individuals found that subjects with BED were significantly more likely than those without BED to receive a diagnosis of major depressive disorder (51%), panic disorder (9%), or borderline personality disorder (9%) ([Yanovski et al. 1993](#)).

## Pharmacological Treatment

### Antidepressants

Double-blind, placebo-controlled studies suggest that antidepressants are at least as useful in the treatment of BED as they are in BN. Early placebo-controlled studies found desipramine to be effective in reducing binge eating, with an abstinence rate of 60% ([McCann and Agras 1990](#)). Studies of selective serotonin reuptake inhibitors (SSRIs)

have suggested moderate efficacy, with overall remission rates of approximately 40%, compared with 20% for placebo ([Appolinario and McElroy 2004](#); [McElroy et al. 2010](#)). Most studies showed some degree of weight loss, which for the most part was not clinically significant.

## **Antiepileptics**

Anticonvulsants such as topiramate and zonisamide also appear to be useful in the treatment of BED ([McElroy et al. 2006](#)). A 16-week double-blind multisite study in which 394 participants with BED were allocated at random to receive either topiramate or placebo provided evidence for the efficacy of topiramate ([McElroy et al. 2007](#)). The median dosage of topiramate was 300 mg/day. Dropouts were equivalent between groups (29% topiramate; 30% placebo). Fifty-eight percent of subjects in the topiramate group and 29% of those in the placebo group were in remission at the end of the study period. The mean weight loss was 4.5 kg in the topiramate group versus a small weight gain in the placebo group. The most common side effects specific to topiramate were paresthesia and difficulty concentrating. Hence, topiramate leads to a reasonable rate of remission of the eating disorder combined with substantial and clinically meaningful weight loss.

## **Other Medications**

A recent multisite study suggested that lisdexamfetamine, a dextroamphetamine-like drug FDA approved for the treatment of attention-deficit/hyperactivity disorder, may be useful, at least in the short term, for the treatment of BED ([McElroy et al. 2015](#)). Two hundred sixty individuals with BED were randomly allocated to receive active drug (30,

50, or 70 mg/day) or placebo. Exclusion criteria resulted in a group of subjects with very little comorbid psychopathology; hence, results relate only to this subgroup of BED patients. Lisdexamfetamine was administered for 8 weeks with a 1-week follow-up after discontinuation. Results were in favor of medication, with 50% of patients in the group receiving lisdexamfetamine 70 mg/day achieving 4 weeks without binge eating prior to the end of treatment, compared with 21.3% of patients on placebo. Results for patients receiving 50 mg/day were similar to those for the 70-mg/day group, but there was no difference between medication and placebo for the 30-mg/day group. Mean weight loss was 4.3 kg for the high-dosage group, compared with no loss for the placebo group. These results are encouraging both for binge-eating reduction and for weight loss, although long-term studies are now needed to examine maintenance of therapeutic gains and to extend the findings to a more representative group of patients.

A placebo-controlled study in 50 overweight participants with BED compared orlistat (a lipase inhibitor), given at a dosage of 120 mg three times daily, with placebo, both groups also receiving an abbreviated form of CBT ([Grilo et al. 2005](#)). At the end of treatment, 64% of those in the orlistat group and 36% of those in the placebo group were in remission. The proportions achieving at least a 5% weight loss were 36% for orlistat and 8% for placebo. However, after discontinuation of both treatments, there was no difference in abstinence rates between groups (52% in both groups).

Although in earlier studies the serotonin-norepinephrine reuptake inhibitor sibutramine appeared to be successful in reducing both binge eating and weight, it is no longer



available in the United States because of associated cardiovascular effects ([Grilo et al. 2014](#)).

## Comprehensive Treatment

BED presents three problems to the clinician: binge eating, overweight, and comorbid psychopathology, particularly depression. Hence, comprehensive treatment should address all of these problems. There are few direct comparisons of psychotherapy and medication, and the situation is further complicated by the larger placebo responses found in BED as compared with BN, possibly accounting for the lack of efficacy of pharmacological agents in smaller-scale studies. For patients who prefer medication, current evidence suggests that topiramate has the most evidence for efficacy in reducing binge eating and weight, although acceptability may be low due to side effects. Lisdexamfetamine may provide an additional effective approach to treatment focused on reducing binge eating. However, lisdexamfetamine is a Drug Enforcement Administration-controlled medication with potential for abuse and dependence; therefore, careful monitoring of dosage and vigilance for signs of misuse are needed. Less is known about medications that may add to the effects of psychotherapies such as CBT and interpersonal therapy, both of which are associated with substantial reductions in binge eating that appear to be well maintained, although weight losses are small. Hence, augmentation studies are needed to guide clinical decision making. However, consideration might be given to combining a weight-reducing agent with one of the effective psychotherapies.

---

# Anorexia Nervosa

---

AN is a relatively rare disorder characterized by marked weight loss, intense fear of gaining weight, and disturbance in the experience of body shape (i.e., feeling fat despite marked weight loss). It is the most lethal psychiatric disorder. A meta-analysis of 41 cohorts from peer-reviewed studies published between 1966 and 2010 found that AN patients were 5.2 times more likely to die prematurely than females in the general population and 18.1 times more likely to die by suicide ([Keshaviah et al. 2014](#)). Because of the disabling nature and chronicity of the condition and the lack of evidence-based treatments for the chronic form of the disorder, it has become apparent that identification and treatment of the disorder early in its course are essential.

A specific family therapy (family-based treatment [FBT]) for adolescents that aims to help parents take charge of their child's eating appears to be successful in both the short and the long term, with about 50% of adolescent patients with anorexia recovered both at the end of treatment and at follow-up ([Lock et al. 2005, 2010](#)). In the largest trial to date ([Agras et al. 2014](#)), 164 adolescents with AN were randomly allocated to either FBT or systems family therapy (SyFT). There were no statistically significant differences in outcome at either end-of-treatment or 1-year follow-up, with 40% recovering with FBT. However, FBT produced significantly faster weight gain early in treatment, which may have led to fewer hospitalizations than SyFT and hence to lower treatment costs (FBT \$8,963, SyFT \$18,005). Therefore, for adolescent AN, family therapy in general and FBT in particular are evidence-based treatments ([Hay et al. 2014](#)).

# Pharmacological Treatment

Controlled pharmacological studies in both adolescents and adults have generally shown a lack of efficacy. Most studies of antipsychotic agents in the treatment of AN, including chlorpromazine, pimozide, sulpiride, olanzapine, and risperidone, showed no evidence of efficacy for weight gain ([Dally and Sargant 1960](#); [Hagman et al. 2011](#); [Kafantaris et al. 2011](#); [Vandereycken 1984](#); [Vandereycken and Pierloot 1982](#)). Similarly, antidepressants have proved disappointing ([Mitchell et al. 2013](#)). An inpatient study found that fluoxetine was not effective in hospitalized patients with AN ([Attia et al. 1998](#)). In this study, 31 women hospitalized with AN participated in a 7-week randomized, double-blind trial of fluoxetine at a mean dosage of 56 mg/day. Four patients in each group terminated the trial early. Although all patients in the study showed improvement, no significant differences were seen between active medication and placebo. In addition, there was no apparent effect of medication on depression or obsessional symptoms. This study suggested that fluoxetine had no effect over and above that of an inpatient program and adds to the literature's consistent failure to show a beneficial effect of antidepressant medication during the period of weight regain.

Despite promising findings in an earlier small-scale outpatient study ([Kaye et al. 2001](#)), a double-blind, placebo-controlled trial in 93 adult outpatients found no benefit for fluoxetine in either promoting weight maintenance or prolonging time to relapse ([Walsh et al. 2006a](#)). As is usual in this population, a large proportion of patients dropped out or terminated early from treatment (51% of fluoxetine-treated and 63% of placebo-treated patients). A fairly high

proportion of patients were dissatisfied with treatment. The very high dropout rates make statistical comparisons between groups difficult because of the large amount of data being carried forward in an intent-to-treat analysis. Nonetheless, the only difference between groups was a statistical advantage for fluoxetine in reducing anxiety levels.

Given the finding that fluoxetine confers no benefit for adult patients with AN either during the weight-gain period in the hospital or during outpatient treatment, one must conclude that use of fluoxetine is not indicated in the treatment of AN except to treat comorbid psychopathology. However, there have been no satisfactory studies of other SSRIs in adolescents with AN, and such studies would appear warranted, given the high priority for treatment early in the course of AN.

Most patients with AN can be treated as outpatients. However, treatment can be difficult because of the patient's reluctance to gain weight. Weight should be monitored at every outpatient visit, and it is important that weight be measured in a hospital gown to prevent the use of lead weights to which some patients with anorexia resort. Other methods of inflating weight are less easy to detect, such as drinking large quantities of water before being weighed. Indications for hospitalization include weight less than 75% of ideal body weight for age and height, heart rate below 40 beats/minute, blood pressure below 90/60 mm Hg, potassium levels below 3 mEq/L, temperature below 97°F, and very rapid weight loss. In addition, because of the associated psychopathology in this disorder, the usual indications for hospitalization for severe psychopathology should be followed.

---

## Conclusion

---

The place of psychopharmacological agents in the treatment of BN has been well worked out. Treatment with sequential trials of different antidepressants should result in abstinence rates of about 40%. The addition of CBT enhances the effectiveness of antidepressants. It is becoming clear that agents such as topiramate and similar anticonvulsants are useful in the treatment of BED, with the added advantage of facilitating substantial weight loss in the overweight patient. The recent FDA approval of lisdexamfetamine dimesylate recognizes the potential benefit of this medication in BED. In the case of AN, there is little evidence that pharmacological agents are helpful in either inpatient or outpatient treatment of the adult patient, except to treat comorbid psychiatric disorders. There is insufficient information regarding adolescent AN to provide guidance regarding the use of medication at this point.

---

## References

---

- Agras WS, Dorian B, Kirkley BG, et al: Imipramine in the treatment of bulimia: a double-blind controlled study. *International Journal of Eating Disorders* 6:29-38, 1987
- Agras WS, Rossiter EM, Arnow B, et al: Pharmacologic and cognitive-behavioral treatment for bulimia nervosa: a controlled comparison. *Am J Psychiatry* 159:325-333, 1991 1728190
- Agras WS, Rossiter EM, Arnow B, et al: One-year follow-up of psychosocial and pharmacologic treatments for

bulimia nervosa. J Clin Psychiatry 55(5):179-183, 1994  
8071266

Agras WS, Crow SJ, Halmi KA, et al: Outcome predictors for the cognitive behavior treatment of bulimia nervosa: data from a multisite study. Am J Psychiatry 157(8):1302-1308, 2000 10910795

Agras WS, Lock J, Brandt H, et al: Comparison of 2 family therapies for adolescent anorexia nervosa: a randomized parallel trial. JAMA Psychiatry 71(11):1279-1286, 2014  
25250660

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC, American Psychiatric Association, 2013

Appolinario JC, McElroy SL: Pharmacological approaches in the treatment of binge eating disorder. Curr Drug Targets 5(3):301-307, 2004 15058314

Attia E, Haiman C, Walsh BT, Flater SR: Does fluoxetine augment the inpatient treatment of anorexia nervosa? Am J Psychiatry 155(4):548-551, 1998 9546003

Barlow J, Blouin J, Blouin A, Perez E: Treatment of bulimia with desipramine: a double-blind crossover study. Can J Psychiatry 33(2):129-133, 1988 3284630

Blouin J, Blouin A, Perez E, Barlow J: Bulimia: independence of antibulimic and antidepressant properties of desipramine. Can J Psychiatry 34(1):24-29, 1989  
2647270

Dally PJ, Sargent W: A new treatment of anorexia nervosa. BMJ 1(5188):1770-1773, 1960 13813846

Fichter MM, Leibl K, Rief W, et al: Fluoxetine versus placebo: a double-blind study with bulimic inpatients undergoing intensive psychotherapy. Pharmacopsychiatry 24(1):1-7, 1991 2011615

- Fluoxetine Bulimia Nervosa Collaborative Study Group:  
Fluoxetine in the treatment of bulimia nervosa. A  
multicenter, placebo-controlled, double-blind trial. *Arch  
Gen Psychiatry* 49(2):139-147, 1992 1550466
- Garner DM, Olmsted MP, Garfinkel PE: Similarities among  
bulimic groups selected by different weights and weight  
histories. *J Psychiatr Res* 19(2-3):129-134, 1985  
3862827
- Grilo CM, Masheb RM, Salant SL: Cognitive behavioral  
therapy guided self-help and orlistat for the treatment of  
binge eating disorder: a randomized, double-blind,  
placebo-controlled trial. *Biol Psychiatry* 57(10):1193-  
1201, 2005 15866560
- Grilo CM, Masheb RM, White MA, et al: Treatment of binge  
eating disorder in racially and ethnically diverse obese  
patients in primary care: randomized placebo-controlled  
clinical trial of self-help and medication. *Behav Res Ther*  
58:1-9, 2014 24857821
- Hagman J, Gralla J, Sigel E, et al: A double-blind, placebo-  
controlled study of risperidone for the treatment of  
adolescents and young adults with anorexia nervosa: a  
pilot study. *J Am Acad Child Adolesc Psychiatry*  
50(9):915-924, 2011 21871373
- Hay PJ, Claudino AM: Evidence-based treatment for the  
eating disorders, in *The Oxford Handbook of Eating  
Disorders*. Edited by Agras WS. New York, Oxford  
University Press, 2010, pp 452-479
- Hay P, Chinn D, Forbes D, et al; Royal Australian and New  
Zealand College of Psychiatrists: Royal Australian and  
New Zealand College of Psychiatrists clinical practice  
guidelines for the treatment of eating disorders. *Aust N  
Z J Psychiatry* 48(11):977-1008, 2014 25351912
- Hoopes SP, Reimherr FW, Hedges DW, et al: Treatment of  
bulimia nervosa with topiramate in a randomized,  
double-blind, placebo-controlled trial, part 1:

- improvement in binge and purge measures. *J Clin Psychiatry* 64(11):1335-1341, 2003 14658948
- Horne RL, Ferguson JM, Pope HG Jr, et al: Treatment of bulimia with bupropion: a multicenter controlled trial. *J Clin Psychiatry* 49(7):262-266, 1988 3134343
- Hudson JI, Hiripi E, Pope HG Jr, Kessler RC: The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* 61(3): 348-358, 2007 16815322
- Hudson JI, Coit CE, Lalonde JK, Pope HG Jr: By how much will the proposed new DSM-5 criteria increase the prevalence of binge eating disorder? *Int J Eat Disord* 45(1):139-141, 2012 22170026
- Hughes PL, Wells LA, Cunningham CJ, Ilstrup DM: Treating bulimia with desipramine. A double-blind, placebo-controlled study. *Arch Gen Psychiatry* 43(2):182-186, 1986 3511878
- Kafantaris V, Leigh E, Hertz S, et al: A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol* 21(3):207-212, 2011 21663423
- Kaye WH, Nagata T, Weltzin TE, et al: Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 49(7):644-652, 2001 11297722
- Kennedy SH, Goldbloom DS, Ralevski E, et al: Is there a role for selective monoamine oxidase inhibitor therapy in bulimia nervosa? A placebo-controlled trial of brofaromine. *J Clin Psychopharmacol* 13(6):415-422, 1993 8120155
- Keshaviah A, Edkins K, Hastings ER, et al: Re-examining premature mortality in anorexia nervosa: a meta-analysis redux. *Compr Psychiatry* 55(8):1773-1784, 2014 25214371
- Leombruni P, Amianto F, Delsedime N, et al: Citalopram versus fluoxetine for the treatment of patients with



- bulimia nervosa: a single-blind randomized controlled trial. *Adv Ther* 23(3):481–494, 2006 16912031
- Lock J, Agras WS, Bryson S, Kraemer HC: A comparison of short- and long-term family therapy for adolescent anorexia nervosa. *J Am Acad Child Adolesc Psychiatry* 44(7):632–639, 2005 15968231
- Lock J, Le Grange D, Agras WS, et al: Randomized clinical trial comparing family-based treatment with adolescent-focused individual therapy for adolescents with anorexia nervosa. *Arch Gen Psychiatry* 67(10):1025–1032, 2010 20921118
- Marcus MD, Wing RR, Lamparski DM: Binge eating and dietary restraint in obese patients. *Addict Behav* 10(2):163–168, 1985 3859990
- McCann UD, Agras WS: Successful treatment of compulsive binge-eating with desipramine: a double-blind placebo-controlled study. *Am J Psychiatry* 147:1509–1513, 1990 2221164
- McElroy SL, Kotwal R, Guerdjikova AI, et al: Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry* 67(12):1897–1906, 2006 17194267
- McElroy SL, Hudson JI, Capece JA, et al; Topiramate Binge Eating Disorder Research Group: Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol Psychiatry* 61(9):1039–1048, 2007 17258690
- McElroy SL, Guerdjikova AI, O'Melia AM, et al: Pharmacotherapy of the eating disorders, in *The Oxford Handbook of Eating Disorders*. Edited by Agras WS. New York, Oxford University Press, 2010, pp 452–479
- McElroy SL, Hudson JI, Mitchell JE, et al: Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry* 72(3):235–246, 2015 25587645

- Milano W, Siano C, Putrella C, Capasso A: Treatment of bulimia nervosa with fluvoxamine: a randomized controlled trial. *Adv Ther* 22(3):278-283, 2005 16236688
- Mitchell JE, Crow SJ: Medical comorbidities of eating disorders, in *The Oxford Handbook of Eating Disorders*. Edited by Agras WS. New York, Oxford University Press, 2010, pp 259-266
- Mitchell JE, Pyle RL, Eckert ED, et al: A comparison study of antidepressants and structured intensive group psychotherapy in the treatment of bulimia nervosa. *Arch Gen Psychiatry* 47(2):149-157, 1990 2405806
- Mitchell JE, Roerig J, Steffen K: Biological therapies for eating disorders. *Int J Eat Disord* 46(5):470-477, 2013 23658094
- Mond JM: Classification of bulimic-type eating disorders: from DSM-IV to DSM-5. *J Eat Disord* 1:33-37, 2013 24999412
- Nickel C, Tritt K, Muehlbacher M, et al: Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord* 38(4):295-300, 2005 16231337
- Pope HG Jr, Hudson JI: Treatment of bulimia with antidepressants. *Psychopharmacology (Berl)* 78(2):176-179, 1982 6817375
- Pope HG Jr, Hudson JI, Jonas JM, Yurgelun-Todd D: Bulimia treated with imipramine: a placebo-controlled, double-blind study. *Am J Psychiatry* 140(5):554-558, 1983 6342421
- Pope HG Jr, Keck PE Jr, McElroy SL, Hudson JI: A placebo-controlled study of trazodone in bulimia nervosa. *J Clin Psychopharmacol* 9(4):254-259, 1989 2671058
- Romano SJ, Halmi KA, Sarkar NP, et al: A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful acute fluoxetine treatment. *Am J Psychiatry* 159(1):96-102, 2002 11772696

- Spitzer RL, Yanovski S, Wadden T, et al: Binge eating disorder: its further validation in a multisite study. *Int J Eat Disord* 13(2):137-153, 1993 8477283
- Sysko R, Sha N, Wang Y, et al: Early response to antidepressant treatment in bulimia nervosa. *Psychol Med* 40(6):999-1005, 2010 20441691
- Telch CF, Agras WS, Rossiter EM: Binge-eating increases with increasing adiposity. *International Journal of Eating Disorders* 7:115-119, 1988
- Vandereycken W: Neuroleptics in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled study with sulpiride. *Br J Psychiatry* 144:288-292, 1984 6367876
- Vandereycken W, Pierloot R: Pimozide combined with behavior therapy in the short-term treatment of anorexia nervosa. A double-blind placebo-controlled cross-over study. *Acta Psychiatr Scand* 66(6): 445-450, 1982 6758492
- Walsh BT, Stewart JW, Wright L, et al: Treatment of bulimia with monoamine oxidase inhibitors. *Am J Psychiatry* 139(12):1629-1630, 1982 6959533
- Walsh BT, Gladis M, Roose SP, et al: Phenelzine vs placebo in 50 patients with bulimia. *Arch Gen Psychiatry* 45(5):471-475, 1988 3282482
- Walsh BT, Wilson GT, Loeb KL, et al: Medication and psychotherapy in the treatment of bulimia nervosa. *Am J Psychiatry* 154(4):523-531, 1997 9090340
- Walsh BT, Kaplan AS, Attia E, et al: Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *JAMA* 295(22):2605-2612, 2006a 16772623
- Walsh BT, Sysko R, Parides MK: Early response to desipramine among women with bulimia nervosa. *Int J Eat Disord* 39(1):72-75, 2006b 16254873
- Yanovski SZ, Nelson JE, Dubbert BK, Spitzer RL: Association of binge eating disorder and psychiatric

comorbidity in obese subjects. Am J Psychiatry  
150(10):1472-1479, 1993 8379549

## CHAPTER 53

# Treatment of Insomnia

Andrew D. Krystal, M.D., M.S.

**Disturbances** of sleep occur at some point in the life of essentially everyone. However, the presence of a clinically significant insomnia disorder requires that the sleep disturbance meet a specific set of criteria: 1) there is a complaint of difficulty falling asleep or staying asleep; 2) this complaint is associated with clinically significant distress and/or daytime functional impairment; 3) these difficulties occur despite an adequate opportunity for sleep; and 4) the sleep disturbance is present for three or more nights per week for at least 3 months ([American Academy of Sleep Medicine 2014](#); [American Psychiatric Association 2013](#); [Krystal 2007](#)).

Available research suggests that insomnia disorder has a population prevalence of approximately 10% and is associated with impairments in quality of life; accidents; falls in the elderly; inability to function; increased risk of hypertension; and increased risk of major depressive disorder, anxiety disorders, suicidality, and substance-related disorders ([Avidan et al. 2005](#); [Baglioni et al. 2011](#); [Bathgate et al. 2016](#); [Breslau et al. 1996](#); [Ford and Kamerow 1989](#); [Harvey 2008](#); [Johnson et al. 2000](#); [Kessler et al. 2012](#); [Koski et al. 1998](#); [Léger et al. 2008](#); [Morin et al. 2011](#); [Ohayon 2002](#); [Ohayon and Reynolds 2009](#); [Roth et al. 2011](#); [Stone et al. 2014](#); [Vgontzas et al. 2013](#); [Winsper and Tang 2014](#)). Insomnia disorder most often occurs along with psychiatric and medical conditions ([Ford and Kamerow 1989](#); [Sarsour et al. 2010](#)). For many years, insomnia, especially when chronic, was assumed to be a symptom of these conditions ([National Institutes of Health 1984, 2005](#)). On this basis, directing treatment specifically to chronic insomnia was discouraged. Instead, it was recommended that treatment be administered for the associated medical and psychiatric conditions under the assumption that the insomnia would improve along with the other symptoms of the medical-psychiatric condition ([National Institutes of Health 1984, 2005](#)). Over time, the accumulating evidence suggested that this model is fundamentally flawed ([Krystal 2015](#); [National Institutes of Health 2005](#)). In approximately 15% of the patients with insomnia who have so-called primary insomnia, no associated condition exists to treat ([Edinger et al. 2011](#); [Ohayon 1997](#)). Evidence also indicates that treating the associated medical-psychiatric condition often fails to alleviate the insomnia and that insomnia has an adverse effect on the treatment response and course of depression, pain conditions, and anxiety disorders ([Krystal 2015](#); [Krystal et al. 2012](#); [National Institutes of Health 2005](#)). Further undermining the model that insomnia is invariably a symptom of psychiatric and medical conditions are the data referred to earlier indicating that insomnia is a risk factor for subsequent suicidality and psychiatric and medical conditions ([Avidan et al. 2005](#); [Baglioni](#)

et al. 2011; Bathgate et al. 2016; Breslau et al. 1996; Ford and Kamerow 1989; Harvey 2008; Johnson et al. 2000; Kessler et al. 2012; Koski et al. 1998; Stone et al. 2014; Vgontzas et al. 2013; Winsper and Tang 2014). These observations have led to a change in the paradigm for insomnia treatment.

It is now appreciated that the relation between insomnia and associated conditions is complex and often bidirectional and that directing treatment specifically to insomnia is generally warranted whether that insomnia occurs on its own or as a comorbid condition with psychiatric or medical conditions (National Institutes of Health 2005). Two primary types of treatment are available for specifically targeting insomnia disorder: 1) cognitive-behavioral therapy for insomnia (CBTI), the primary nonpharmacological therapy for insomnia, and 2) pharmacological therapy. A large evidence base supports the efficacy of CBTI for the treatment of insomnia, including primary insomnia and insomnia occurring with pain and major depressive disorder (Edinger et al. 2001, 2005; Manber et al. 2016; Morin et al. 2006; National Institutes of Health 2005). Pharmacotherapy, the focus of this chapter, is, by far, the most commonly administered treatment for insomnia disorder.

In this chapter, I review the neuropharmacology of pharmacological therapies for insomnia and examine their characteristics and clinical application. This information will optimize the medication management of insomnia.

---

## Sleep-Wake Pharmacology— Basis for Understanding Pharmacological Treatments for Insomnia

---

The pharmacological systems that regulate sleep-wake function consist of two types: 1) systems that promote sleep and 2) systems that promote wakefulness (Table 53-1) (Saper et al. 2005). These systems are mutually inhibitory such that greater activity in sleep-promoting systems inhibits the wake-promoting systems and vice versa, thereby stabilizing the state of an individual into either sleep or wake. The most important sleep-promoting systems include  $\gamma$ -aminobutyric acid (GABA), galanin, adenosine, and melatonin, whereas the wake-promoting systems include histamine, acetylcholine, norepinephrine, serotonin, and hypocretin/orexin (Saper et al. 2005). Agents that have therapeutic effects in treating insomnia either enhance the activity of one or more sleep-promoting systems or block the effects of one or more wake-promoting systems (Krystal et al. 2013b).

---

**TABLE 53-1. Sleep-wake neurotransmitters (sleep promoting and wake promoting)**

---

Key sleep-promoting systems	Key wake-promoting systems
$\gamma$ -Aminobutyric acid	Hypocretin/orexin
Galanin	Norepinephrine
Melatonin	Histamine
	Acetylcholine
	Serotonin
	Dopamine

---

Although there have long been agents available that differ in which of these systems they affect, it has generally been believed that the pharmacological mechanism of action of insomnia agents has no effect on their clinical effects (Krystal et al. 2013b). Clinical effects have been assumed to be determined by dose and pharmacokinetics (Krystal et al. 2013b). The higher the dosage, the greater the clinical sleep-enhancing effect; the higher the dosage and the more rapid the absorption, the sooner the clinical effect occurs; and the higher the dosage and the longer the elimination half-life, the longer the duration of sleep enhancement (Krystal et al. 2013b). This model emerged when the pharmacological management of insomnia was dominated by a group of agents—benzodiazepines (e.g., triazolam, temazepam, flurazepam) and nonbenzodiazepines (e.g., zolpidem, zaleplon, eszopiclone)—that had a common mechanism: sleep enhancement via positive allosteric modulation of GABA<sub>A</sub> receptors (Krystal 2009; Krystal et al. 2013b). Systematic data on clinical effects were essentially available only for these agents for which the pharmacokinetics/dose model is largely correct. Their peak effect occurs at the time of peak blood level, the speed of onset of clinical effects is proportional to rate of absorption, and the duration of effects is proportional to the elimination half-life. However, medications are available for the treatment of insomnia that have a fundamentally different mechanism and specifically block a single wake-promoting system (Krystal et al. 2013b). These agents with targeted, less global effects have the promise of an improved risk-benefit ratio when used in patients who have the type of sleep problem that is effectively treated with a particular agent. Studies characterizing the clinical effects of these medications have only relatively recently been carried out, and these studies verify the improved risk-benefit ratio and indicate that the model in which dose and pharmacokinetics are the prime drivers of clinical effects such that the mechanism of action is irrelevant to clinical effects is incorrect (Herring et al. 2016; Krystal et al. 2010, 2011; Michelson et al. 2014).

One agent that illustrates this point is doxepin 3–6 mg, a highly selective histamine H<sub>1</sub> receptor antagonist that enhances sleep by specifically blocking the wake-promoting effects of histamine (Krystal et al. 2010, 2011, 2013b). The peak therapeutic effect does not occur at peak blood level, which is approximately 3–4 hours after ingestion, but instead occurs at the end of the night about 4 hours later (Krystal et al. 2010, 2011, 2013b). According to the model in which pharmacokinetics and dose dominate clinical effects, this would not be possible and a drug with peak effect at the end of the night would be useless because it would cause prohibitive morning sedation or impairment (Krystal et al. 2013b). Because clinical effects should be proportional to blood level, and blood level only decreases incrementally over time, a drug with its biggest effect in hour 8 of an 8-hour night should have effects that are nearly as large in hour 9, the first hour of the day, at which time sleep-enhancing effects are problematic (Krystal et al. 2013b). Yet doxepin 3–6 mg has its greatest effects in hour 8 without clinically significant effects during waking 1 hour later (Krystal et al. 2010, 2011). This profile of effects is incompatible with a model in which therapeutic effects are dominated by pharmacokinetic factors and indicates that factors other than pharmacokinetics play an important role in determining clinical effects (Krystal et al. 2013b). These factors include the specific properties of the pharmacological system(s) modulated by a given drug and the activity in other systems that can affect sleep-wake function, which are determined by factors such as time of day and the behavior of the individual taking the medication and the psychosocial context (e.g., stress, novel environment, excitement) (Krystal et al. 2013b). The relevance of other systems was not apparent during the era when GABA<sub>A</sub>-positive allosteric modulators dominated insomnia pharmacotherapy, because those agents broadly

inhibit brain function, nonspecifically shutting down all of the wake-promoting systems. Agents that specifically inhibit a single wake-promoting system have brought to light how activity in systems that are not inhibited can contribute to clinical effects.

When using doxepin 3–6 mg as an example, the clinical effects of specifically blocking the histamine system reflect both the characteristics of the histamine system and the activity in parallel wake-promoting systems. Histamine is under control of the circadian clock, and its release varies systematically over the 24-hour cycle (Krystal et al. 2013b). When its release is minimal, the clinical effects of blocking histamine H<sub>1</sub> receptors should be minimal, whereas at times of significant release of histamine, a therapeutic effect can be expected. However, the activity of other sleep-wake-modulating systems that are not inhibited by doxepin 3–6 mg also plays a role. Whether blockade of histamine H<sub>1</sub> receptors manifests in a clinical sleep-enhancing effect will depend on the activity in other wake-promoting systems. If this activity is high, those systems will themselves sustain wakefulness even with significant blockade of H<sub>1</sub> receptors (Krystal et al. 2013b).

The activity in these parallel wake-promoting systems can be dependent on psychosocial context; for example, in an individual who is stressed or excited, noradrenergic neuronal activity is likely to be high and could maintain wakefulness despite histamine H<sub>1</sub> receptor antagonism (Krystal et al. 2013b). Another example of effects of time of day is that after an individual awakens for the day during the usual waking period, activity in the neuropeptide hypocretin/orexin system is increased and can maintain wakefulness even if H<sub>1</sub> receptors are blocked (Krystal et al. 2013b). This explains why doxepin 3–6 mg might have its largest effects in hour 8 of an 8-hour night and not have impairing effects after waking: at the end of the night, histamine release is high, and the parallel wake-promoting activity is normally relatively minimal, yet after waking, activity in parallel wake-promoting systems increases and can maintain wakefulness despite blockade of H<sub>1</sub> receptors (Krystal et al. 2013b). Thus, to determine the likely clinical effects of a medication, it is necessary to know not only dose and pharmacokinetic parameters but also mechanism of action in terms of which pharmacological system(s) it modulates, whether that system is modulated by the circadian rhythm and state (e.g., activity, stress, novelty), and what the circadian and state dependence are of the parallel pharmacological systems that could oppose or enhance clinical effects.

Accordingly, the model that is the basis for the current chapter is that “mechanism matters” and that three primary factors determine the clinical effects of medications used to treat insomnia: 1) mechanism of action, 2) drug pharmacokinetics, and 3) dosage. I review the characteristics of the various medications available for the treatment of insomnia organized by pharmacological mechanism of action. This includes reviews of the important sleep-promoting system-enhancing drugs, which consist of the benzodiazepines, nonbenzodiazepines, and melatonin receptor agonists, and the important wake-promoting system antagonists, which consist of the selective antihistamines, selective hypocretin/orexin receptor antagonists, selective adrenergic receptor antagonists, and nonselective wake-promoting system antagonists. It must be understood that in this chapter, the clinical effects of the agents with highly specific pharmacological effects can only be partially characterized because the activity in parallel systems that are not inhibited can vary greatly based on factors such as behavior and psychosocial context, as described earlier, making clinical effects more variable within and between individuals. As a result, rather than trying to characterize the full range of possible clinical effects as influenced by these factors for each agent, I indicate for each agent what the clinical effects are likely to be, assuming no contributions from behavioral



or psychosocial context factors, and then also indicate whether behavioral and psychosocial context factors could contribute to clinical effects.

---

## Pharmacological Treatments for Insomnia

---

### Agents That Improve Sleep by Enhancing Sleep-Promoting Systems

#### GABA<sub>A</sub>-Positive Allosteric Modulators

**Benzodiazepines.** The benzodiazepines are a group of medications that are GABA<sub>A</sub>-positive allosteric modulators and share a chemical structure (Krystal 2009; Minkel and Krystal 2013). The binding site on the GABA<sub>A</sub> receptor complex to which these agents bind is referred to as the *benzodiazepine binding site*. Through binding to this site, these agents broadly enhance GABA-mediated inhibition, which inhibits all of the wake-promoting systems and promotes sleep (Sieghart and Sperk 2002).

*Benzodiazepines used for the treatment of insomnia.* Five agents are indicated for the treatment of insomnia by the U.S. Food and Drug Administration (FDA): triazolam, flurazepam, temazepam, estazolam, and quazepam (Krystal 2009). Several other agents—clonazepam, alprazolam, and lorazepam—are commonly used to treat insomnia but have approved indications for conditions other than insomnia, such as anxiety and the treatment of seizures (Krystal 2009).

*Clinical therapeutic effects as indicated by available studies.* Triazolam, flurazepam, estazolam, quazepam, and temazepam have been found to have efficacy for the treatment of both sleep-onset problems and sleep-maintenance difficulty in at least one placebo-controlled trial (Krystal 2009).

*Effects on systems other than sleep-wake systems.* GABA is the predominant inhibitory neurotransmitter in the brain. For this reason, the benzodiazepines, which broadly enhance GABA<sub>A</sub>-mediated inhibition, can have very broad effects and affect many brain systems. Some of the associated effects can be therapeutic for some patients, including anxiety reduction, myorelaxant, and antiseizure effects (Krystal 2009). Other associated effects represent adverse effects, including cognitive impairment, motor impairment, and abuse potential (Krystal 2009).

*Optimal target patient population.* Benzodiazepines are best suited for use in those who can benefit from the effects these agents may have on systems other than sleep-wake systems, including those with anxiety or pain problems. These agents also have beneficial effects for sleep-onset problems that are stronger than other available options (Krystal 2009). However, the adverse effects of these medications outweigh the beneficial effects for most patients; for some with sleep-onset problems and comorbid conditions, these may have the best risk-benefit ratio of the available agents.

**Nonbenzodiazepines.** The term *nonbenzodiazepine* has been used to describe a set of agents that work by the same mechanism as the benzodiazepines, positive allosteric

modulation of GABA<sub>A</sub> receptors, but do not have the chemical structure of the benzodiazepines (Krystal 2009; Minkel and Krystal 2013).

*Nonbenzodiazepines used for the treatment of insomnia.* Three agents are indicated for the treatment of insomnia by the FDA: zolpidem, zaleplon, and eszopiclone (Krystal 2009). Zolpidem is also available in formulations other than an immediate-release formulation, including an extended-release version and a transoral version that is absorbed through the oral mucosa to a degree.

*Clinical therapeutic effects as indicated by available studies.* Zolpidem, zaleplon, and eszopiclone have been found to have efficacy for the treatment of sleep-onset problems in at least one placebo-controlled trial (Krystal 2009). However, only eszopiclone has been found to have therapeutic effects for sleep-maintenance problems (Krystal et al. 2003; Walsh et al. 2007). In addition, the extended-release formulation of zolpidem has been found to have beneficial effects on sleep maintenance (Krystal et al. 2008a), and both zaleplon and the transoral formulation of zolpidem have been found to have therapeutic effects for helping people return to sleep after middle-of-the-night awakenings (Roth et al. 2013; Zammit et al. 2006).

*Effects on systems other than sleep-wake systems.* Because the nonbenzodiazepines are GABA<sub>A</sub> allosteric modulators and GABA is widely distributed throughout the brain, like the benzodiazepines, the nonbenzodiazepines have the potential to have broad inhibitory effects on brain function. However, some evidence indicates that the clinical effects of nonbenzodiazepines are more limited than those of the benzodiazepines (Jia et al. 2009; Sanna et al. 2002). Benzodiazepines bind to four types of GABA<sub>A</sub> receptors that are believed to mediate the clinical effects of these agents, and evidence shows that the nonbenzodiazepines bind less broadly to these GABA<sub>A</sub> receptors, but the profile of binding differs among them (Jia et al. 2009; Sanna et al. 2002). Zolpidem and zaleplon bind relatively specifically to GABA<sub>A</sub> receptors, which are sleep promoting and also associated with cognitive and motor impairment, whereas eszopiclone tends to bind to GABA<sub>A</sub> receptors that are also associated with sleep enhancement and some degree of psychomotor impairment but relatively greater myorelaxant, anxiolytic, and possibly antidepressant effects. Clinical evidence for this is that unlike zolpidem, eszopiclone has been found to lead to improvement in anxiety, depression, and pain when combined with the usual therapy for these conditions in placebo-controlled trials (Fava et al. 2006, 2009, 2011; Goforth et al. 2014; Krystal et al. 2007b; Pollack et al. 2008).

*Optimal target patient population.* Nonbenzodiazepines are among the most widely administered insomnia therapies because of their strong effects on sleep onset and the perception that they have a better safety profile than the benzodiazepines. Generally, nonbenzodiazepines are the treatments of choice for pharmacotherapy of sleep-onset problems. Zolpidem (modified-release) and eszopiclone are also primary agents to consider for treating problems with sleep maintenance when they co-occur with sleep-onset problems; however, when sleep-maintenance problems occur without sleep-onset difficulty, other agents appear to have a more favorable risk-benefit profile (see “Selective Histamine H<sub>1</sub> Receptor Antagonists” section later in this chapter). The exception is for those individuals who have intermittent problems waking up in the middle of the night and are appropriate candidates for use of an as-needed rescue medication to help speed the return to sleep. In this case, transoral zolpidem and zaleplon are the treatments of choice

based on the available data ([Roth et al. 2013](#); [Zammit et al. 2006](#)). Finally, because only eszopiclone has been found to improve anxiety, depression, and pain outcomes when administered along with the usual first-line treatment for these conditions when they co-occur with insomnia, this medication should be considered as a first-line therapy for patients with insomnia occurring with these conditions ([Fava et al. 2006, 2009, 2011](#); [Goforth et al. 2014](#); [Krystal et al. 2007b](#); [Pollack et al. 2008](#)).

## Melatonin Receptor Agonists

Melatonin receptor agonists have melatonin receptor agonism as their primary clinical effect.

**Melatonin receptor agonists used for the treatment of insomnia.** Two selective melatonin receptor agonists are available: melatonin, available over the counter, and ramelteon, available by prescription only and FDA approved for the treatment of insomnia ([Krystal 2009](#)).

Melatonin is released by the pineal gland during the dark period of the circadian cycle ([Dubocovich et al. 2003](#)). Sleep enhancement is believed to occur via agonist effects at membrane-bound G protein-coupled melatonin type 1 (MT<sub>1</sub>) receptors, which inhibit the activity of neurons in the suprachiasmatic nucleus of the hypothalamus, the main circadian pacemaker ([Dubocovich et al. 2003](#)). Melatonin also binds to G protein-coupled MT<sub>2</sub> receptors, which are also located on suprachiasmatic nucleus neurons and induce shifts in the phase of the circadian rhythm ([Dubocovich et al. 2003](#)).

Ramelteon is a highly specific MT<sub>1</sub> and MT<sub>2</sub> agonist thought to have sleep-enhancing effects through its actions at the MT<sub>1</sub> receptor ([Krystal 2009](#)). It is substantially more potent than melatonin in affecting these receptors. It has an FDA indication for the treatment of insomnia only when the patient has problems with prolonged sleep onset.

*Clinical therapeutic effects as indicated by available studies.* A sizable set of studies that used a variety of dosages, formulations, and timing of dosing have been carried out to assess the effects of melatonin on individuals with sleep difficulty ([Buscemi et al. 2005](#); [Ferracioli-Oda et al. 2013](#)). These studies indicate that melatonin seems to be associated with improvement in sleep latency in insomnia patients with sleep-onset difficulties. Whether the degree of improvement associated with melatonin use is sufficient to be perceived as beneficial by many insomnia patients remains unclear ([Morin et al. 2015](#)). Furthermore, the optimal dose of melatonin for treatment of insomnia has yet to be established. Perhaps the most interest related to the use of melatonin to treat insomnia is in those with sleep difficulties co-occurring with autism or other neurodevelopmental disorders because reports indicate therapeutic effects ([Niederhofer et al. 2003](#); [Wirojanan et al. 2009](#)).

Ramelteon has been shown in several placebo-controlled trials to have therapeutic effects only on sleep-onset difficulties ([Krystal 2009](#)).

*Safety profile.* Melatonin has highly selective effects on melatonin receptors, and as a result, it has an excellent safety profile ([Wilson et al. 2010](#)). However, as mentioned earlier, the effects on MT<sub>2</sub> and melatonin type 3 (MT<sub>3</sub>) receptors can affect physiology, although by far the most important clinical effect mediated by MT<sub>2</sub> and MT<sub>3</sub> binding is MT<sub>2</sub>-mediated shifts in circadian rhythm ([Dubocovich et al. 2003](#)). This is believed to be responsible for the observation that melatonin is associated with greater therapeutic effects in those with

delayed sleep phase syndrome, in which the circadian sleep-wake cycle is shifted forward, than in insomnia patients (Buscemi et al. 2005; Ferracioli-Oda et al. 2013).

Like melatonin, ramelteon has an excellent safety profile as a result of having pharmacological effects that are limited to melatonin receptors (Krystal 2009). It does not have abuse potential and is safe in those with sleep apnea and chronic obstructive pulmonary disease (Kryger et al. 2007, 2009).

*Optimal target patient population.* The available data indicate that melatonin should be considered as first-line therapy for patients with insomnia occurring with autism and other neurodevelopmental problems as well as for those with insomnia occurring in the setting of circadian rhythm disorders (Buscemi et al. 2005; Ferracioli-Oda et al. 2013; Niederhofer et al. 2003; Wirojanan et al. 2009). Otherwise, melatonin can be considered for use in those with insomnia affecting only sleep onset.

Because ramelteon has effects only on sleep-onset difficulties, its use should be limited to those with only sleep-onset difficulties. It is especially well suited for use in those with obstructive sleep apnea and chronic obstructive pulmonary disease who have sleep-onset problems. It should also be considered for treating sleep-onset problems occurring in the setting of substance abuse or in individuals prone to substance abuse, but no studies have established its utility for this purpose.

## Agents That Improve Sleep by Blocking Wake-Promoting Systems

### Selective Histamine H<sub>1</sub> Receptor Antagonists

Selective H<sub>1</sub> receptor antagonists promote sleep by blocking the arousing effects of histamine through antagonism of the histamine H<sub>1</sub> receptor (Krystal et al. 2013b). The only highly selective histamine H<sub>1</sub> receptor antagonist is doxepin 3–6 mg. Doxepin was originally developed for treatment of depression and was FDA approved for treatment of depression and anxiety in dosages of 75–300 mg/day. In this dosage range, doxepin has clinically significant antagonism of several receptors, including adrenergic, serotonergic, and cholinergic receptors, and the serotonin and norepinephrine transporters in addition to H<sub>1</sub> receptor antagonism (Krystal et al. 2013b). However, because H<sub>1</sub> receptor antagonism is by far doxepin's most potent effect, at low enough dosages, this agent can have clinically significant effects only at H<sub>1</sub> receptors. The available evidence suggests that in the 3–6 mg range, doxepin is a highly selective H<sub>1</sub> receptor antagonist (Krystal et al. 2013b).

Available data from placebo-controlled trials carried out with doxepin 3 and 6 mg provided the first information about the clinical effects of selective wake-promoting system antagonism and, as discussed earlier, indicate that they differ from the clinical effects of the GABA<sub>A</sub> allosteric modulators (benzodiazepines and nonbenzodiazepines) (Krystal et al. 2013b). In addition to dose and pharmacokinetics, which essentially determine the clinical effects of those other agents, the clinical effects of doxepin are dependent on factors such as time of day and the state of the patient (e.g., activity, stress, novelty) (Krystal et al. 2010, 2011, 2013b). This dependence of clinical effects on factors other than dose and pharmacokinetics exists for all selective wake-promoting system antagonists and therefore represents a new paradigm for understanding the clinical effects of insomnia medications. As discussed earlier, the dependence of clinical effects of the selective antagonists on

factors other than dose and pharmacokinetics reflects that 1) the activity in the targeted wake-promoting systems is dependent on factors such as time of day and the state of the patient, and this will affect the degree of clinical effect occurring with antagonism; and 2) each wake-promoting system functions in parallel with other wake-promoting systems, which are not blocked by selective antagonism, and the activity in these systems is also affected by factors such as time of day and patient state (Krystal et al. 2013b). The reason this is not the case for the GABA<sub>A</sub> allosteric modulators is that they broadly inhibit all of the wake-promoting systems, and the clinical effects of enhancing GABA<sub>A</sub> activity are relatively less dependent on time of day and patient state factors (Krystal et al. 2013b).

### **Selective H<sub>1</sub> receptor antagonists used for the treatment of insomnia.**

Many medications that have histamine H<sub>1</sub> receptor antagonist effects are currently available and used to treat insomnia (Krystal et al. 2013b). However, the only highly selective H<sub>1</sub> receptor antagonist currently used in the treatment of insomnia is doxepin in 3- and 6-mg/day dosages. It is approved by the FDA for the treatment of insomnia with an indication only for treating problems staying asleep.

*Clinical therapeutic effects as indicated by available studies.* The clinical trials carried out with doxepin 3 and 6 mg indicate that this medication has consistent therapeutic effects on sleep maintenance, particularly in the last third of the night, without consistent therapeutic effects on sleep-onset problems (Krystal et al. 2010, 2011, 2013b). Notably, the largest effect size appears not at peak blood level (3–4 hours after dosing) but in the last hour of an 8-hour night. As discussed earlier, this could not occur with a GABA<sub>A</sub> allosteric modulator without prohibitive morning impairment. The fact that the largest effect occurs at a time other than at peak blood level and that morning impairment was not elevated over other medications that do not have significant effects in hour 8 is a clear indicator that clinical effects are dependent on factors beyond dose and pharmacokinetics (Krystal et al. 2010, 2011, 2013b). It is hypothesized that the reason the therapeutic effects are greatest at the end of the night is that the activity of histamine neurons is relatively high during this period, whereas the activity in the parallel wake-promoting systems is relatively low (Krystal et al. 2013b). However, after waking, the activity in the histamine system may increase further, and the activity in parallel wake-promoting systems increases, thereby sustaining normal waking function despite significant H<sub>1</sub> blockade (Krystal et al. 2013b).

*Effects on systems other than sleep-wake systems.* Given the relatively greater potency of doxepin for H<sub>1</sub> receptors over other receptors, it should be possible, in theory, to find a dosage for each individual that causes clinically significant H<sub>1</sub> receptor antagonist effects and no effects on any other pharmacological systems. The observed clinical effects indicate that the 3- and 6-mg/day dosages achieve this type of selectivity for many individuals (Krystal et al. 2010, 2011). However, for some individuals, these dosages may be above the range at which only histamine H<sub>1</sub> receptor antagonist effects are seen. When this is the case, the special advantages of highly selective antagonism are lost, and individuals may experience morning sedation and other adverse effects including anticholinergic (e.g., dry mouth, constipation, blurred vision) and antiadrenergic (e.g., orthostatic hypotension) symptoms.

*Optimal target patient population.* Because of the pharmacological selectivity of doxepin 3 and 6 mg, it can have an improved risk-benefit profile over other agents when

used to treat the type of problem that it specifically addresses: sleep-maintenance problems, particularly problems staying asleep at the end of the night (Krystal et al. 2013b). For this reason, doxepin 3–6 mg should be the treatment of choice for such individuals. Because of the absence of consistent therapeutic effects for sleep-onset problems, this medication should be reserved for those individuals with difficulties staying asleep, particularly toward the end of the night, who do not have problems falling asleep. The lack of abuse potential suggests that this medication might be particularly useful in abuse-prone individuals with sleep-maintenance problems. The fact that H<sub>1</sub> receptor antagonism is the key mechanism of anti-allergy effects also suggests that this medication should be among the treatments of choice for sleep difficulties occurring with significant allergy symptoms.

### Selective Hypocretin/Orexin Receptor Antagonists

Hypocretin and orexin are the peptides released by neurons located in the lateral hypothalamus that are among the most important factors maintaining wakefulness (Krystal et al. 2013a; Sakurai 2014). The wake-promoting effects of these peptides are mediated by their binding to two receptors referred to as OX<sub>1</sub> and OX<sub>2</sub> (Sakurai 2014). Selective hypocretin/orexin receptor antagonists enhance sleep by blocking OX<sub>1</sub> receptors, OX<sub>2</sub> receptors, or both. The tremendous specificity of this effect is illustrated by the fact that there are only 10,000–20,000 hypocretin/orexin-releasing neurons in the entire brain (Sakurai 2014). This specificity provides the potential for drugs that block OX<sub>1</sub> and OX<sub>2</sub> receptors to promote sleep while having minimal effects on other brain functions. Because hypocretin/orexin neurons do modulate activity in many brain areas, these agents would be expected to have some effects on functions other than sleep. However, the relative lack of effect on areas of the brain mediating cognitive and motor function suggests that these agents have the potential to be without many of the adverse effects that have been associated with agents predominantly used to treat insomnia such as the benzodiazepines and nonbenzodiazepine GABA<sub>A</sub> allosteric modulators.

**Selective hypocretin/orexin receptor antagonists used for the treatment of insomnia.** The only available hypocretin/orexin receptor antagonist currently available for clinical use is suvorexant, which is a dual (OX<sub>1</sub> and OX<sub>2</sub>) receptor antagonist (Herring et al. 2016; Michelson et al. 2014). The FDA granted it approval for the treatment of insomnia with indicators for treating sleep-onset and sleep-maintenance difficulties.

*Clinical therapeutic effects as indicated by available studies.* The clinical effects of suvorexant have been documented in several large-scale placebo-controlled trials (Herring et al. 2016; Michelson et al. 2014). Two were in primary insomnia patients, and one included patients with comorbid conditions, but these individuals were not included in large enough numbers to allow subgroup analysis. These studies indicate that this medication has therapeutic effects on sleep onset and sleep maintenance, consistent with its FDA indications.

*Effects on systems other than sleep-wake systems.* Suvorexant has minimal effects on systems other than the hypocretin/orexin system. As a result, the primary adverse effects of these agents are relatively limited and due to decreased hypocretin/orexin-mediated function. The primary such effect is daytime sedation or fatigue, but cough, dry



mouth, abnormal dreams, and headache also occur with this medication ([Herring et al. 2016](#); [Michelson et al. 2014](#)).

*Optimal target patient population.* Hypocretin/orexin receptor antagonists are among the agents that could be considered for first-line use in patients with problems both falling and staying asleep. An additional target population is insomnia patients with mild to moderate chronic obstructive pulmonary disease or obstructive sleep apnea because of evidence that these drugs do not exacerbate these conditions ([Sun et al. 2015, 2016](#)). The amygdala, lateral septum, periaqueductal gray, and parabrachial nucleus have important projections to hypocretin/orexin neurons, which are believed to mediate stress- or anxiety-associated increases in arousal; thus, hypocretin/orexin receptor antagonists should, in theory, be particularly useful for patients with sleep problems occurring in the setting of stress or anxiety ([Krystal et al. 2013a](#); [Scammell and Winrow 2011](#)). Hypocretin/orexin receptor antagonists also would be expected to be particularly helpful for those trying to sleep at a time of day that is not their circadian sleep period, because evidence showed that activity in the hypocretin/orexin neurons is driven by the circadian clock and is a prime factor allowing the maintenance of wakefulness during the usual circadian wake period ([Krystal et al. 2013a](#)). Similarly, individuals who tend to get energized in the late evening and have difficulty shutting down to sleep also would likely be helped by selective hypocretin/orexin receptor antagonists. However, studies are needed to determine whether these theoretical optimal target patient populations are actually best treated with hypocretin/orexin receptor antagonists.

### Selective $\alpha_1$ -Adrenergic Receptor Antagonists

Medications that are selective  $\alpha_1$ -adrenergic receptor antagonists have long been available by prescription for the treatment of hypertension and benign prostatic hypertrophy. These agents include prazosin, silodosin, doxazosin, tamsulosin, alfuzosin, and terazosin. These agents may have sleep-enhancing effects by blocking the wake-promoting effects of norepinephrine, one of the important wake-promoting systems ([Krystal and Davidson 2007](#); [Krystal et al. 2013b](#); [Saper et al. 2005](#)). These drugs do so by blocking  $\alpha_1$ -adrenergic receptors, which are primarily excitatory postsynaptic receptors. These agents have long been of interest for modulating anxiety. Evidence that central noradrenergic hyperactivity plays an important role in mediating anxiety has existed for more than 40 years ([Charney and Redmond 1983](#)). A sizable literature indicates that agents that dampen central noradrenergic neuronal activity or blunt noradrenergic system-mediated activation, such as  $\alpha_1$ -adrenergic receptor antagonists, have clinical anxiolytic effects. Within this context, selective  $\alpha_1$ -adrenergic receptor antagonists have found application in the treatment of sleep difficulties.

A series of relatively recent studies documented the therapeutic effects of prazosin, a selective  $\alpha_1$ -adrenergic receptor antagonist, on sleep difficulties in patients with posttraumatic stress disorder (PTSD) ([Goddard et al. 2010](#); [Raskind et al. 2003, 2007, 2013](#); [Taylor et al. 2008](#)). Because of the selectivity of this agent for  $\alpha_1$  receptors, these agents have the potential to improve sleep difficulties in patients with anxiety-related difficulties in a specific, targeted way. They would be expected to have minimal effects on brain function in areas not significantly activated by noradrenergic neurons, including areas related to reward, cognition, and motor function, and, like the selective hypocretin/orexin receptor antagonists and selective  $H_1$  receptor antagonists, have the potential to improve sleep difficulties without many of the adverse effects that have limited the use of benzodiazepines and nonbenzodiazepines. As with the other selective agents,

the potential for adverse daytime sedating effects is also limited by the other parallel wake-promoting systems that are not inhibited by  $\alpha_1$ -adrenergic receptor antagonism, which can maintain wakefulness even though adrenergic-mediated arousal is blunted. As a result, selective  $\alpha_1$ -adrenergic receptor antagonists can specifically improve adrenergic-mediated arousal, primarily driven by stress or anxiety and novelty, in a highly targeted way, thereby minimizing associated adverse effects.

**Selective  $\alpha_1$ -adrenergic receptor antagonists used for the treatment of insomnia.** Although several selective  $\alpha_1$ -adrenergic receptor antagonists are available, the only one that has been significantly studied and used to any significant extent for treating sleep problems is prazosin (Goddard et al. 2010; Krystal and Davidson 2007; Raskind et al. 2003, 2007, 2013; Taylor et al. 2008). However, no selective  $\alpha_1$ -adrenergic receptor antagonists have an FDA indication for treating insomnia.

*Clinical therapeutic effects as indicated by available studies.* The available studies suggest that prazosin consistently improves sleep-maintenance difficulties and nightmares in patients with PTSD (Goddard et al. 2010; Krystal and Davidson 2007; Raskind et al. 2003, 2007, 2013; Taylor et al. 2008). Studies of the effects of this agent on primary insomnia or insomnia occurring with conditions other than PTSD have not been carried out.

*Effects on systems other than sleep-wake systems.* Prazosin has minimal effects on systems other than the noradrenergic. As a result, the primary adverse effects of this agent is relatively limited and due to decreased noradrenergic-mediated function. The primary such effect is orthostatic hypotension and associated dizziness (Goddard et al. 2010; Raskind et al. 2003, 2007, 2013; Taylor et al. 2008). Dry mouth, sweating, nasal congestion, and sedation also have been reported to occur.

*Optimal target patient population.* Prazosin is currently the treatment of choice for patients with sleep difficulties occurring in the setting of PTSD. Although studies are lacking, the use of this agent in treating sleep problems in patients with other anxiety disorders is of high interest. It also should be noted that prazosin is the only medication shown to have a strong effect on nightmares in any context. Nightmares are common in PTSD patients but also occur in those without PTSD, and no established therapies are available to use in this case. As a result, when faced with the need to treat nightmares in a patient who does not have PTSD, it would be reasonable to consider a trial of prazosin.

### **Nonselective Wake-Promoting System Antagonists**

Some agents that were originally developed for the treatment of allergies are generally referred to as *antihistamines*, because they all have significant histamine  $H_1$  receptor antagonism. However, none of these agents are particularly potent or selective  $H_1$  receptor antagonists, and all have clinically significant effects on pharmacological systems other than the histamine system (Krystal et al. 2013b). Notably, agents such as doxepin and mirtazapine are more potent and selective histamine  $H_1$  receptor antagonists than any of these antihistamines, but they were never referred to by this name because they were originally developed for the treatment of depression and not allergy. As a result, they are generally referred to as *antidepressants*. Thus, it is important to appreciate that the term *antihistamine* is more a reflection of the original targeted disorder than it is an indicator of drug pharmacology. A more appropriate term for these agents would be



*nonselective antihistamines.* The nonselective antihistamines primarily used for the treatment of insomnia are agents that are available over the counter. They all have significant muscarinic cholinergic receptor antagonism in addition to H<sub>1</sub> receptor antagonism, and some have other important pharmacological effects (Krystal et al. 2013b). There is reason to believe that these nonhistaminergic effects influence both clinical effects on sleep problems and the side-effect profile (Krystal et al. 2013b). These agents promote sleep primarily by blocking the arousing effects of both histamine and acetylcholine.

**Nonselective antihistamines used for the treatment of insomnia.** Two nonselective antihistamines are the predominant members of this group of medications used for insomnia treatment: diphenhydramine and doxylamine (Krystal et al. 2013b). Both are active ingredients in many over-the-counter sleep treatments.

*Clinical therapeutic effects as indicated by available studies.* Remarkably little systematic research has been carried out on the sleep effects of the nonselective antihistamines considering how frequently these agents are used to treat sleep difficulties. Only two placebo-controlled trials have been completed (Glass et al. 2008; Morin et al. 2005). One was a crossover study including 20 older adults with primary insomnia indicating that diphenhydramine 50 mg decreased number of awakenings compared with placebo but had no other significant effects on sleep problems (Glass et al. 2008). The other study evaluated diphenhydramine 25 mg in a parallel-group trial in approximately 120 adults with relatively mild insomnia (Morin et al. 2005). In this study, diphenhydramine led to significant improvement in self-reported sleep efficiency (time asleep/time in bed) but not in polysomnographic sleep efficiency or self-reported or polysomnographic sleep-onset latency or total sleep time.

*Effects on systems other than sleep-wake systems.* The adverse effects of the nonselective antihistamines include, in addition to daytime sedation, side effects primarily reflecting cholinergic receptor antagonism such as dry mouth, dizziness, constipation, and blurred vision (Glass et al. 2008; Krystal et al. 2013b; Morin et al. 2005). The cholinergic receptor antagonism also increases the risk for urinary retention, memory impairment, and delirium, particularly in older individuals.

*Optimal target patient population.* The limited available data do not make a strong case for the utility of the nonselective antihistamines. However, to the extent that they have therapeutic effects, they appear to be limited to improvements in sleep maintenance and not sleep onset (Glass et al. 2008; Morin et al. 2005). Thus, use should be limited to those without sleep-onset difficulty who have problems with sleep maintenance. The H<sub>1</sub> and cholinergic receptor antagonism of the agents suggests that they would be best suited for use in individuals experiencing sleep problems related to allergies or those with nasal congestion due to other causes such as upper respiratory infection.

## **Antidepressants**

The group of agents developed for the treatment of depression are referred to as *antidepressants*. They have broad pharmacological effects, being antagonists at several receptors, including at least one wake-promoting system, which leads these medications to have sleep-promoting effects (Krystal 2010). These medications are used off label for the treatment of insomnia, often at dosages lower than the antidepressant dosage. With a few exceptions, the risk-benefit profile of these medications for the treatment of insomnia has

not been evaluated in placebo-controlled trials. This is a significant limitation to including them in an evidence-based approach to insomnia therapy. However, it can be assumed that their nonspecific pharmacology leads them to have therapeutic effects on conditions other than insomnia, some of which are common comorbid conditions such as depression, anxiety, and pain, but at the same time associates these medications with a relatively high side-effect burden (Krystal et al. 2013b).

**Antidepressants used for the treatment of insomnia.** The antidepressants most commonly used to treat insomnia include amitriptyline, doxepin, trimipramine, trazodone, and mirtazapine (Krystal 2010). Amitriptyline, doxepin (25–50 mg), and trimipramine promote sleep primarily through antagonism of norepinephrine, histamine, and acetylcholine receptors, whereas trazodone promotes sleep primarily through antagonism of norepinephrine, histamine, and serotonin type 2 (5-HT<sub>2</sub>) receptors, and mirtazapine promotes sleep primarily through antagonism of histamine and 5-HT<sub>2</sub> receptors.

*Clinical therapeutic effects as indicated by available studies.* Of the antidepressants used to treat insomnia, double-blind, placebo-controlled studies of insomnia treatment have been carried out only with trimipramine, doxepin (25–50 mg), and trazodone (Krystal 2010). Trimipramine has been studied in primary insomnia patients at dosages from 50 to 200 mg and was found to improve self-reported sleep quality and sleep efficiency (total sleep time/time in bed) but not sleep-onset latency (Hohagen et al. 1994; Riemann et al. 2002). Studies carried out in insomnia patients with doxepin 25–50 mg indicate that, unlike doxepin 3–6 mg, therapeutic effects on sleep onset, sleep maintenance, and sleep quality were seen (Hajak et al. 1996, 2001; Rodenbeck et al. 2003). Trazodone has been found to have therapeutic effects on sleep when used as adjunctive treatment to antidepressant medications in depressed patients with insomnia (Kaynak et al. 2004; Nierenberg et al. 1994). Trazodone (50 mg) also was evaluated in a placebo-controlled trial in primary insomnia patients, and although improvement was reported in some sleep indices in the first week of treatment, no significant effects compared with placebo were found in the second week of this 2-week study (Walsh et al. 1998). A pilot trial of trazodone as a treatment for insomnia in abstinent alcoholic individuals suggested therapeutic effects on sleep-maintenance problems (Le Bon et al. 2003).

*Effects on systems other than sleep-wake systems.* All of the antidepressants with sleep-enhancing effects have effects on pharmacological systems other than those related to enhancing sleep. Some of these effects can be assets to therapy because they include therapeutic effects on conditions that often co-occur with sleep disturbance, including depression, anxiety, and pain (Krystal 2010; Krystal et al. 2013b). However, some non-sleep-related effects may lead to adverse effects. The specific adverse effects seen depend on both mechanism of action and dose. The higher the dose, the greater the effects on more pharmacological systems, including those mediating side effects. Those agents with significant muscarinic receptor antagonism are associated with a risk of dry mouth, constipation, blurred vision, urinary retention, dizziness, memory impairment, and delirium (Krystal 2010; Krystal et al. 2013b) (Table 53–2). Those with significant adrenergic receptor antagonism are associated with a risk of orthostatic hypotension and dizziness (see Table 53–2). Weight gain, although incompletely understood, appears to be particularly likely with agents with histamine, 5-HT<sub>2C</sub>, and acetylcholine receptor antagonism.

**TABLE 53-2. Properties of agents commonly used to treat insomnia**

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target aspect
<b>Benzodiazepines</b>						
Triazolam	GABA	—	Insomnia	0.125–0.8	2–5.5	Onset, maintenance
Temazepam	GABA	—	Insomnia	7.5–30	8–20	Onset, maintenance
Flurazepam	GABA	—	Insomnia	15–30	40–250	Onset, maintenance
Lorazepam	GABA	—	Anxiety	0.125–1	12–15	Non-maintenance
Clonazepam	GABA	—	Anxiety, seizures	0.25–2	35–40	Non-maintenance
Alprazolam	GABA	—	Anxiety	1–3	12–14	Non-maintenance
<b>Nonbenzodiazepines</b>						
Zolpidem	GABA	—	Insomnia: sleep onset	5–10	2.0–5.5	Onset

*Note.* 5-HT=serotonin; Ach=acetylcholine; COPD=chronic obstructive pulmonary disease; GABA=γ-aminobutyric acid; HA=histamine; N/A=not applicable; NE=norepinephrine; PTSD=posttraumatic stress disorder.

<sup>a</sup>At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or both.

Agent	Enhancement of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target aspect
Zolpidem extended release	GABA	—	Insomnia: sleep onset; sleep maintenance in first 6 hours of the night	6.25–12.5	2.0–5.5	Onset of sleep
Transoral zolpidem	GABA	—	Insomnia: middle of the night	1.75–3.5	2.0–5.5	Middle of the night
Zaleplon	GABA	—	Insomnia: middle of the night	10–20	0.9–1.1	Onset of sleep
Eszopiclone	GABA	—	Insomnia: sleep onset and sleep maintenance	1–3	6–7	Onset of sleep

#### Selective melatonin receptor agonists

Melatonin	Melatonin	—	N/A (available over the counter as herbal supplement)	0.3–10	0.6–1	Onset of sleep
Ramelteon	Melatonin	—	Insomnia: sleep onset	8	0.8–2	Onset of sleep

#### Selective histamine H<sub>1</sub> receptor antagonists

*Note.* 5-HT=serotonin; Ach=acetylcholine; COPD=chronic obstructive pulmonary disease; GABA=γ-aminobutyric acid; HA=histamine; N/A=not applicable; NE=norepinephrine; PTSL

<sup>a</sup>At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance

Agent	Enhance- ment of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target aspects
Doxepin	—	HA	Insomnia: sleep maintenance	3–6	10–50	Main

#### Selective hypocretin/orexin receptor antagonists

Suvorexant	—	Hypocretin/orexin	Insomnia: sleep onset and maintenance	10–20	9–13	Onset main
------------	---	-------------------	--	-------	------	---------------

#### $\alpha_1$ -Adrenergic receptor antagonists

Prazosin	—	NE	Hypertension	2–15	2–3	Main in pa
----------	---	----	--------------	------	-----	------------------

#### Nonspecific wake-promoting system antagonists

Diphenhydramine	—	HA, Ach	Over-the-counter sleep and allergy medication	25–50	5–11	Main
-----------------	---	---------	--	-------	------	------

*Note.* 5-HT=serotonin; Ach=acetylcholine; COPD=chronic obstructive pulmonary disease; GABA= $\gamma$ -aminobutyric acid; HA=histamine; N/A=not applicable; NE=norepinephrine; PTSD=

<sup>a</sup>At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance

<b>Agent</b>	<b>Enhance- ment of</b>	<b>Blockade of</b>	<b>FDA indication</b>	<b>Usual dosage (mg)</b>	<b>Elimination half-life (hours)</b>	<b>Target aspects</b>
Doxylamine	—	HA, Ach	Over-the-counter sleep and allergy medication	25-50	10-12	Non
Amitriptyline	—	NE, HA, Ach	Depression	10-100	10-100	Non
Doxepin	—	NE, HA, Ach	Depression	25-75	10-50	Ons m
Trimipramine	—	NE, HA, Ach	Depression	25-100	15-40	Main

*Note.* 5-HT=serotonin; Ach=acetylcholine; COPD=chronic obstructive pulmonary disease; GABA=γ-aminobutyric acid; HA=histamine; N/A=not applicable; NE=norepinephrine; PTSD=

<sup>a</sup>At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance

Agent	Enhance- ment of	Blockade of	FDA indication	Usual dosage (mg)	Elimination half-life (hours)	Target aspiration
Trazodone	—	5-HT <sub>2</sub> , NE, HA	Depression	25– 150	7–15	Non
Mirtazapine	—	5-HT <sub>2</sub> , HA	Depression	7.5–30	20–40	Non
Olanzapine	—	HA, NE, Ach, 5-HT <sub>2</sub> , DA	Psychosis	2.5–20	20–54	Non
Quetiapine	—	HA, NE, Ach, 5-HT <sub>2</sub> , DA	Psychosis	25– 200	7	Non

*Note.* 5-HT=serotonin; Ach=acetylcholine; COPD=chronic obstructive pulmonary disease; GABA=γ-aminobutyric acid; HA=histamine; N/A=not applicable; NE=norepinephrine; PTSD=posttraumatic stress disorder.

<sup>a</sup>At least one placebo-controlled trial reporting efficacy for either sleep-onset, sleep-maintenance, or total sleep time.

**Optimal target patient population.** Antidepressants with sleep-enhancing effects are best suited for use in patients with sleep problems occurring in conjunction with a condition that they effectively treat. These conditions vary depending on the medication but may include depression, anxiety, or pain (see [Table 53-2](#)) ([Krystal 2010](#)). Two main approaches are used for treating insomnia occurring comorbidly with another such condition. One is to administer single-agent therapy with one of these antidepressants. The other is to combine a sleep-targeted drug with a treatment aimed at improving the

associated condition. No data indicate which approach is preferred. However, an advantage of the two-treatment approach is that it allows a wider range of treatments for the associated conditions, including nonsedating interventions. For example, in a depressed patient with insomnia disorder, one could combine bupropion as an antidepressant with a sleep-targeted intervention, whereas bupropion alone lacks sleep-enhancing effects and thus could not reasonably be used as a single-agent therapy (Krystal et al. 2007b). Antidepressants also can be considered for use in treatment-resistant insomnia because of their broad pharmacological effects.

## Antipsychotics

The antipsychotics share similarities to the antidepressants in being medications with broad pharmacological effects that were developed for an indication other than insomnia disorder but are used off label in treating insomnia at lower-than-usual dosages. In this case, they were developed for treatment of psychosis, although some have more recently received FDA indications for bipolar mania and depression as well. Like the antidepressants, the antipsychotics are antagonists at several receptors, at least one of which includes a wake-promoting system, which is the basis for their sleep-promoting effects (Krystal 2010; Krystal et al. 2008b). Very limited data are available on the risk-benefit profile of these medications for the treatment of insomnia. In fact, even fewer placebo-controlled trials have been carried out with antipsychotics than with antidepressants, which is a significant limitation to including the antipsychotics in an evidence-based approach to insomnia therapy. However, it can be assumed that their nonspecific pharmacology leads them to have therapeutic effects on conditions other than insomnia, some of which are common comorbid conditions such as schizophrenia, mania, delirium, depression, anxiety, and pain, but at the same time associates these medications with a relatively high side-effect burden (Krystal 2010; Krystal et al. 2008b, 2013b).

**Antipsychotics used for the treatment of insomnia.** The antipsychotics most commonly used to treat insomnia include olanzapine and quetiapine (Krystal 2010; Krystal et al. 2008b). Both of these agents promote sleep primarily through antagonism of histamine, norepinephrine, acetylcholine, 5-HT<sub>2</sub>, and dopamine receptors (Krystal 2010; Krystal et al. 2008a).

*Clinical therapeutic effects as indicated by available studies.* No large-scale systematic studies of the use of any of these agents in the treatment of insomnia have been done. Several small studies have been carried out in healthy control subjects and patients with schizophrenia and mood disorders, which included polysomnographic endpoints that provided a preliminary indication that olanzapine improves both sleep-onset and sleep-maintenance problems (Krystal 2010). An open-label trial of quetiapine 25–75 mg in primary insomnia patients provided preliminary evidence that this agent improves sleep-onset latency and total sleep time (Krystal 2010). A double-blind, placebo-controlled, randomized trial of quetiapine 25 mg was carried out in insomnia patients but did not find any significant effects of drug compared with placebo (Tassniyom et al. 2010).

*Effects on systems other than sleep-wake systems.* All of the antipsychotics with sleep-enhancing effects have effects on pharmacological systems other than those related to enhancing sleep. Some of these effects can be assets to therapy because they include therapeutic effects on conditions that often co-occur with sleep disturbance, including schizophrenia, mania, depression, anxiety, and pain (Krystal 2010; Krystal et al. 2008b). However, some non-sleep-related effects may lead to adverse effects. Like with the



antidepressants, the specific adverse effects seen with the antipsychotics depend on both mechanism of action and dose. The higher the dose, the greater the effects on more pharmacological systems, including those mediating side effects (see [Table 53-2](#)). Those agents with significant dopamine receptor antagonism are associated with a risk of parkinsonian side effects, acute dystonic reactions, and tardive dyskinesia ([Krystal et al. 2008b](#)). Those with muscarinic cholinergic receptor antagonism are associated with a risk of dry mouth, constipation, blurred vision, urinary retention, dizziness, memory impairment, and delirium ([Krystal 2010](#); [Krystal et al. 2013b](#)). Those with significant adrenergic receptor antagonism are associated with a risk of orthostatic hypotension and dizziness. Weight gain, although incompletely understood, appears to be particularly likely with agents with histamine, 5-HT<sub>2</sub>, and acetylcholine receptor antagonism.

*Optimal target patient population.* Antipsychotics with sleep-enhancing effects are best suited for use in patients with sleep problems occurring in conjunction with a condition that they effectively treat. These conditions vary depending on the medication but may include schizophrenia, mania, delirium, depression, anxiety, or pain (see [Table 53-2](#)) ([Krystal 2010](#); [Krystal et al. 2008a](#)). Antipsychotics also can be considered for use in treatment-resistant insomnia patients because of their broad pharmacological effects, but the cost of this relatively broad pharmacological effect is a relatively unfavorable side-effect profile that must be taken into account when deciding whether to administer these agents.

---

## Conclusion

---

An increasing set of medications is becoming available to help patients with insomnia. For many years, investigators believed that the mechanism of action of insomnia medications was without clinical implications. Clinical effects were assumed to be determined primarily by dose and drug pharmacokinetic properties. It is now clear that this is not the case. Mechanism of action matters. Clinical effects reflect not only dose and pharmacokinetics but also the specific properties of the pharmacological system(s) being modulated by a given drug and the nature and state of other parallel pharmacological systems that continue to function during the period of action of that drug. As a result, factors such as time of day, the behavior of the patient, and the patient's psychosocial context (e.g., stress, novelty, excitement) can play a role in determining the clinical effects of medications used to treat insomnia. This has become apparent only through experience with the relatively more recently available agents, including selective antagonists of a single wake-promoting system. These agents promise improved risk-benefit ratio over older, broadly acting agents for specific subgroups of patients who have the specific type of sleep problem targeted by a given selective wake-promoting system antagonist. To take advantage of this promise requires knowledge of the specific clinical effects of each agent and the type of sleep difficulty that they best treat. It is also important to appreciate the instances when it is best to use a nonselective, more broadly acting agent. Knowledge of the properties of each agent and the best target patient subpopulation can then serve as a basis for optimally matching patients to therapies in clinical practice. I hope this chapter provided the scientific basis and practical information needed to work toward achieving this type of personalization of insomnia therapies and ultimately to achieving better clinical outcomes in insomnia patients.

---

## References

---

- American Academy of Sleep Medicine: International Classification of Sleep Disorders: Diagnostic and Coding Manual, 3rd Edition. Westchester, IL, American Academy of Sleep Medicine, 2014
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Avidan AY, Fries BE, James ML, et al: Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. *J Am Geriatr Soc* 53(6):955-962, 2005 15935017
- Baglioni C, Battagliese G, Feige B, et al: Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 135(1-3):10-19, 2011 21300408
- Bathgate CJ, Edinger JD, Wyatt JK, et al: Objective but not subjective short sleep duration associated with increased risk for hypertension in individuals with insomnia. *Sleep* 39(5):1037-1045, 2016 26951399
- Breslau N, Roth T, Rosenthal L, et al: Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 39(6):411-418, 1996 8679786
- Buscemi N, Vandermeer B, Hooton N, et al: The efficacy and safety of exogenous melatonin for primary sleep disorders: a meta-analysis. *J Gen Intern Med* 20(12): 1151-1158, 2005 16423108
- Charney DS, Redmond DE Jr: Neurobiological mechanisms in human anxiety: evidence supporting central noradrenergic hyperactivity. *Neuropharmacology* 22(12B): 1531-1536, 1983 6142428
- Dubocovich ML, Rivera-Bermudez MA, Gerdin MJ, et al: Molecular pharmacology, regulation and function of mammalian melatonin receptors. *Front Biosci* 8: d1093-d1108, 2003 12957828
- Edinger JD, Wohlgemuth WK, Radtke RA, et al: Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *JAMA* 285(14):1856-1864, 2001 11308399
- Edinger JD, Wohlgemuth WK, Krystal AD, et al: Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. *Arch Intern Med* 165(21):2527-2535, 2005 16314551
- Edinger JD, Wyatt JK, Stepanski EJ, et al: Testing the reliability and validity of DSM-IV-TR and ICSD-2 insomnia diagnoses: results of a multitrait-multimethod analysis. *Arch Gen Psychiatry* 68(10):992-1002, 2011 21646568
- Fava M, McCall WV, Krystal A, et al: Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry* 59(11):1052-1060, 2006 16581036
- Fava M, Asnis GM, Shrivastava R, et al: Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. *J Clin Psychopharmacol* 29(3):222-230, 2009 19440075
- Fava M, Asnis GM, Shrivastava RK, et al: Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. *J Clin Psychiatry* 72(7):914-928, 2011 21208597
- Ferracioli-Oda E, Qawasmi A, Bloch MH: Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS One* 8(5):e63773, 2013 23691095
- Ford DE, Kamerow DB: Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *JAMA* 262(11):1479-1484, 1989 2769898
- Glass JR, Sproule BA, Herrmann N, et al: Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *J Clin*

- Psychopharmacol 28(2):182-188, 2008 18344728
- Goddard AW, Ball SG, Martinez J, et al: Current perspectives of the roles of the central norepinephrine system in anxiety and depression. *Depress Anxiety* 27(4):339-350, 2010 19960531
- Goforth HW, Preud'homme XA, Krystal AD: A randomized, double-blind, placebo-controlled trial of eszopiclone for the treatment of insomnia in patients with chronic low back pain. *Sleep* 37(6):1053-1060, 2014 24882900
- Hajak G, Rodenbeck A, Adler L, et al: Nocturnal melatonin secretion and sleep after doxepin administration in chronic primary insomnia. *Pharmacopsychiatry* 29(5):187-192, 1996 8895944
- Hajak G, Rodenbeck A, Voderholzer U, et al: Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. *J Clin Psychiatry* 62(6):453-463, 2001 11465523
- Harvey AG: Insomnia, psychiatric disorders, and the transdiagnostic perspective. *Current Directions in Psychological Science* 17(5):299-303, 2008
- Herring WJ, Connor KM, Ivgy-May N, et al: Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. *Biol Psychiatry* 79(2):136-148, 2016 25526970
- Hohagen F, Montero RF, Weiss E, et al: Treatment of primary insomnia with trimipramine: an alternative to benzodiazepine hypnotics? *Eur Arch Psychiatry Clin Neurosci* 244(2):65-72, 1994 7948056
- Jia F, Goldstein PA, Harrison NL: The modulation of synaptic GABA(A) receptors in the thalamus by eszopiclone and zolpidem. *J Pharmacol Exp Ther* 328(3):1000-1006, 2009 19033556
- Johnson EO, Chilcoat HD, Breslau N: Trouble sleeping and anxiety/depression in childhood. *Psychiatry Res* 94(2):93-102, 2000 10808035
- Kaynak H, Kaynak D, Gözükmizi E, et al: The effects of trazodone on sleep in patients treated with stimulant antidepressants. *Sleep Med* 5(1):15-20, 2004 14725822
- Kessler RC, Berglund PA, Coulouvrat C, et al: Insomnia, comorbidity, and risk of injury among insured Americans: results from the America Insomnia Survey. *Sleep* 35(6):825-834, 2012 22654202
- Koski K, Luukinen H, Laippala P, et al: Risk factors for major injurious falls among the home-dwelling elderly by functional abilities: a prospective population-based study. *Gerontology* 44(4):232-238, 1998 9657085
- Kryger M, Wang-Weigand S, Roth T: Safety of ramelteon in individuals with mild to moderate obstructive sleep apnea. *Sleep Breath* 11(3):159-164, 2007 17294232
- Kryger M, Roth T, Wang-Weigand S, Zhang J: The effects of ramelteon on respiration during sleep in subjects with moderate to severe chronic obstructive pulmonary disease. *Sleep Breath* 13(1):79-84, 2009 18584227
- Krystal AD: Treating the health, quality of life, and functional impairments in insomnia. *J Clin Sleep Med* 3(1):63-72, 2007 17557457
- Krystal AD: A compendium of placebo-controlled trials of the risks/benefits of pharmacological treatments for insomnia: the empirical basis for U.S. clinical practice. *Sleep Med Rev* 13(4):265-274, 2009 19153052
- Krystal AD: Antidepressant and antipsychotic drugs. *Sleep Med Clin* 5(4):571-589, 2010 21499530
- Krystal AD: New developments in insomnia medications of relevance to mental health disorders. *Psychiatr Clin North Am* 38(4):843-860, 2015 26600112
- Krystal AD, Davidson JR: The use of prazosin for the treatment of trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 61(8):925-927, 2007 17397667
- Krystal AD, Walsh JK, Laska E, et al: Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* 26(7):793-799, 2003 14655910

- Krystal A, Fava M, Rubens R, et al: Evaluation of eszopiclone discontinuation after cotherapy with fluoxetine for insomnia with coexisting depression. *J Clin Sleep Med* 3(1):48-55, 2007a 17557453
- Krystal AD, Thase ME, Tucker VL, et al: Bupropion HCL and sleep in patients with depression. *Current Psychiatry Reviews* 3(2):123-128, 2007b
- Krystal AD, Erman M, Zammit GK, et al; ZOLONG Study Group: Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep* 31(1):79-90, 2008a 18220081
- Krystal AD, Goforth HW, Roth T: Effects of antipsychotic medications on sleep in schizophrenia. *Int Clin Psychopharmacol* 23(3):150-160, 2008b 18408529
- Krystal AD, Durrence HH, Scharf M, et al: Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. *Sleep* 33(11): 1553-1561, 2010 21102997
- Krystal AD, Lankford A, Durrence HH, et al: Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. *Sleep* 34(10):1433-1442, 2011 21966075
- Krystal AD, McCall WV, Fava M, et al: Eszopiclone treatment for insomnia: effect size comparisons in patients with primary insomnia and insomnia with medical and psychiatric comorbidity. *Prim Care Companion CNS Disord* 14(4):PCC.11m01296, 2012 23251857
- Krystal AD, Benca RM, Kilduff TS: Understanding the sleep-wake cycle: sleep, insomnia, and the orexin system. *J Clin Psychiatry* 74 (suppl 1):3-20, 2013a 24107804
- Krystal AD, Richelson E, Roth T: Review of the histamine system and the clinical effects of H1 antagonists: basis for a new model for understanding the effects of insomnia medications. *Sleep Med Rev* 17(4):263-272, 2013b 23357028
- Le Bon O, Murphy JR, Staner L, et al: Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 23(4):377-383, 2003 12920414
- Léger D, Poursain B, Neubauer D, et al: An international survey of sleeping problems in the general population. *Curr Med Res Opin* 24(1):307-317, 2008 18070379
- Manber R, Buysse DJ, Edinger J, et al: Efficacy of cognitive-behavioral therapy for insomnia combined with antidepressant pharmacotherapy in patients with comorbid depression and insomnia: a randomized controlled trial. *J Clin Psychiatry* 77(10):e1316-e1323, 2016 27788313
- Michelson D, Snyder E, Paradis E, et al: Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 13(5):461-471, 2014 24680372
- Minkel J, Krystal AD: Optimizing the pharmacologic treatment of insomnia: current status and future horizons. *Sleep Med Clin* 8(3):333-350, 2013 24015116
- Morin CM, Koetter U, Bastien C, et al: Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep* 28(11):1465-1471, 2005 16335333
- Morin CM, Bootzin RR, Buysse DJ, et al: Psychological and behavioral treatment of insomnia: update of the recent evidence (1998-2004). *Sleep* 29(11):1398-1414, 2006 17162986
- Morin CM, LeBlanc M, Bélanger L, et al: Prevalence of insomnia and its treatment in Canada. *Can J Psychiatry* 56(9):540-548, 2011 21959029
- Morin CM, Drake CL, Harvey AG, et al: Insomnia disorder. *Nat Rev Dis Primers* 1:15026, 2015 27189779
- National Institutes of Health: Consensus conference: drugs and insomnia: the use of medications to promote sleep. *JAMA* 251(18):2410-2414, 1984 6142971

- National Institutes of Health: National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005. *Sleep* 28(9): 1049-1057, 2005 16268373
- Niederhofer H, Staffen W, Mair A, et al: Brief report: melatonin facilitates sleep in individuals with mental retardation and insomnia. *J Autism Dev Disord* 33(4):469-472, 2003 12959427
- Nierenberg AA, Adler LA, Peselow E, et al: Trazodone for antidepressant-associated insomnia. *Am J Psychiatry* 151(7):1069-1072, 1994 8010365
- Ohayon MM: Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. *J Psychiatr Res* 31(3):333-346, 1997 9306291
- Ohayon MM: Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 6(2):97-111, 2002 12531146
- Ohayon MM, Reynolds CF 3rd: Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). *Sleep Med* 10(9):952-960, 2009 19748312
- Pollack M, Kinrys G, Krystal A, et al: Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. *Arch Gen Psychiatry* 65(5):551-562, 2008 18458207
- Raskind MA, Peskind ER, Kanter ED, et al: Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 160(2):371-373, 2003 12562588
- Raskind MA, Peskind ER, Hoff DJ, et al: A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 61(8):928-934, 2007 17069768
- Raskind MA, Peterson K, Williams T, et al: A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry* 170(9):1003-1010, 2013 23846759
- Riemann D, Voderholzer U, Cohrs S, et al: Trimipramine in primary insomnia: results of a polysomnographic double-blind controlled study. *Pharmacopsychiatry* 35(5):165-174, 2002 12237787
- Rodenbeck A, Cohrs S, Jordan W, et al: The sleep-improving effects of doxepin are paralleled by a normalized plasma cortisol secretion in primary insomnia: a placebo-controlled, double-blind, randomized, cross-over study followed by an open treatment over 3 weeks. *Psychopharmacology (Berl)* 170(4):423-428, 2003 13680082
- Roth T, Coulouvrat C, Hajak G, et al: Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol Psychiatry* 69(6):592-600, 2011 21195389
- Roth T, Krystal A, Steinberg FJ, et al: Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. *Sleep* 36(2):189-196, 2013 23372266
- Sakurai T: The role of orexin in motivated behaviours. *Nat Rev Neurosci* 15(11):719-731, 2014 25301357
- Sanna E, Busonero F, Talani G, et al: Comparison of the effects of zaleplon, zolpidem, and triazolam at various GABA(A) receptor subtypes. *Eur J Pharmacol* 451(2): 103-110, 2002 12231378
- Saper CB, Scammell TE, Lu J: Hypothalamic regulation of sleep and circadian rhythms. *Nature* 437(7063):1257-1263, 2005 16251950
- Sarsour K, Morin CM, Foley K, et al: Association of insomnia severity and comorbid medical and psychiatric disorders in a health plan-based sample: insomnia severity and comorbidities. *Sleep Med* 11(1):69-74, 2010 19410512

- Scammell TE, Winrow CJ: Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol* 51:243-266, 2011 21034217
- Sieghart W, Sperk G: Subunit composition, distribution and function of GABA(A) receptor subtypes. *Curr Top Med Chem* 2(8):795-816, 2002 12171572
- Stone KL, Blackwell TL, Ancoli-Israel S, et al; Osteoporotic Fractures in Men Study Group: Sleep disturbances and risk of falls in older community-dwelling men: the outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. *J Am Geriatr Soc* 62(2):299-305, 2014 24428306
- Sun H, Palcza J, Rosenberg R, et al: Effects of suvorexant, an orexin receptor antagonist, on breathing during sleep in patients with chronic obstructive pulmonary disease. *Respir Med* 109(3):416-426, 2015 25661282
- Sun H, Palcza J, Card D, et al: Effects of suvorexant, an orexin receptor antagonist, on respiration during sleep in patients with obstructive sleep apnea. *J Clin Sleep Med* 12(1):9-17, 2016 26194728
- Tassniyom K, Paholpak S, Tassniyom S, et al: Quetiapine for primary insomnia: a double blind, randomized controlled trial. *J Med Assoc Thai* 93(6):729-734, 2010 20572379
- Taylor FB, Martin P, Thompson C, et al: Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. *Biol Psychiatry* 63(6): 629-632, 2008 17868655
- Vgontzas AN, Fernandez-Mendoza J, Liao D, et al: Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev* 17(4):241-254, 2013 23419741
- Walsh JK, Erman M, Erwin CW: Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. *Human Psychopharmacology: Clinical and Experimental* 13(3):191-198, 1998
- Walsh JK, Krystal AD, Amato DA, et al: Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep* 30(8):959-968, 2007 17702264
- Wilson SJ, Nutt DJ, Alford C, et al: British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol* 24(11):1577-1601, 2010 20813762
- Winsper C, Tang NK: Linkages between insomnia and suicidality: prospective associations, high-risk subgroups and possible psychological mechanisms. *Int Rev Psychiatry* 26(2):189-204, 2014 24892894
- Wirojanan J, Jacquemont S, Diaz R, et al: The efficacy of melatonin for sleep problems in children with autism, fragile X syndrome, or autism and fragile X syndrome. *J Clin Sleep Med* 5(2):145-150, 2009 19968048
- Zammit GK, Corser B, Doghramji K, et al: Sleep and residual sedation after administration of zaleplon, zolpidem, and placebo during experimental middle-of-the-night awakening. *J Clin Sleep Med* 2(4):417-423, 2006 17557470

## CHAPTER 54

# Treatment of Chronic Pain

Kurt Kroenke, M.D.

Pain is the most common symptom reported in both the general population and the general medical setting (Kroenke 2003b; Sternbach 1986; Verhaak et al. 1998). Pain complaints account for more than 40% of all symptom-related outpatient visits, or over 100 million ambulatory encounters in the United States alone each year (Schappert 1992). Among the 30 diseases producing the most disability in the United States, pain conditions account for the 1st (low back pain), 4th (neck pain), 5th (other musculoskeletal disorders), 9th (osteoarthritis), and 14th (migraine headache) leading causes (Murray et al. 2013). The total costs (health care, lost productivity, and other costs) attributable to pain in the United States is more than \$600 billion annually, a figure that exceeds the annual costs of heart disease (\$309 billion), cancer (\$243 billion), and diabetes (\$188 billion) (Henschke et al. 2015). In 2008, analgesics constituted 10.1% of all drugs prescribed for adults (ranking a close second to antidepressants, at 10.8%) (Institute of Medicine 2011). Yet nonopioid analgesics fail to provide adequate relief for many patients (Curatolo and Bogduk 2001; Nuckols et al. 2014), and physicians' concerns about regulatory restrictions and risks of tolerance or addiction constrain the prescribing of opioid analgesics for noncancer pain (Joranson et al. 2002). Moreover, opioids themselves may provide only moderate reductions in chronic pain (Furlan et al. 2006; Martell et al. 2007) and may fail to improve (or may even worsen) psychological outcomes (e.g., depression) or functional status even when they do alleviate the pain (Moulin et al. 1996). At the same time, clinicians are being pressured to respond to pain as the "fifth vital sign" (Joint Commission on Accreditation of Healthcare Organizations 2000). In House Resolution 1863, the National Pain Care Policy Act of 2003, Congress declared the period 2001–2010 the "Decade of Pain Control and Research." Indeed, persistent pain is a major international health problem (Gureje et al. 1998), prompting the World Health Organization to endorse a global campaign against pain (Breivik 2002). Persistent pain may lead to excessive surgery or other expensive or invasive procedures and is the leading reason for use of complementary and alternative medicine (CAM) (Astin 1998).

---

## Psychiatric Comorbidity

---

Pain is even more prevalent in patients with psychiatric comorbidity, particularly mood disorders. The overlap between pain and depression ranges from 30% to 60% (Ang et al. 2006; Bair et al. 2003; Magni et al. 1993). Pain is a strong predictor of both the onset and

the persistence of depression ([Ohayon and Schatzberg 2003](#)), and depression is likewise a powerful predictor of pain, particularly persistent pain ([Bair et al. 2003](#); [Gureje et al. 1998](#)). Concurrent pain and depression have a much greater impact than either disorder alone on multiple domains of functional status as well as health care utilization ([Bair et al. 2003](#)). Comorbid depression worsens disability and decreases active coping in patients suffering from pain ([Arnow et al. 2006](#); [Demyttenaere et al. 2006](#)). Comorbidity decreases the likelihood of a favorable response of either condition to treatment and also diminishes patient satisfaction with treatment ([Bair et al. 2004](#); [DeVeauugh-Geiss et al. 2010](#); [Karp et al. 2005](#); [Kroenke et al. 2008](#); [Mavandadi et al. 2007](#); [Thielke et al. 2007](#)). Thus, reliable methods for assessing the presence and severity of pain in patients with depression (particularly those not responding to initial treatment) and strategies for effectively and efficiently integrating evidence-based depression care into the management of patients with chronic pain are sorely needed ([Kroenke 2003a](#)).

Although not as extensively studied, the comorbidity of pain with anxiety appears to be nearly as strong as its comorbidity with depression ([Bair et al. 2008, 2013](#); [Kroenke 2003b](#); [Kroenke and Price 1993](#); [Kroenke et al. 1994, 1997](#); [McWilliams et al. 2003](#)). Indeed, a global study conducted by the World Health Organization in 17 countries and involving more than 85,000 community-dwelling adults showed that pain is associated with mood and anxiety disorders, but not with alcohol use disorders ([Gureje et al. 2008](#)). The prevalence of specific mood and anxiety disorders was lowest among persons with no pain, intermediate among those with one pain site, and highest among those with multiple pain sites. Relative to persons not reporting pain, the age-sex adjusted odds ratios were 1.8 (95% confidence interval [CI]=1.7-2.0) for mood disorders and 1.9 (95% CI=1.8-2.1) for anxiety disorders for persons with single-site pain, and 3.7 (95% CI=3.3-4.1) for mood disorders and 3.6 (95% CI=3.3-4.0) for anxiety disorders among those with multisite pain.

---

## Definition and Classification of Pain

---

The [International Association for the Study of Pain \(2012\)](#) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Although there are more complex approaches to classifying pain, a pragmatic and frequently used system broadly classifies pain as either *nociceptive* or *neuropathic* ([Basbaum et al. 2005](#)). Nociceptive pain includes most cases of acute pain in which a strong, noxious stimulus impacts the skin or deep tissue. Acute pain resolves after the noxious stimulus has been removed, but inflammatory and other mechanisms may lead to persistence of nociceptive pain for weeks, months, or years (i.e., chronic pain). Many pain conditions, including arthritis and other musculoskeletal disorders, migraine and tension headache, and chronic widespread pain conditions such as fibromyalgia, would be classified under the broad rubric of nociceptive pain.

A second type of chronic pain, neuropathic pain, arises from injury to the peripheral or central nervous system. Examples include postherpetic neuralgia, painful diabetic neuropathy, phantom limb pain, and sciatica. Neuropathic pain is often characterized as burning, paroxysmal, stabbing, buzzing, or electric shock-like. Some conditions, such as low back pain, may include both nociceptive components (arising from the muscles or contiguous tissues) and neuropathic components (radicular pain or sciatica).

Persons with chronic pain often suffer from spontaneous ongoing pain. Also, stimuli that are normally not painful (movement, light touch) become painful, a phenomenon known as *allodynia*. Examples include pain produced by touching sunburned skin or moving an



arthritic joint. *Hyperalgesia* is exacerbated pain produced by a stimulus that is expected to be only mildly painful (e.g., slapping sunburned skin). These phenomena may be related to central sensitization, which has been proposed as a common mechanism underlying unexplained pain syndromes such as fibromyalgia.

Sometimes the broader category of nociceptive pain is subclassified into *somatic* pain (triggered in the skin, muscles, joints, or fascia) and *visceral* pain (heart, lungs, gastrointestinal or genitourinary system, or other deeper organs). The latter is diffuse and poorly localized, reflecting differences in innervation between somatic and visceral tissue. Somatosensory fibers are precisely located in the spinal cord and brain, whereas afferent viscerosensory fibers overlap each other and converge at several levels within the nervous system. Although some of the principles of pain management are relevant to visceral pain, in this chapter we concentrate on the management of chronic pain due to nociceptive pain of the somatic variety and neuropathic pain conditions. Together, these account for the majority of chronic pain conditions seen in clinical practice. Moreover, visceral pain is more commonly a harbinger of a serious underlying disorder with specific treatments targeting the disease itself rather than mere analgesia. In contrast, pain itself becomes the primary “disease” or target of therapy in a large proportion of chronic somatic and neuropathic pain disorders.

---

## Treatment of Pain

---

### Overview

The focus of this chapter is twofold. First, we discuss major classes of medications as they relate to pain management. Because a number of drugs are effective across multiple types of pain disorders, it is useful to consider them in a cross-cutting as well as a disease-specific fashion. Nonpharmacological treatments are also reviewed. In the following main section (“Selected Pain Disorders”), we briefly address several specific categories of disorders chosen because they 1) account for the most common types of chronic pain, 2) are conditions for which pain management is the principal focus, and 3) have been studied in numerous clinical trials. In short, prevalence, pain management as a priority rather than disease modification, and evidence-based therapy are the three selection criteria for the discussion of specific disorders. Even within these two broad foci (disorders and treatments), there will perforce be some intermingling. For example, certain drug classes have been heavily studied within certain pain disorders, and conversely, certain pain disorders have been a common target of several classes of medications or other treatments.

The prototypical diseases discussed are musculoskeletal disorders (principally fibromyalgia, low back pain, and osteoarthritis), headaches, and neuropathic pain. Musculoskeletal disorders account for more than two-thirds of pain-related outpatient visits, and headaches follow as the next most prevalent pain disorder. Neuropathic pain not only is prevalent but also is a popular target for clinical trials in pain management, and therefore is a common reason pain. Acute pain (e.g., injuries, postoperative pain), cancer pain, and visceral pain are not addressed. Although a moderate amount of thefor seeking U.S. Food and Drug Administration (FDA) approval of pain as a drug indication. Although pharmacotherapy receives the greatest attention in this chapter, we briefly review nonpharmacological treatments due to their important role in the management of chronic

information presented in this chapter is relevant to the treatment of pain in these and other conditions (especially the discussion of specific analgesics), a detailed discussion of these specialized topics is beyond the scope of this chapter.

## Strength of Evidence

The majority of the information in this chapter was derived from meta-analyses and systematic reviews. Individual randomized controlled trials (RCTs) are not presented unless they reported on a promising treatment for which multiple trials had not yet been performed. Certainly, evidence is strongest for those treatments that have shown efficacy in multiple trials rather than just a single RCT, particularly because individual trials sometimes yield contradictory findings. Uncontrolled or open-label studies provide still weaker evidence and are cited in only a few instances.

In meta-analyses and systematic reviews, the magnitude of a treatment's effect on particular domains such as pain and physical function is often reported as an *effect size*. The effect size is a standard way to determine the degree of improvement (or change) related to a particular therapy compared with a placebo or other type of control group. The effect size is calculated as the mean change in the treatment group minus the mean change in the control group, divided by the pooled standard deviation. By convention, an effect size of less than 0.2 is considered trivial; 0.2–0.5, small; 0.5–0.8, moderate; 0.8–1.2, important; and 1.2 or greater, very important ([Cohen 1998](#)).

Effect size can be useful when comparing continuous variables such as mean differences (e.g., in pain scores). When comparing response rates on a categorical variable (e.g., “improved” or “≥50% reduction in pain”), the *number needed to treat* (NNT) is another common metric. The NNT is calculated as the reciprocal of the absolute difference between treatment groups. For example, if a clinical trial demonstrates that 60% of subjects improve while taking a new analgesic versus 35% of subjects receiving a placebo, that is an absolute difference of 25%. The NNT is the reciprocal of that:  $1 \div 0.25 = 4$ . This means that for every four patients who receive the analgesic, one additional patient would achieve a therapeutic response over and above placebo (i.e., the other three patients may have done just as well taking the placebo). Actually, an NNT of  $\leq 5$  typically represents a reasonably good analgesic.

When studying the same pain condition, the NNT may also be useful in comparing different drugs. For example, in one study of acute pain after certain operative procedures, 10 mg of morphine, 30 mg of ketorolac, and 100 mg of meperidine (all administered by intramuscular injection) and 1,000 mg of acetaminophen (administered orally) all had NNTs between 3 and 4; furthermore, their 95% confidence intervals overlapped, implying no significant difference in the analgesic efficacy between intramuscular opioids, intramuscular nonsteroidal anti-inflammatory drugs (NSAIDs), and oral acetaminophen ([Barden et al. 2004](#)). However, analgesic effect may depend on the type of pain condition being treated or clinical context as well. For example, one study found that the NNT for acetaminophen after dental extraction was 3.8, compared with 1.9 after orthopedic surgery ([Barden et al. 2004](#)). Also, small sample sizes may affect the precision of NNT estimates; some feel that NNT calculations based on trial data involving fewer than 500 subjects should be interpreted cautiously. Second, it is more problematic to compare the NNTs of different drugs estimated from separate studies than to compare the NNTs estimated for different drugs tested in the same clinical trial. Third, NNTs derived from studying analgesics in acute pain conditions may not be readily generalizable to their efficacy in the treatment of chronic pain.

# Pharmacotherapy

## Nonopioid Analgesics

The anti-inflammatory properties of the extract of willow bark have been known for centuries. Salicylic acid was discovered as the extract's active ingredient in the nineteenth century and was subsequently acetylated to improve its gastrointestinal tolerability; acetylsalicylic acid became the prototypical analgesic aspirin. Aspirin and other related compounds constitute a class of drugs known as NSAIDs. All NSAIDs have three desirable pharmacological effects—anti-inflammatory, analgesic, and antipyretic. NSAIDs and acetaminophen are among the most commonly prescribed medications for acute and chronic pain and can also be obtained without a prescription.

Acetaminophen has analgesic and antipyretic effects similar to those of the NSAIDs but lacks a specific anti-inflammatory effect. Despite the widespread use of acetaminophen, its analgesic mechanism is poorly understood. Acetaminophen is a slightly weaker analgesic than NSAIDs (<10 point difference on a 100-point visual analog pain scale) (Lee et al. 2004; Towheed et al. 2006; Wegman et al. 2004) but is a reasonable first-line option because of its more favorable safety profile and low cost. A recent trial found acetaminophen to be no more effective than placebo in acute back pain (Williams et al. 2014), whereas a much earlier trial found acetaminophen to be equivalent to low- or high-dose ibuprofen in treating knee osteoarthritis (Bradley et al. 1991). It is possible that analgesic effectiveness may vary with type of pain condition, duration (acute vs. chronic), comparison group, and other factors. Acetaminophen is associated with asymptomatic elevations of aminotransferase levels at dosages of 4 g/day even in healthy adults, although the clinical significance of these findings is uncertain (Watkins et al. 2006). Thus, known liver disease is a reason either to use analgesics other than acetaminophen or to lower the acetaminophen maximum daily dosage to 2,000 mg or less.

NSAIDs block the enzymatic activity of cyclo-oxygenase (COX), which uses arachidonic acid to generate prostanoids. Prostanoids influence immune, cardiovascular, gastrointestinal, renovascular, pulmonary, central nervous system, and reproductive function. Although gastrointestinal adverse effects have traditionally been considered the most common and worrisome complication, cardiovascular risk has gained increasing attention (Antman et al. 2007). Aspirin was the first and at one time the most commonly used NSAID.

There are two major COX isoenzymes: COX-1 is expressed constantly in most tissues, whereas COX-2 is induced by inflammation. NSAIDs vary in their chemical structure and relative ability to block the COX-1 versus the COX-2 isoenzymes. Several prostaglandins are both hyperalgesic and gastroprotective. Thus, nonselective COX inhibition with NSAIDs like aspirin, ibuprofen, indomethacin, and naproxen, which inhibit both COX-1 and COX-2 enzymes, provides effective pain relief for inflammatory conditions but carries a risk for erosive gastritis and gastrointestinal bleeding. Selective COX-2 inhibitors (valdecoxib, rofecoxib, celecoxib) have less gastrointestinal toxicity because of the relative paucity of COX-2 expression in the gastrointestinal tract compared with inflammatory tissue. However, data from meta-analyses and registries have shown an increased risk of cardiovascular events and mortality from COX-2 use, particularly in patients with known cardiovascular disease who receive prolonged treatment. Rofecoxib (Vioxx) has been withdrawn from the market, and all COX-2 inhibitors should be used cautiously, if at all, in patients with cardiovascular disease or risk factors for cardiovascular disease. All NSAIDs, including nonselective COX inhibitors and COX-2 agents, appear equally effective in the

treatment of pain disorders ([Chou et al. 2006](#)). The NSAID that appears to be the safest in terms of cardiovascular risk is naproxen.

In July 2015, the FDA decided to strengthen its existing label warning that NSAIDs increase the chance of a heart attack or stroke. Although there is some risk even with short-term use or in patients without a history of cardiovascular (CV) disease or risk factors, both longer duration of use and presence of CV disease or risk factors substantially increase CV risk in patients receiving NSAIDs. However, the actual increased risk in a specific patient is still low, and given the prevalence of and disability associated with chronic pain and the limitations of other treatment options, NSAIDs are likely to remain a staple of pain management. Concerns about chronic use are particularly focused on special populations including those at greater risk of cardiovascular (e.g., known CV disease or >2 CV risk factors), gastrointestinal, or renal complications ([Marks et al. 2012](#)).

## Opioid Analgesics

The analgesic effects of opium have been known to mankind for more than 5,000 years. However, their inherent abuse risk soon became evident. Ever since, society has attempted to find a balance between licit and illicit use, therapeutic versus adverse effects, and medical needs and legal issues. Despite all the legal, administrative, and social interference, no other class of drugs has remained in use for as long as the opioids ([Schug 2005](#)).

Opioids have a leading place in the treatment of acute pain and advanced cancer pain of moderate to severe intensity, because in both instances treatment is expected to be of short to medium duration. In contrast, opioid treatment for chronic noncancer pain is frequently delayed until first- or second-line treatments have failed because of less clarity about the benefits of chronic use and greater concerns about addiction, long-term effects (e.g., immunological, reproductive), opioid-induced hyperalgesia, and regulatory difficulties.

The Controlled Substances Act of 1970 divided substances to be regulated into five schedules, as determined by the U.S. Drug Enforcement Administration. These schedules govern the legal distribution and use of most substances with a significant abuse liability. Schedule I drugs have the highest abuse potential; they are available for research only and have no approved medical uses. Schedule II–IV substances have decreasing abuse liabilities (II is the highest) and approved medical uses. Physicians are licensed to prescribe these compounds, and pharmacies can dispense them, although pharmacies do not stock all of these substances. Schedule II compounds have more stringent record-keeping and storage requirements than do Schedule III and Schedule IV substances. Schedule V substances have a recognized abuse liability (and approved medical uses) but are generally not as highly regulated vis-à-vis record keeping. Most opioids prescribed for pain are now Schedule II substances, and refills are not authorized; instead, each dispensation requires a new prescription. Exceptions are combination analgesics (e.g., those containing acetaminophen) that contain less than 90 mg of codeine per unit dose, which are Schedule III substances; and tramadol, which is a Schedule IV substance.

Opioids were initially reserved for the short-term treatment of pain following surgery, trauma, and other acute conditions as well as palliative therapy for cancer and other terminal diseases. In the 1990s, however, there was advocacy for improved treatment of chronic pain, which led to a more liberal use of opioids ([Franklin 2014](#); [Nuckols et al. 2014](#); [Rauenzahn and Del Fabbro 2014](#); [Reuben et al. 2015](#)). In the first decade of the twenty-first century, the number of opioid prescriptions increased by more than 60%. Opioids are now the leading cause of overdose deaths (about 16,000 deaths in the United

States annually) and are also associated with diversion to nonmedical uses. Because the long-term benefits of opioid therapy for chronic pain have not been well established, there are increasing state and federal regulations that are making the prescribing of opioids more onerous for both clinicians and patients. Nonetheless, many experts still believe that opioids have a role in that subset of patients whose chronic pain has been refractory to other treatments, as long as there is appropriate monitoring of response, attention to adverse effects, and minimization of diversion and abuse.

**Tramadol.** Tramadol is unique in that it has both opioid and nonopioid effects. Although its mode of action is not completely understood, it exerts an analgesic effect through binding to the  $\mu$  opioid receptor as an agonist (opioid effect) and weakly inhibiting the reuptake of serotonin and norepinephrine (nonopioid effect), similar to the effect of tricyclic antidepressants (TCAs). Tramadol is available in both short- and long-acting formulations. The starting dosage for the short-acting formulation is 50 mg once or twice daily, with gradual titration to a maximum of 400 mg/day. Dosage reduction is necessary in those with renal or hepatic disease. The risk of respiratory depression and, presumably, addiction is lower than with other opiates. However, it still should be used with some caution in persons recovering from substance use disorders. Dose reduction is recommended in older adult patients (>75 years) and in those with renal impairment (creatinine clearance <30 mL/minute) or cirrhosis of the liver. Multiple trials have demonstrated the efficacy of tramadol in pain disorders, particularly osteoarthritis, fibromyalgia, and neuropathic pain.

[Hollingshead et al. \(2006\)](#) conducted a systematic review of six trials evaluating tramadol in neuropathic pain. All four trials comparing tramadol with placebo showed benefit with tramadol: the NNT with tramadol versus placebo to reach at least 50% pain relief was 3.8. Single trials comparing tramadol with clomipramine or morphine were inconclusive.

In summary, the clinical trial evidence across a number of pain disorders is much stronger for tramadol, which has led to its recommendation as at least a second-line treatment for conditions such as osteoarthritis, fibromyalgia, and neuropathic pain. Because it is a Schedule IV medication, tramadol may be an appropriate option when other analgesics have failed and before initiating other opioid analgesics, all of which are Schedule II.

**Efficacy of opioids.** [Furlan et al. \(2006\)](#) conducted a meta-analysis of opioid use for chronic noncancer pain. Included were 41 trials involving 6,019 patients: 80% of the patients had nociceptive pain (osteoarthritis, rheumatoid arthritis, or back pain); 12%, neuropathic pain (postherpetic neuralgia, diabetic neuropathy, or phantom limb pain); 7%, fibromyalgia; and 1%, mixed pain. For certain analyses, the authors classified opioids as weak (propoxyphene, tramadol, codeine) or strong (all other opioids). Tramadol was the agent studied in 17 trials (3,433 patients), propoxyphene or dextropropoxyphene in 3 trials (1,074 patients), codeine in 7 trials (444 patients), oxycodone in 6 trials (517 patients), and morphine in 8 trials (551 patients). Average duration of treatment was 5 weeks (range, 1–16 weeks). On average, 33% of patients in the opioid groups dropped out (15% because of inadequate pain relief and 21% because of side effects; some patients reported both reasons), as did 38% in the placebo groups (30% because of inadequate pain relief and 10% because of side effects).

Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain. The only opioid studied for fibromyalgia was tramadol (two trials, 228 patients), where it proved effective. The effect size for opioids

compared with placebo was moderate for pain ( $-0.60$ ) and small for functional outcomes ( $-0.31$ ). Only eight trials compared opioids with other analgesics; in these trials, opioids did not differ significantly from nonopioids in terms of pain relief (effect size,  $-0.05$ ) and were significantly worse than nonopioids in terms of functional outcomes, although only slightly so (effect size,  $0.16$ ). The authors concluded that the strong opioids (oxycodone, morphine) were significantly more effective than other drugs (effect size,  $-0.34$ ), but this assessment was based on only two trials, one of which was an open-label study ([Furlan et al. 2006](#)).

A systematic review reported on 11 studies (2,877 patients) that assessed quality of life in patients with chronic nonmalignant pain who were receiving long-term opioid treatment ([Devulder et al. 2005](#)). Six studies were randomized trials, and five were observational studies. Of the four trials in which baseline values were reported, three showed an improvement in quality of life. Similarly, quality of life improved in four of the five observational studies. Although these results suggest potential quality-of-life benefits from opioid long-term treatment, the authors concluded that further methodologically rigorous studies were needed to confirm the findings and to elucidate the potential adverse effects of physical tolerance, withdrawal, and addiction on functional status.

**Adverse effects.** [Moore and McQuay \(2005\)](#) conducted a systematic review of 34 trials with 4,212 patients that provided information on adverse events related to opioid use in treating noncancer pain. Most opioids used (accounting for 90% of patients) were for treating moderate rather than severe pain. Dry mouth (affecting 25% of patients), nausea (21%), and constipation (15%) were the most common adverse events. A substantial proportion of patients taking opioids (22%) withdrew because of adverse events. Because most trials were short ( $<4$  weeks) and did not use titrated doses, the implications for long-term use in clinical practice are less certain. [Eisenberg et al. \(2006\)](#) also reported on adverse events in their systematic review of opioids for neuropathic pain. Compared with placebo recipients, opioid recipients had higher rates of nausea (33% vs. 9%), constipation (33% vs. 10%), drowsiness (29% vs. 12%), dizziness (21% vs. 6%), and vomiting (15% vs. 3%). Among studies reporting causes of withdrawal, more patients receiving opioids withdrew because of adverse effects (11% vs. 4%). Finally, in the review by [Furlan et al. \(2006\)](#), only three side effects occurred significantly more frequently with opioids than with placebo: nausea, constipation, and somnolence. These rates were 14%, 9%, and 6% higher in opioid recipients, respectively.

A large population-based study from Denmark found that opioid usage was significantly associated with more severe pain, poorer self-rated health, lower quality of life, less physical activity, lower employment, higher levels of health care utilization, and more subjects living alone ([Højsted and Sjøgren 2007](#)). The cross-sectional nature of the study does not prove causation, and it is certainly possible that the opioid users would have fared worse without opioid treatment. However, it does raise questions of whether opioid treatment of chronic pain is achieving the key goals of pain relief, improved functional status, and better quality of life.

Studies have indicated that endocrinological abnormalities such as hypogonadism and erectile dysfunction may be associated with opioid therapy ([Ballantyne and Mao 2003](#); [Daniell 2002](#)). In women, opioid use has been associated with amenorrhea and decreased sex hormone levels ([Daniell 2008](#)). Two small trials evaluating opioid use in chronic pain reported analyzable data regarding sexual activity, and both found that patients taking opioids had better self-reported sexual function than those taking placebo ([Furlan et al. 2006](#)). Improvement of well-being secondary to better pain control may account for this.



Clearly, the incidence and clinical significance of opioid-related hypogonadism need to be better defined.

A feared consequence of long-term opioid use is cognitive dysfunction. Studies have suggested that opioid treatment for chronic pain may be associated with impaired neuropsychological performance regarding reaction times, psychomotor speed, and working memory (Højsted and Sjøgren 2007). However, many other factors may be playing a role, including pain itself, concomitant medications, and psychiatric comorbidity. A systematic review concluded that stable doses of opioids do not impair driving performance (Fishbain et al. 2003).

A recent systematic review on long-term opioid treatment (>3 months) for chronic pain reported the following conclusion:

No study of opioid therapy versus no opioid therapy evaluated long-term (>1 year) outcomes related to pain, function, quality of life, opioid abuse, or addiction. Good- and fair-quality observational studies suggest that opioid therapy for chronic pain is associated with increased risk for overdose, opioid abuse, fractures, myocardial infarction, and markers of sexual dysfunction, although there are few studies for each of these outcomes; for some harms, higher doses are associated with increased risk. Evidence on the effectiveness and harms of different opioid dosing and risk mitigation strategies is limited. (Chou et al. 2015b, p. 276)

**Tolerance and addiction.** The risks of prescription opioid addiction, abuse, and diversion among chronic pain patients are not well understood. In part, this is due to inconsistent use of terminology and the difficulty of defining *addiction* and *abuse* in patients receiving opioids for chronic pain (Heit 2003; Savage et al. 2003). The term *dependence* is particularly problematic because confusion can occur between physical dependence, psychological dependence, and substance dependence (as defined in DSM-IV-TR [American Psychiatric Association 2000]). Some experts believe that the term *addiction* should be reserved for the specific condition defined as substance dependence in DSM-IV-TR. *Misuse* describes other problematic opioid use, including DSM-IV-TR substance abuse and other nontherapeutic uses that do not meet DSM-IV-TR criteria. *Diversion* includes selling, sharing, and trading of prescription opioids.

A systematic review of the literature on the risk of iatrogenic addiction in patients treated with opioids for acute and subacute pain yielded 41 eligible articles (Wasan et al. 2006). However, there were no randomized trials or comparative longitudinal studies, and the results of nine studies of low methodological quality yielded conflicting findings. The authors concluded that it is not known whether the risk for iatrogenic addiction among patients treated for acute or subacute pain is relatively high (>10%) or low (<0.1%).

In a 10-year follow-up study of patients treated with opioids for chronic pain, tolerance was not a problem in the majority of patients (Jensen et al. 2006). In contrast, a retrospective study of 104 chronic pain patients younger than 50 years and 102 patients older than 60 years showed that younger patients and those with nociceptive pain (as compared with neuropathic pain) had much higher escalation of opioid doses over a 15-month follow-up period (Buntin-Mushock et al. 2005). Another worrying finding of this study was that although the younger patients had a dosage increase of 640% (from 49 to 365 mg/day of morphine equivalent) during the observation period, the pain visual analog scale scores did not change at all. Although this does not mean that addiction is playing an important role, it does suggest that decisions about dose escalation may need to vary depending on the type of pain, patient age, treatment response, and other factors. Failure of pain to improve with moderate dosage increases in an individual patient may indicate that opioids are not the optimal treatment rather than that continuing dose escalations are needed. Some experts have classified patients or pain syndromes as opioid responsive

versus opioid resistant (Smith 2005). Indeed, some patients may develop opioid-induced hyperalgesia where the balance between anti-nociceptive and pro-nociceptive systems is upregulated after opioid exposure, leading to an enhanced vulnerability to pain (Angst and Clark 2006; Højsted and Sjøgren 2007).

Højsted and Sjøgren (2007) reviewed some important predictors of opioid use. The “rush” the patient experiences after administration of an opioid is caused by a rapid and large increase in dopamine in the brain reward system. Important factors for abuse liability associated with the drug include the speed of access and the concentration at the target sites. On a scale of opioid attractiveness, sustained-release oxycodone had the highest rating and the fentanyl patch had the lowest score; oral transmucosal fentanyl, methadone, and sustained-release morphine had intermediate scores. However, research demonstrating the higher abuse potential of one opioid versus another is limited. Risk factors for opioid abuse in patients with chronic pain are young age, male gender, past alcohol or cocaine abuse, previous drug conviction, mental health disorders, pain in multiple regions, and pain after motor vehicle accidents.

A randomized trial of 11,352 participants with chronic noncancer pain compared the abuse potential of tramadol, NSAIDs, and hydrocodone (Adams et al. 2006). Abuse was defined by an algorithm as including increasing doses without physician approval, use for purposes other than the ones intended, inability to stop using the drug, and withdrawal. The percentage of subjects who scored positive for abuse at least once during the 12-month follow-up period was 2.5% with NSAIDs, 2.7% with tramadol, and 4.9% with hydrocodone. When more than one algorithm criterion was required, abuse rates were 0.5% with NSAIDs, 0.7% with tramadol, and 1.2% with hydrocodone. Although the authors concluded that the prevalence of abuse/dependence was significantly lower with NSAIDs and tramadol than with hydrocodone, the rates overall are quite low and the between-group differences are rather small.

**General principles of opioid use.** The use of very high doses of opioids is rarely helpful. Purely on the basis that the highest daily dosage of opioids used in existing trials is 180 mg of morphine or its equivalent, opioid reduction or rotation should be considered at this point. More conservative recommendations favor staying under 100 mg morphine equivalent daily dose in most patients. Because of incomplete cross-tolerance (i.e., patients may be tolerant to high doses of the first opioid yet have a lower tolerance to the new opioid), the initial dosage of a new opioid should be equivalent to 50% or less of the dosage of the original opioid. Equianalgesic doses of oral and transdermal opioids are summarized in Table 54-1. When trials of several opioids are ineffective in chronic pain, it is appropriate to consider weaning patients off the drug and discontinuing its use. Weaning can usually be accomplished over 10 days, but the exact weaning schedule depends on dose, drug, and duration of treatment. In cases of addiction, referral to an addiction specialist may be preferable to drug discontinuation. Opioids are often best used as an adjunctive treatment—and in recent guidelines as a last resort (Chou et al. 2014; Dowell et al. 2016)—rather than as the sole therapy for chronic pain. Before starting opioid therapy, patients should understand that the goal of treatment is not the complete elimination of pain but a 25%–50% reduction in its intensity and improvement in mood and functioning.

**TABLE 54-1. Oral and transdermal opioid analgesic equivalence**

Drug	Dose (mg)	Duration (hours) <sup>a</sup>
------	-----------	-------------------------------



Drug	Dose (mg)	Duration (hours) <sup>a</sup>
Morphine	30	2–4
Codeine	200 <sup>b</sup>	3–4
Hydrocodone	30–40 <sup>c</sup>	4–6
Oxycodone	20	4–4
Hydromorphone	7.5	4–4
Meperidine	300 <sup>b</sup>	4–4
Methadone	20 <sup>d</sup>	4–8
Fentanyl (transdermal)	12.5 µg/hour <sup>e</sup>	48–72

<sup>a</sup>Duration of analgesia is dose-dependent; the higher the dose, usually the longer the duration.

<sup>b</sup>These high doses of codeine and meperidine are not recommended clinically.

<sup>c</sup>Equianalgesic data are more variable for hydrocodone than for most other opioids.

<sup>d</sup>For opioid-tolerant patients converted to methadone, starting doses should be 10%–25% of the equianalgesic dose. Also, the half-life of methadone can vary widely, from 12 to 190 hours.

<sup>e</sup>1 µg/hour transdermally is approximately equal to morphine 2 mg/24 hours orally.

A review of 13 guidelines addressing opioid prescribing in adults with chronic pain (Nuckols et al. 2014) found that most guidelines recommend that clinicians should 1) avoid doses greater than 90–200 mg of morphine equivalents per day (ideally less than 100 mg); 2) have additional knowledge to prescribe methadone (as well as buprenorphine); 3) recognize risks of fentanyl patches, titrate cautiously, and reduce doses by at least 25%–50% when switching opioids; and 4) use opioid risk assessment tools, written treatment agreements, and urine drug testing to mitigate risks. However, most recommendations are supported by observational data or expert consensus rather than findings from clinical trials. Principles for the use of opioids in chronic pain are summarized in Table 54-2.

**TABLE 54-2. Opioid management strategy for treatment of chronic pain**

1. Maximize non-opioid analgesic strategies first (i.e., a “delayed” opioid approach).
  2. Inform subjects of risks, including addiction, before initiating opioid therapy.
  3. Although the evidence is not strong, four strategies are either encouraged by some expert pain groups or mandated by prescribing regulations in some states:
    - a. Opioid risk tools: Stratify risk with screening measures such as Opioid Risk Tool (ORT) and Screener and Opioid Assessment for Patients with Pain (SOAPP).
    - b. Opioid agreements (contracts): Facilitate the use of opioid agreements (contracts) for patients initiating or increasing opioids. Key points include stipulating the frequency of obtaining medications, timely refills but no early replacement for lost or stolen prescriptions, safe storage, no sharing, single-source prescribing, monitoring through urine screens, and adherence to monitoring visits.
    - c. Urine drug screening (UDS): Conduct initial and periodic UDS for opioids as well as illicit drugs.
    - d. Prescription Drug Monitoring Program (PDMP): Use the state PDMP to monitor all sources of controlled substances.
  4. Immediate-release opioids are recommended for initial therapy and breakthrough pain, although sustained-released opioids may have an important role in long-term therapy.
  5. Short-acting opioid dose is typically 10%–20% of total daily dose (e.g., if 24-hour scheduled morphine totals 50 mg, give 5–10 mg short-acting morphine for breakthrough pain).
  6. Schedule follow-up visits at 2- to 3-month intervals, performing periodic urine testing to confirm adherence.
  7. Monitor pain severity and pain-related functional impairment at follow-up visits, because analgesic response may wane in some patients over time.
  8. Avoid opioid dose escalations without first assessing pain severity and interference.
  9. View opioid initiation as an empirical trial. Consider discontinuing opioids if not beneficial.
  10. Consider opioid rotation if tolerance to one opioid is suspected. When doing so, consider reducing morphine-equivalent dose (MED) of new opioid by 30%–50% to accommodate for unknown cross-tolerance and then titrate to goal.
  11. If patient is a high-risk candidate for opioids (particularly those with a current or past substance use disorder including alcohol or drugs or with psychiatric comorbidity such as depression), consider referral to a pain specialist.
  12. Minimize use of sedative-hypnotics, benzodiazepines, and other controlled substances.
  13. Consider referral to pain specialty program if MED exceeds 80–120 mg/day.
- 

*Source.* Adapted from [Chou et al. 2014](#); [Dowell et al. 2016](#); [Nuckols et al. 2014](#); [Reuben et al. 2015](#).

**Long-acting opioids.** A systematic review ([Carson et al. 2011](#)) compared the effectiveness and harms of long-acting opioids and of long-acting opioids compared with short-acting opioids in adults with chronic noncancer pain. Although the authors identified 10 head-to-head trials comparing two or more long-acting opioids, the evidence was insufficient to determine if there are differences among long-acting opioids in effectiveness or harms. The 8 high-quality trials found no difference in pain relief or functional outcomes between long-acting opioids. Evidence was insufficient to determine if long-acting opioids as a class are more effective or are associated with fewer harms than short-acting opioids.

**Methadone.** The principal use of methadone has been as a maintenance drug to prevent withdrawal in opioid-addicted adults. The stigma as a “drug for addicts” has been one factor limiting its use as an analgesic in clinical practice. It has gained increased use in the treatment of intractable pain in end-of-life care and other palliative care settings. Concerns regarding use of methadone for pain relate to its long and unpredictable half-life and the associated risk of a delayed overdose. Furthermore, there are large individual variations in presumed equianalgesic doses of methadone relative to other opioids. This prevents the use of simple equianalgesic tables to calculate the required dose of methadone during rotation from other opioids.

Although methadone has increasingly been used for the treatment of chronic noncancer pain, published data are rather modest. In a literature review of 21 studies, only 1 small randomized trial ( $N=19$ ) was found; the remainder were either cases series ( $N=7$ ) or case reports ( $N=13$ ) ([Sandoval et al. 2005](#)). Methadone was administered primarily when previous opioid treatment was ineffective or poorly tolerated. Thus, the evidence base is currently inadequate and does not support a first-line role for methadone in chronic pain therapy.

Regarding safety, a review of 168 studies ([Weimer and Chou 2014](#)) found insufficient evidence for most safety questions, including risk factors associated with methadone-overdose deaths and adverse events, the comparative mortality of methadone versus other opioids, the harms associated with methadone use during pregnancy, and the effects of risk-mitigation strategies such as electrocardiogram monitoring, strategies for managing patients with prolonged QTc intervals on screening, urine drug testing, alternative dosing regimens for initiation and titration of therapy, and timing of follow-up.

**Buprenorphine.** Buprenorphine was introduced into the United States in 1985 as an opioid analgesic and like other opioids was found to have the potential to be intravenously abused ([Chen et al. 2014](#)). To address this issue, naloxone (an opioid receptor antagonist) was added, and the combination buprenorphine-naloxone (bup/nal; Suboxone) was approved by the FDA in 2002 as a Schedule III drug for office-based addiction treatment. Compared with other opioids, buprenorphine has somewhat lower addiction potential, fewer side effects, and a longer duration of action. The low dose of naloxone contained in bup/nal can reverse opioid side effects such as respiratory depression, sedation, and hypotension without significantly reversing analgesia. In 2007, the World Health Organization recognized buprenorphine and bup/nal as a treatment for opioid dependence. By 2011, there had been more than 7 million buprenorphine-related prescriptions in the United States alone, with the majority of these being for bup/nal. It remains unclear whether bup/nal is superior to methadone for maintenance therapy in opioid-addicted patients.

Bup/nal is a sublingual combination tablet composed of buprenorphine and naloxone in a fixed 4:1 ratio. Although FDA approved only for addiction treatment, bup/nal has been increasingly used off-label as a treatment for chronic pain. This is particularly the case for patients currently or previously on opioids who have developed tolerance or, alternatively, addiction problems. One potential mechanism for its analgesic efficacy in opioid-tolerant patients may be reversal of opioid-induced hyperalgesia. The rationale for bup/nal’s use in opioid-naïve chronic pain patients is less clear, since its unique pharmacological properties make bup/nal a relatively weak analgesic. Finally, buprenorphine and bup/nal prescribing is currently restricted to clinicians with special credentialing. For all of these reasons, more research is needed before bup/nal becomes a mainstream treatment for chronic pain.

## Antidepressants

### Tricyclic antidepressants and selective serotonin reuptake inhibitors.

TCAs have the longest track record in the treatment of multiple pain conditions. Typically, lower dosages of TCAs have been used in clinical trials of pain management (e.g., 25–100 mg of amitriptyline or equivalent) compared with the dosages usually necessary for treating depression. Advantages of TCAs include good evidence from multiple clinical trials, decades of clinical experience with TCAs in pain management, and the low cost of these generic agents. Disadvantages include the side effects associated with TCAs (which may be less, however, when prescribing the lower doses used for analgesia), including worrisome cardiovascular side effects (e.g., hypertension, postural hypotension, arrhythmias) and a risk of falling in elderly patients, and potential lethality in overdoses.

A meta-analysis of 96 RCTs evaluating antidepressants for the treatment of conditions manifested by somatic symptoms (the majority involving painful symptoms) included 55 TCA trials, of which 76% showed benefits; 28 trials using antiserotonin agents (principally headache trials using mianserin, a drug approved in Europe but not in the United States), of which 57% showed benefits; and 17 trials using selective serotonin reuptake inhibitor (SSRI) antidepressants, of which 47% showed positive results (O'Malley et al. 1999). Only a few trials were head-to-head comparisons of two antidepressants. Indirect comparisons did not show a significant difference by type of antidepressant using meta-regression, but TCAs were superior to SSRIs ( $P < 0.02$ ) using a bivariate tally procedure. Admittedly, such statistical comparisons are not as conclusive as direct comparisons of antidepressants within the same trial. Another review concluded that SSRIs appeared to have a relatively weak effect in ameliorating chronic pain (Jung et al. 1997).

**Serotonin-norepinephrine reuptake inhibitors.** *Duloxetine.* A review of 30 trials in patients with diabetic neuropathy (12 trials), fibromyalgia (9 trials), low back pain (6 trials), and osteoarthritis (3 trials) found that the serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant duloxetine 60 mg once daily was effective in reducing pain in all four conditions (Pergolizzi et al. 2013). Duloxetine showed a rapid onset of action, with separation from placebo beginning at week 1. In a number of trials, both patients with depression and those without depression were enrolled, although path analysis estimated that more than two-thirds of the analgesic effect in duloxetine-treated patients was attributable to a direct analgesic effect, with less than one-third possibly explained by an antidepressant effect (Brannan et al. 2005; Brecht et al. 2007; Perahia et al. 2006; Marangell et al. 2011). Two trials in low back pain found no differential efficacy of duloxetine over placebo between patients who were using concomitant NSAIDs or acetaminophen and those who were not (Skljarevski et al. 2012). Two trials in osteoarthritis found that efficacy was similar in older and younger patients, and that increasing the dosage to 120 mg in nonresponding patients did not provide additional benefit (Micca et al. 2013). Meta-analyses comparing duloxetine and paroxetine have not shown differing effects on pain, although a number of these trials were conducted in depressed patients without high levels of pain at baseline (Krebs et al. 2008; Thaler et al. 2012).

*Milnacipran.* Approved some years ago in Europe for the treatment of depression, milnacipran is comparable to SSRIs as an antidepressant (Papakostas and Fava 2007). Although milnacipran is FDA approved only for treatment of fibromyalgia, levomilnacipran (an enantiomer of milnacipran) is FDA approved for treatment of depression. Substantial data (five trials involving 4,138 participants) confirm the effectiveness of milnacipran 100

mg or 200 mg for fibromyalgia, although there are not adequate data to demonstrate its efficacy for neuropathic pain ([Derry et al. 2012](#)) A meta-analysis of 5 milnacipran trials (4,129 patients), 4 duloxetine trials (1,411 patients), and 10 amitriptyline trials (612 patients) showed all three drugs to be superior to placebo, with small differential effects of the drugs on several fibromyalgia symptoms but overall similar acceptability and effectiveness ([Häuser et al. 2011](#)). However, the methodological quality of the amitriptyline trials was poor compared with that of the trials of the other two drugs.

*Venlafaxine.* There is only modest evidence for the efficacy of venlafaxine in treating fibromyalgia—four open-label cohort studies and one randomized trial ([VanderWeide et al. 2015](#))—and no rigorous studies in any other pain condition. Thus, while clinically used in treating pain, venlafaxine is not FDA approved for any pain disorder.

**Other antidepressants.** Mirtazapine was studied in a 6-week open-label trial of 594 patients with a primary diagnosis of at least one chronic pain syndrome ( $\geq 3$  months) and a clinical diagnosis of depression ([Freynhagen et al. 2006](#)). The mean daily dose was  $35 \pm 10$  mg at study endpoint, and a statistically significant reduction in pain ( $P < 0.0001$ ) was found. Pain improvement was not related to age or type of pain syndrome.

## Anticonvulsants

Anticonvulsant drugs have been used in the management of pain since the 1960s. The clinical impression is that they are useful for chronic neuropathic pain, especially when the pain is lancinating or burning. Three of the most extensively studied anticonvulsants are gabapentin, pregabalin, and carbamazepine. Gabapentin and pregabalin have the strongest evidence for the treatment of pain. These two *gabapentinoids* act as neuromodulators by selectively binding to the  $\alpha_2\delta$ -subunit protein of calcium channels in various regions of the brain and the superficial dorsal horn of the spinal cord. This results in inhibition of the release of excitatory neurotransmitters that are important in the production of pain. Gabapentin and pregabalin are analogs of  $\gamma$ -aminobutyric acid (GABA), but they have no activity at GABA receptors and do not alter GABA uptake or degradation.

**Gabapentin.** A systematic review of 15 trials (1,468 participants) evaluating gabapentin included 1 acute pain trial and 14 trials involving neuropathic pain (7 studies of diabetic neuropathy, 2 of postherpetic neuralgia, and 1 each of cancer-related neuropathy, phantom limb pain, spinal cord injury, Guillain-Barré syndrome, and miscellaneous neuropathies) ([Wiffen et al. 2005a](#)). In the 14 chronic neuropathic pain trials, 42% of participants improved taking gabapentin versus 19% taking placebo, and the NNT for improvement in all trials with evaluable data was 4.3 (95% CI=3.5–5.7). Withdrawal rates were 14% for gabapentin versus 10% for placebo. The study of acute postoperative pain (70 patients) showed no benefit for gabapentin. Thus, there is good evidence that gabapentin is more effective than placebo in the treatment of chronic neuropathic pain.

**Pregabalin.** Pregabalin is a novel compound that has analgesic, anticonvulsant, and anxiolytic effects ([Shneker and McAuley 2005](#)). In 19 studies involving 7,003 participants, pregabalin at doses of 300 mg, 450 mg, and 600 mg daily was effective in patients with postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, and fibromyalgia ([Moore et al. 2009](#)). Pregabalin at 150 mg daily was generally ineffective. Regarding fibromyalgia specifically, six trials (2,242 participants) have demonstrated the efficacy of pregabalin and gabapentin for fibromyalgia, but most of the trials (five of the six) studied pregabalin ([Häuser et al. 2009](#)). Whereas both pregabalin and gabapentin are

FDA approved for neuropathic pain, only pregabalin is approved for fibromyalgia. Pregabalin, gabapentin, and duloxetine have similar efficacy for diabetic neuropathic pain ([Quilici et al. 2009](#)). Pregabalin is also approved as an adjunctive therapy for adults with partial-onset seizures. The U.S. Drug Enforcement Administration has placed pregabalin in Schedule V of the Controlled Substance Act (indicating a low potential for abuse), possibly because of withdrawal symptoms that were found during clinical trials. The most common adverse events are related to the central nervous system and include somnolence, dizziness, and peripheral edema. Dose-related weight gain can occur and is highest at a dosage of 600 mg/day. For pain disorders, the usual dosage is 300–450 mg/day, administered in twice-daily doses.

**Carbamazepine.** A systematic review of 12 trials (404 participants) included 4 placebo-controlled trials of trigeminal neuralgia, of which 2 with evaluable data yielded an NNT of 1.8 (95% CI=1.4–2.8) ([Wiffen et al. 2005b](#)). For diabetic neuropathy the data were insufficient to calculate an NNT. There was no evidence that carbamazepine was effective for acute pain. In summary, carbamazepine appears effective for trigeminal neuralgia, but the amount and quality of evidence for gabapentin and pregabalin are stronger for other types of neuropathic pain.

**Other anticonvulsants.** Systematic reviews have revealed a lack of analgesic efficacy for either phenytoin or clonazepam ([Birse et al. 2012](#); [Corrigan et al. 2012](#)).

## Other Pharmacological Agents

**Skeletal muscle relaxants.** Most skeletal muscle relaxants are approved by the FDA for treating either spasticity (baclofen, dantrolene, and tizanidine) or musculoskeletal pain (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine) ([Chou and Peterson 2005](#)). There is insufficient evidence to prove that skeletal muscle relaxants differ in their efficacy, adverse events, or safety. Most trials have focused on acute rather than chronic pain. Cyclobenzaprine has been studied in several fibromyalgia trials and is discussed further in the “Fibromyalgia” section (under “Pharmacotherapy”). Indeed, cyclobenzaprine is the best-studied muscle relaxant in musculoskeletal disorders overall; in 21 fair-quality trials, it has consistently proven superior to placebo for relieving pain, reducing muscle spasms, and improving functional status. Cyclobenzaprine 5-mg doses are equally as effective as 10-mg doses (each given three times a day) but cause fewer side effects. Also, 20-mg doses (thrice daily) are not more effective than 10-mg doses and cause more side effects.

**Topical analgesics.** A potential advantage of topical agents is avoidance of the systemic side effects often associated with oral medications. Disadvantages are that only localized areas of pain can be effectively treated and that irritating skin reactions occur in a minority of patients. Several topical analgesics—lidocaine, capsaicin, and salicylate—have been studied in multiple trials. Postherpetic neuralgia is an FDA-approved indication for the lidocaine 5% patch, which is discussed in more detail in the “Neuropathic Pain” section. In a meta-analysis of systemic administration of local anesthetics for neuropathic pain, [Tremont-Lukats et al. \(2005\)](#) reviewed 19 studies (706 patients total; 10 trials of lidocaine and 9 trials of mexiletine, an antiarrhythmic agent that is also used off-label for pain). Lidocaine (most commonly 5 mg/kg administered intravenously over 30–60 minutes) and mexiletine (median dosage: 600 mg/day administered orally) were similar in efficacy and tolerance to morphine, amitriptyline, and gabapentin. However, the effects of



parenteral lidocaine are short lived, and mexiletine is not yet widely used or recommended as first- or second-line therapy.

Capsaicin is an alkaloid derived from chili peppers that acts on vanilloid type 1 receptors; repeated application of capsaicin is thought to desensitize cation channel receptors, leading to depletion of substance P from primary afferent neurons ([Chong and Hester 2007](#)). The main disadvantage of capsaicin is the initial burning sensation, which may persist for days. Capsaicin must be applied three to four times per day over the entire painful area for up to 8 weeks before optimal pain relief can be achieved. [Mason et al. \(2004a\)](#) reviewed the clinical trial evidence for using capsaicin to treat chronic pain. Six double-blind, placebo-controlled trials (656 patients) were pooled for analysis of neuropathic conditions, and three double-blind, placebo-controlled trials (368 patients) were pooled for analysis of musculoskeletal conditions. In patients with neuropathic pain, 57% of patients achieved at least 50% pain relief with capsaicin versus 42% of patients taking placebo. In patients with musculoskeletal conditions, the response rates were 38% versus 25%. Approximately one-third of patients experienced local adverse events with capsaicin. The authors concluded that capsaicin has moderate to poor efficacy in the treatment of chronic musculoskeletal or neuropathic pain but may be useful as an adjunctive therapy or sole therapy for a small number of patients who are unresponsive to, or intolerant of, other treatments.

The same authors also reviewed the evidence for topical salicylates ([Mason et al. 2004b](#)). In three trials evaluating 182 patients with acute conditions, topical salicylates were significantly more efficacious in relieving pain than placebo (NNT=2.1; 95% CI=1.7-2.8). In six trials evaluating 429 patients with chronic conditions, topical salicylates were also better than placebo (NNT=5.3; 95% CI=3.6-10.2). However, larger, more rigorous trials tended to have negative results. Based on limited information, the authors concluded that topical salicylates may be efficacious in the treatment of acute pain, although trials of its use in treating musculoskeletal and arthritic pain suggested moderate to poor efficacy. Finally, systematic reviews ([J. Lin et al. 2004](#); [Mason et al. 2004c](#)) as well as an RCT suggest that topical NSAIDs may be beneficial (ibuprofen for osteoarthritis of the knee has been studied the most) ([Underwood et al. 2008](#)).

**Cannabinoids.** The presence of specific high-affinity cannabinoid type 1 (CB<sub>1</sub>) receptor binding sites has been demonstrated in the central nervous system and in certain peripheral tissues, whereas CB<sub>2</sub> receptors are expressed in high quantities in immune tissues and cells. Two main endogenous cannabinoids have been described, and their role in modulating pain has been increasingly recognized. The social stigma associated with cannabinoids and the politicolegal issues related to cannabis use for medical purposes have been barriers to research. However, advocacy for increased legalization in the United States might prompt further research and clinical use for chronic pain.

There are two FDA-approved cannabinoids (dronabinol and nabilone) for chemotherapy-associated nausea and vomiting and appetite stimulation in wasting illnesses. A recent review of all types of cannabinoids (FDA-approved drugs, medical marijuana, and other preparations) found 6 trials (325 patients) investigating chronic pain, 6 trials (396 patients) examining neuropathic pain, and 12 trials (1,600 patients) focused on multiple sclerosis ([Hill 2015](#)). Several of the trials had positive results, suggesting potential benefits for these indications. However, the heterogeneous preparations in which cannabinoids are available and can be ingested (both legal and illicit) make consistent product quality, dosing, and potential efficacy as well as adverse events rather unpredictable. For example, only 6 published trials (226 patients) have investigated smoked or vaporized marijuana for

chronic noncancer pain; 5 of the trials focused on neuropathic pain and, while showing short-term benefits, had substantial methodological shortcomings, including inadequate blinding ([Deshpande et al. 2015](#)). Moreover, the long-term psychoactive and neurocognitive effects of medical marijuana remain unknown.

## Nonpharmacological Treatments

Nonpharmacological treatments will not be discussed in detail but need to be mentioned because of their important role in the management of chronic pain. Medications are typically targeted to the symptoms, but dysfunctional beliefs, attitudes, coping styles, and behaviors frequently develop in patients with chronic pain and contribute to its perpetuation and their disability. Moreover, just as in other chronic medical disorders, pharmacotherapy is necessary but not sufficient for optimizing outcomes. For example, the patient with diabetes not only needs insulin or other hypoglycemic drugs but also requires dietary changes, exercise, and other lifestyle modifications to achieve target blood glucose levels. Cognitive-behavioral therapy, pain self-management, and exercise are among the most evidence-based approaches and are discussed below, along with several other behavioral interventions. [Table 54-3](#) summarizes the level of evidence for a variety of nonpharmacological interventions in the treatment of chronic pain.

**TABLE 54-3. Nonpharmacological therapies for chronic pain**

Strength of evidence <sup>a</sup>	Therapy	References
<b>Strong</b>		
	Cognitive-behavioral therapy	<a href="#">Dixon et al. 2007</a> ; <a href="#">Institute of Medicine 2011</a> ; <a href="#">Jackson et al. 2006</a> ; <a href="#">Morley et al. 2013</a>
	Pain self-management	<a href="#">Du et al. 2011</a> ; <a href="#">Institute of Medicine 2011</a> ; <a href="#">McBeth et al. 2012</a> ; <a href="#">Warsi et al. 2003</a>
	Exercise	<a href="#">Fricton et al. 2009</a> ; <a href="#">Häuser et al. 2010</a> ; <a href="#">Institute of Medicine 2011</a> ; <a href="#">Kelley et al. 2011</a> ; <a href="#">McBeth et al. 2012</a> ; <a href="#">Naugle et al. 2012</a> ; <a href="#">van Middelkoop et al. 2011</a>
<b>Moderate</b>		

<sup>a</sup>Evidence based on number and sample size of trials, methodological quality of trials, and outcomes, including effect sizes.

<sup>b</sup>The most frequently studied herbals for pain include feverfew, devil's claw, and white willow bark.



Strength of evidence <sup>a</sup>	Therapy	References
	Acupuncture	Dhanani et al. 2011; Ernst et al. 2011; Furlan et al. 2012; Institute of Medicine 2011; Manheimer et al. 2005; Manheimer et al. 2007; Rubinstein et al. 2010; Tan et al. 2007; A. White et al. 2007
	Yoga	Crawford et al. 2014; Posadzki et al. 2011; Sharma and Haider 2013; Tan et al. 2007; Wren et al. 2011
	Mindfulness/meditation/acceptance-based	Crawford et al. 2014; Reiner et al. 2013; Tan et al. 2007; Veehof et al. 2011
	Chiropractic (spinal manipulation)	Furlan et al. 2012; Institute of Medicine 2011; Rubinstein et al. 2010; Tan et al. 2007
	Massage	Dhanani et al. 2011; Furlan et al. 2012; Institute of Medicine 2011; Tan et al. 2007
	Tai chi	Crawford et al. 2014; Dhanani et al. 2011
	Music therapy	Crawford et al. 2014
<b>Mixed (inconclusive)</b>		
	Biofeedback	Crawford et al. 2014; Dhanani et al. 2011; Tan et al. 2007
	Hypnosis	Crawford et al. 2014; Dhanani et al. 2011; Jensen and Patterson 2014; Tan et al. 2007
	Herbal therapy <sup>b</sup>	Dhanani et al. 2011; Rubinstein et al. 2010

<sup>a</sup>Evidence based on number and sample size of trials, methodological quality of trials, and outcomes, including effect sizes.

<sup>b</sup>The most frequently studied herbals for pain include feverfew, devil's claw, and white willow bark.

Strength of evidence <sup>a</sup>	Therapy	References
	Guided imagery	<a href="#">Crawford et al. 2014</a> ; <a href="#">Posadzki and Ernst 2011a</a> ; <a href="#">Posadzki et al. 2012</a>
	Qigong	<a href="#">Crawford et al. 2014</a>
	Epidural corticosteroids	<a href="#">Chou et al. 2015b</a> ; <a href="#">Institute of Medicine 2011</a> ; <a href="#">Manchikanti et al. 2015</a>
	Injection therapy/denervation procedures	<a href="#">Henschke et al. 2010</a> ; <a href="#">Institute of Medicine 2011</a>
	Osteopathic manipulation	<a href="#">Posadzki and Ernst 2011b</a>
	Internet-based psychological therapies	<a href="#">Bender et al. 2011</a> ; <a href="#">Eccleston et al. 2014</a>
<b>Minimal to low</b>		
	Transcutaneous electrical nerve stimulation	<a href="#">Bennett et al. 2011</a> ; <a href="#">Crawford et al. 2014</a> ; <a href="#">Nnoaham and Kumbang 2008</a> ; <a href="#">van Middelkoop et al. 2011</a> ; <a href="#">Zeng et al. 2015</a>
	Magnets (static or pulsed electromagnets)	<a href="#">Eccles 2005</a> ; <a href="#">Institute of Medicine 2011</a> ; <a href="#">McCarthy et al. 2006</a> ; <a href="#">Pittler et al. 2007</a> ; <a href="#">Tan et al. 2007</a>
	Noninvasive brain stimulation	<a href="#">O'Connell et al. 2014</a>

<sup>a</sup>Evidence based on number and sample size of trials, methodological quality of trials, and outcomes, including effect sizes.

<sup>b</sup>The most frequently studied herbals for pain include feverfew, devil's claw, and white willow bark.

## Psychotherapy and Behavioral Interventions

**Cognitive-behavioral therapy.** Cognitive-behavioral therapy (CBT) has by far the largest body of evidence supporting its effectiveness in the treatment of various types of chronic pain disorders. [Kroenke and Swindle \(2000\)](#) reviewed 31 trials of CBT for the treatment of somatic syndromes, of which more than half involved pain conditions, including 5 trials of back pain, 3 of irritable bowel syndrome, 3 of noncardiac chest pain, 2 of fibromyalgia, and 4 of other pain disorders. Most of those trials (14 of 17) involving pain disorders found CBT to be beneficial. An update of this review found additional studies confirming the effectiveness of CBT ([Jackson et al. 2006](#)). Also, a systematic review of treatment for somatoform disorders (in which multiple pain symptoms are often present)

found that CBT was effective in 11 of 13 RCTs (Kroenke 2007). Both group CBT and individual CBT appeared to be effective, as did briefer courses of CBT (e.g., 3–6 sessions). When administered for pain and other somatic disorders, it is important that CBT be *somatically focused*, having a somewhat different orientation than CBT provided for depressive and anxiety disorders. Patients with chronic pain and other somatic syndromes present with physical rather than psychological symptoms and often attribute their symptoms to physical disorders (i.e., medical factors). Thus, the mental health professional accustomed to providing CBT for psychiatric disorders may require some additional training in CBT appropriate for treating chronic pain and other somatic syndromes.

**Pain self-management programs.** Pain self-management (PSM) programs that emphasize self-efficacy have consistently demonstrated effectiveness in improving health outcomes and reducing health care utilization among patients with arthritis and various rheumatic conditions (Du et al. 2011; Institute of Medicine 2011; McBeth et al. 2012; Warsi et al. 2003). Self-management for both acute (Damush et al. 2003) and chronic (Von Korff and Moore 2001) low back pain has also proven effective. Indeed, CBT and PSM are the two best-established psychobehavioral approaches to treating chronic musculoskeletal pain (Bradley and Alberts 1999). In fact, PSM incorporates important components of CBT with additional educational and behavioral strategies. Another important component of PSM programs is emotional coping and management (Lorig and Holman 2003). One advantage of PSM compared with CBT in the medical setting is that it may be effectively administered by varying levels of trained individuals, including lay personnel (Cohen et al. 1986; Kroenke et al. 2009a).

**Other psychological interventions.** Other reviews of psychological interventions for pain have shown a similar predominance of CBT trials (Morley et al. 2013). A meta-analysis of 27 RCTs of psychological interventions for treating arthritis found that CBT was used in 23 trials, stress management in 5, and biofeedback, emotional disclosure, and hypnosis in 1 trial each (several trials used more than one intervention) (Dixon et al. 2007). The reduction in pain was statistically significant but clinically rather small (pooled effect size: 0.18). Three systematic reviews of psychological treatments for somatic syndromes (many of which are manifested predominantly by pain) have also been heavily weighted with CBT studies (Allen et al. 2002; Henningsen et al. 2007; Raine et al. 2002). A large trial (N=1,337 patients) of telephone-based, nurse-administered problem-solving therapy (which is one of the evidence-based psychotherapies for depression) proved the therapy beneficial in primary care patients with chronic pain (Ahles et al. 2006), although further research is needed before one could recommend this over CBT or PSM programs.

Exercise

Exercise has been extensively studied in chronic pain patients and has been demonstrated to be an effective adjunctive treatment for several types of chronic pain disorders. Evidence regarding its effectiveness is discussed in more detail in the “Fibromyalgia” and “Osteoarthritis” sections. Six general issues relevant to initiating and maintaining an exercise program for chronic pain are summarized in Table 54-4.

**TABLE 54-4. Key principles for initiating and maintaining exercise for chronic pain**

Principle	Comments
-----------	----------

<b>Principle</b>	<b>Comments</b>
Type of exercise	Aerobic exercise is particularly important for some types of chronic pain (e.g., fibromyalgia), whereas strengthening and flexibility exercises may be helpful in others (back pain, osteoarthritis).
Catastrophizing as a barrier	Fear that movement or activity will worsen pain is common. Emphasizing that gradual activity will not cause further harm but instead can be beneficial is essential to activation and rehabilitation.
Stage of change	For patients in precontemplation phase, motivating them to initiate exercise is the challenge. For many others who begin an exercise program, getting them to maintain regular exercise for more than a few months is the critical issue. This is analogous to weight loss, smoking cessation, and other lifestyle or behavioral changes.
Graduated program	Patients should not try to do too much initially. Instead, they should begin slowly and increase the amount of exercise gradually over a matter of weeks to months.
Structured vs. home based	The benefits of structured exercise programs demonstrated in some research studies may have a “voltage drop” when patients are instructed to begin an exercise program on their own. Exercise conducted in clinical settings (e.g., physical therapy, rehabilitation programs) or community settings (e.g., YMCA, fitness centers) may be reinforced by motivation, group participation, expert leadership, guidance, and/or an externally imposed regular schedule.
Monotherapy vs. bundled	Many studies of exercise have included other components, such as education about the particular pain disorder, self-management techniques, relaxation, and other cognitive-behavioral strategies. Certainly, exercise coupled with one or more of these is ideal.

## Combination Therapy

Over time, the treatment of chronic pain often includes stepwise addition to a patient's regimen (and deletion if a therapy shows no benefit) of medications from several classes ([Black and Sang 2005](#); [Gallagher 2005](#)). In addition to medications given to produce analgesia, pain management may include medications to treat the side effects of the analgesics, such as laxatives or stool softeners for patients receiving opioids, gastroprotective medications for those receiving NSAIDs, and psychostimulants to combat excessive somnolence.

Very few studies have tested combinations of treatments to determine their additive value, if any, compared with monotherapy. Only limited data suggest that the combination of acetaminophen with NSAIDs has additive pain-relieving effects ([Schug 2005](#)). The largest trial (892 community-derived subjects) found greater pain relief with the combination of acetaminophen and ibuprofen than with either drug alone ([Doherty et al. 2011](#)). More data show a beneficial effect in combining acetaminophen with opioids, including codeine, tramadol, and morphine. Indeed, one of the more common fixed combinations in a single pill has been the coupling of an opioid, such as codeine, tramadol, oxycodone, or hydrocodone, with a nonopioid analgesic such as acetaminophen or aspirin. One important consideration in using fixed-dose combinations is that the maximum daily dosage of one component may restrict flexibility in optimizing the dosage of the other component. For example, when oxycodone 5 mg is combined with acetaminophen 500 mg, the maximum number of tablets that can be administered is eight in a 24-hour period (i.e., 4,000 mg of acetaminophen). If this is insufficient to manage the patient's pain, the opioid and nonopioid should be given as separate medications to allow further upward titration of the opioid.

Head-to-head clinical trials comparing different analgesics for chronic pain, separately or in combination, are rare. In addition to the acetaminophen-ibuprofen trial ([Doherty et al. 2011](#)), a second example is a small (57 subjects enrolled; 41 trial completers) randomized, double-blind crossover trial in patients with neuropathic pain, which showed that gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent ([Gilron et al. 2005](#)). On the other hand, the gabapentin-morphine combination resulted in a higher frequency of constipation than gabapentin alone and a higher frequency of dry mouth than morphine alone. A third small crossover trial (56 subjects enrolled; 45 trial completers) found the combination of gabapentin and nortriptyline to be superior to either drug alone for neuropathic pain ([Gilron et al. 2009](#)).

The common decision in clinical practice when optimal pain relief has not been achieved is whether to switch to a new treatment or to add it to what is currently being provided. Given the paucity of combination drug trials, this decision is currently guided by practical considerations. Switching to another monotherapy is often less costly than combining two or more treatments and often is done when a patient has had only a minimal response to and/or poor tolerance of the initial treatment. On the other hand, adding a second treatment may be favored when there has been at least a partial response to the first therapy or when the second treatment has a different mechanism of action that may complement the original treatment. Factors influencing combination therapy decisions include not only added efficacy but also costs, side effects, adherence, and patient preferences. Sometimes, the secondary effects of a drug may influence the decision to use it in a particular patient. For example, the side effect of sedation that occurs with certain medications (e.g., gabapentin or pregabalin) may be troublesome in one patient, whereas in another it may be useful to treat comorbid insomnia, particularly if taken at bedtime.

Likewise, the antidepressant effects of a particular adjunctive pain medication (e.g., an SNRI such as duloxetine) may reduce both pain and mood disturbances in the patient with diabetic neuropathic pain and comorbid major depression. TCAs could serve the same purpose, although higher dosages of TCAs are typically required for antidepressant action than for analgesic action, in which case the side effects of higher-dose TCAs, especially their cardiovascular effects, must be considered as well.

---

## Selected Pain Disorders

---

### Neuropathic Pain

[Chou et al. \(2007a\)](#) summarized several key points regarding the prevalence, etiology, and classification of neuropathic pain:

Neuropathic pain (NP) is often classified by etiology or by the presumed site of neurologic involvement (central or peripheral). More complex classification systems based on symptoms, signs, anatomical distribution, or hypotheses regarding etiologies have been proposed, but it is not clear if such classifications are accurate or reproducible. NP is characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching, or shooting. Up to 3% of the general population reports NP at some time. NP is most commonly associated with painful diabetic neuropathy, postherpetic neuralgia (PHN), or lumbar nerve root compression. Diabetic neuropathy occurs in approximately 10% of persons with diabetes. The most common form of diabetic peripheral neuropathy is a distal symmetric polyneuropathy, typically manifested by symptoms beginning in the feet. PHN is defined as pain persisting or recurring at the site of acute herpes zoster 3 or more months after the acute episode. It occurs in up to 25% of patients following an episode of shingles. Symptomatic spinal stenosis and lumbar disc herniation with nerve root compression occur in approximately 3% and 4% of patients with low back pain, respectively. Other causes of NP include cancer-related pain, spinal cord injury, poststroke pain, HIV-associated neuropathy, and phantom limb pain. Uncommon but potentially debilitating NP conditions include trigeminal neuralgia (incidence 4/100,000 population). In the U.S., health care and disability-related costs associated with NP are estimated at almost \$40 billion annually. ([Chou et al. 2007a](#), p. 6)

A meta-analysis of 229 RCTs evaluating pharmacotherapy for neuropathic pain ([Finnerup et al. 2015](#)) showed generally modest effects on pain. One hundred twenty-seven (55%) of the 229 trials involved patients with diabetic painful polyneuropathy or postherpetic neuralgia. Pooled NNTs were 6.4 for SNRIs, mainly including duloxetine (7 of 9 studies positive) and venlafaxine (2 of 5 studies positive); 7.7 for pregabalin; 7.2 for gabapentin; and 10.6 for capsaicin high-concentration patches. NNTs were lower for TCAs, opioids, tramadol, and botulinum toxin A and were undetermined for lidocaine patches. Tolerability and safety were higher for topical drugs, and costs were lower for TCAs and tramadol. These findings led to the following:

1. A strong recommendation for TCAs, SNRIs, pregabalin, and gabapentin as *first-line* treatment;
2. A weak recommendation for lidocaine patches, capsaicin high-concentration patches, and tramadol as *second-line*; and
3. A weak recommendation for opioids and botulinum toxin A as *third-line*.

The recommendations from this comprehensive meta-analysis are generally consistent with previous guidelines from the Agency for Healthcare Research and Quality ([Chou et al.](#)

2007a), the European Federation of Neurological Sciences ([Attal et al. 2006](#)), the International Association for the Study of Pain (IASP) ([Dworkin et al. 2007](#)), and several other specialty organizations ([Bril et al. 2011](#)). They also concluded that diabetic and nondiabetic painful polyneuropathies are similar in symptomatology and response to treatment. The only exceptions noted were that HIV- and chemotherapy-induced neuropathy may be more refractory to treatment. The principal opioids studied have been oxycodone and tramadol, both of which have proven superior to placebo. Trials of topical capsaicin have provided discrepant results. The antiarrhythmic drug mexiletine, the *N*-methyl-D-aspartate antagonist memantine, and topical capsaicin have not shown convincing efficacy.

The IASP also noted that “Although few clinical trials have been conducted, no medications have demonstrated efficacy in patients with lumbosacral radiculopathy, which is probably the most common type of neuropathic pain” ([Dworkin et al. 2007](#), p. 237). Indeed, an RCT evaluating nortriptyline, morphine, and their combination in patients with chronic lumbar root pain found no greater efficacy with the combination than with either medication alone or placebo ([Khoromi et al. 2007](#)). Also, neuropathy related to HIV and cancer chemotherapy may be more refractory to treatment than other types of neuropathic pain. The IASP also noted that little is known regarding the treatment response of those with mild to moderate neuropathic pain because most trials have enrolled patients with more severe neuropathic pain, and long-term effectiveness is unknown because most RCTs have been of less than 3 months’ duration. The IASP also favored secondary-amine TCAs (nortriptyline and desipramine) over tertiary-amine TCAs (amitriptyline and imipramine) because of their comparable analgesia ([Max et al. 1992](#); [Rowbotham et al. 2005](#); [Watson et al. 1998](#)) and fewer side effects. Finally, the IASP concluded that the magnitude of pain reduction associated with opioid analgesics is at least as great as that obtained with other treatments for neuropathic pain.

Duloxetine, pregabalin, and gabapentin are the three FDA-approved drugs with the greatest amount of trial evidence and appear to have similar efficacy for diabetic neuropathic pain ([Quilici et al. 2009](#)). The most common adverse events for gabapentin and pregabalin include dizziness, somnolence, and weight gain, and nausea can be a perplexing side effect of SNRIs. Sometimes, a drug may be preferentially chosen because of comorbid conditions (e.g., gabapentin or pregabalin for the patient with neuropathic pain and insomnia, or duloxetine when neuropathic pain is accompanied by major depression). Switching or adding medications will frequently be necessary, because no more than 40%–60% of patients obtain partial relief from a single agent ([Dworkin et al. 2007](#)).

## Fibromyalgia

### Mechanisms and Evaluation

Fibromyalgia is one of the most common musculoskeletal disorders seen in rheumatology practice as well as primary care. It is often classified among the functional somatic syndromes (FSSs), which include irritable bowel syndrome, chronic fatigue syndrome, temporomandibular joint disorder, interstitial cystitis, and other symptom-based conditions manifested by a cluster of symptoms for which the pathophysiological mechanism is not well understood ([Aaron and Buchwald 2001](#)). Patients with one FSS often have one or more other FSSs as well as psychological comorbidity, including depression and anxiety, and a history of abuse during childhood or as adults. However, it does not appear that FSSs are entirely explained by psychological factors ([Henningesen et](#)



al. 2003), and emerging research also shows biological factors that may be causative or contributory.

The American College of Rheumatology core diagnostic criteria for fibromyalgia depend entirely on clinical history and exam and do not require any laboratory or radiological testing (Wolfe et al. 2010). Although tender points on physical examination were originally required, the revised diagnostic criteria now require only the following:

1. Generalized pain that is both widespread (i.e., on both the right and left sides of the body, upper and lower halves, and axial as well as proximal arms and legs) and chronic (lasting  $\geq 3$  months)
2. Somatic symptoms of which 3 cardinal symptoms are fatigue, unrefreshing sleep, and cognitive symptoms (sometimes called “fibro fog”) but can also include high numbers of other somatic symptoms

The other diagnostically useful finding is that unlike patients with arthritic conditions (e.g., osteoarthritis, rheumatoid arthritis, systemic lupus), who mainly suffer from arthralgias (pain and tenderness over the joints or periarticular regions), patients with fibromyalgia experience myalgias (pain and tender points in nonarticular regions). In fact, research shows that fibromyalgia patients feel tenderness wherever pressure is applied, including areas previously considered to be “control points” (Clauw 2007). The tenderness simply reflects the fibromyalgia patient’s tendency toward allodynia (experiencing pain from stimuli that would normally be nonpainful) or hyperalgesia (experiencing more severe pain from stimuli that would normally be only mildly painful). Given that the symptoms seem to arise from disturbances in the central processing of pain and that tender points are a relatively nonspecific finding, some have advocated calling the condition *chronic widespread pain* (Lee et al. 2014).

The primary problem in fibromyalgia appears to be not that there is too much input coming from the pressure nociceptors peripherally but rather that there is inadequate filtering of that activity, perhaps because of decreased activity of descending antinociceptive pathways. In fact, multiple mechanisms seem to be operative in fibromyalgia (Abeles et al. 2007). Two key mechanisms are as follows:

1. Functional imaging studies in fibromyalgia patients have shown increased blood flow to pain-relevant areas of the brain at lower thresholds of nociceptive input.
2. There appears to be dysregulation of descending inhibitory pain pathways. Thus, the pain “amplifier” is turned up, and the “mute” button is turned down in fibromyalgia patients. Collectively, this concept is known as *central sensitization* (Bourke et al. 2015).

Not only is fibromyalgia accompanied by psychiatric comorbidity, but it also can coexist with other rheumatological disorders. For example, as many as one-quarter of patients with rheumatoid arthritis and other systemic arthritides may also have fibromyalgia. Thus, if an individual with arthritis or another musculoskeletal disorder also has chronic widespread pain, therapies effective for fibromyalgia should be added to the treatment regimen. Also, communication with the patient, including explanations about central sensitization and abnormal pain processing, may be helpful. Despite assumptions that being “labeled” with fibromyalgia may adversely affect patients, it has been shown that patients have had significant improvement in health satisfaction and symptoms after having received this diagnosis (K.P. White et al. 2002).

## Pharmacotherapy



A comparison of fibromyalgia guidelines from three different countries (Table 54-5) reveals that the most evidence-based medications are TCAs, SNRIs (duloxetine, milnacipran),  $\alpha_2\delta$ -ligand anticonvulsants (pregabalin, gabapentin), and tramadol (Ablin et al. 2013). The strongest evidence is for the three drugs that have received FDA approval for fibromyalgia: pregabalin, duloxetine, and milnacipran. Although several trials (Bennett et al. 2003; Biasi et al. 1998; Russell et al. 2000) have shown the effectiveness of tramadol in fibromyalgia, the few studies of stronger opioids have not established their efficacy, and adverse effects appear to outweigh benefits (Goldenberg et al. 2016). Also, the few studies of NSAIDs in fibromyalgia have also had negative results, suggesting that a class of drugs considered first-line treatment for arthritis and other musculoskeletal disorders may not be effective in treating fibromyalgia.

**TABLE 54-5. Evidence-based fibromyalgia treatments from three national guidelines**

	Canada	Israel	Germany
Treatment	Strength of recommendation <sup>a</sup>		
<b>Pharmacotherapy</b>			
TCA (e.g., amitriptyline)	A	A	B
SNRI (duloxetine, milnacipran)	A	A	B/C
α <sub>2</sub> δ ligands (pregabalin, gabapentin)	A	A	C
Tramadol	C	B	—
SSRI	A	—	C
<b>Nonpharmacological therapies</b>			
Cognitive-behavioral therapy	A	A	A
Exercise (aerobic)	A	A	A
Balneotherapy (spas; hydrotherapy)	—	C	B

*Note.* SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; —=not applicable.

<sup>a</sup>A=should be offered to most patients; B=may be offered to a majority of patients but may not be offered to a substantial minority; C=can be offered to a minority of patients.

*Source.* Adapted from Ablin et al. 2013.

A meta-analysis of four trials found that cyclobenzaprine (10–40 mg/day) was also superior to placebo (Arnold et al. 2000). Although classified as a muscle relaxant, cyclobenzaprine has a chemical structure closely related to that of the TCAs, which may partly account for its effectiveness in fibromyalgia.

In the Phase III trials that led to FDA approval, pregabalin dosages were 300–450 mg/day (divided into twice-daily doses), duloxetine dosages were 60–120 mg once a day,

and milnacipran dosages were 100–200 mg once a day. In all trials, the difference in efficacy between the highest and lowest dosages of each drug was small to minimal, whereas side-effect rates increased somewhat at higher dosages. Thus, the majority of fibromyalgia patients who respond to these drugs will do so with 300 mg of pregabalin, 60 mg of duloxetine, or 100 mg of milnacipran per day. The most bothersome side effect of duloxetine and of milnacipran (as well as venlafaxine) is nausea, which may be lessened by starting therapy at lower dosages (e.g., duloxetine 30 mg/day or venlafaxine 37.5 mg/day) for the first 1–2 weeks and by taking the drug with food. The most bothersome side effects with pregabalin and gabapentin are somnolence (which often improves with treatment and may be reduced by using low initial doses and having the patient take the only dose or the highest dose at bedtime), dizziness, and weight gain.

## Nonpharmacological Treatment

More than with most other pain disorders, nonpharmacological treatment for fibromyalgia is especially important, and few patients should be treated with medication only. Several systematic reviews have shown that the three treatments with the most evidence of efficacy are exercise (particularly aerobic exercise), education about fibromyalgia (either individually or in groups), and CBT ([Goldenberg et al. 2004](#); [Henningesen et al. 2007](#); [Sim and Adams 2002](#); [van Koulil et al. 2007](#)). Similarly, guidelines emphasize CBT and exercise ([Ablin et al. 2013](#)). A systematic review of 34 RCTs (involving 2,276 subjects) evaluated exercise in fibromyalgia and found that aerobic-only exercise had moderate positive effects on global well-being (effect size, 0.49), physical function (effect size, 0.66), and pain (effect size, 0.65) ([Busch et al. 2007](#)). Strength and flexibility exercises were underevaluated. A review of eight RCTs of balneotherapy (pool exercise) also showed beneficial results in fibromyalgia ([Gowans and deHueck 2007](#)), and this may be an alternative as an initial form of exercise for individuals with arthritis, to reduce weight bearing on arthritic joints, or for patients who fear exercise will exacerbate their pain. Seven RCTs of CBT (two of which also included exercise) involving a total of 595 patients showed benefits for CBT in five of the seven trials ([van Koulil et al. 2007](#)). Education about fibromyalgia has been studied in numerous trials, both individually and coupled with one or more other interventions, and appears to have a positive effect ([Goldenberg et al. 2004](#); [Sim and Adams 2002](#)). Education coupled with exercise seems a particularly valuable bundled intervention ([Burckhardt 2006](#); [Karjalainen et al. 2000](#); [Rooks et al. 2007](#)). Educational and self-management resources are readily available online from organizations like the National Fibromyalgia Association, the American College of Rheumatology, and the Arthritis Foundation. Finally, data are inconclusive regarding acupuncture, chiropractic therapy, massage therapy, yoga, trigger point injections, and other nonpharmacological or CAM treatments for fibromyalgia ([Ablin et al. 2013](#); [Goldenberg et al. 2004](#); [Henningesen et al. 2007](#); [Mayhew and Ernst 2007](#); [Sim and Adams 2002](#); [Tan et al. 2007](#)).

## Low Back Pain

A series of systematic reviews by Chou and colleagues ([Chou and Huffman 2007a, 2007b](#); [Chou et al. 2007b](#)) provides a comprehensive update on the evaluation and management of low back pain. The authors describe the burden of back pain:

Low back pain is the fifth most common reason for all physician office visits in the U.S. and the second most common symptomatic reason. Approximately one quarter of U.S. adults reported having low back pain lasting

at least one whole day in the past 3 months, and 7.6% reported at least one episode of severe acute low back pain within a 1-year period. Low back pain is also very costly: Total incremental direct health care costs attributable to low back pain in the U.S. were estimated at \$26.3 billion in 1998. In addition, indirect costs related to days lost from work are substantial, with approximately 2% of the U.S. work force compensated for back injuries each year. (Chou et al. 2007b, p. 478)

The authors go on to describe several other key points relevant to the clinical epidemiology of low back pain. Most low back pain (85%) is nonspecific—that is, it cannot be attributed to a specific disease or spinal abnormality. Classification schemes frequently conflict with one another, and there is little evidence that labeling patients by using specific anatomical diagnoses improves outcomes. In a primary care setting, low back pain is only occasionally caused by a specific serious disorder, such as cancer (0.7% of cases), compression fracture (4%), or spinal infection (0.01%). The estimated prevalence of ankylosing spondylitis in primary care patients ranges from 0.3% to 5%. Spinal stenosis and symptomatic herniated disc are present in about 3% and 4% of patients, respectively. The cauda equina syndrome, due to massive midline disc herniation, is very rare (occurring in 0.04% of patients with low back pain). Urinary retention is 90% sensitive, and the probability of the cauda equina syndrome in back pain patients without urinary retention is approximately 1 in 10,000. The probability of cancer in patients presenting with back pain increases from approximately 0.7% to 9% in patients with a history of cancer (not including nonmelanoma skin cancer). In patients with any one of three other risk factors (unexplained weight loss, failure to improve after 1 month, and age greater than 50 years), the likelihood of cancer only increases to approximately 1.2%.

Table 54-6 outlines some key recommendations with respect to the evaluation and management of low back pain. In the absence of red flags, a conservative approach for at least 4 weeks is usually warranted, even if sciatica is present. Magnetic resonance imaging is the preferred imaging procedure but can be reserved for the minority of patients with red flags or persistent symptoms, especially neurological findings. The two most common indications for surgery are herniated disc with persistent symptoms (especially radiculopathy) and spinal stenosis, which together account for less than 10% of cases of chronic back pain. Trial data suggest that surgery may be only marginally beneficial for pain due to a herniated disc but more helpful for spinal stenosis (Weinstein et al. 2006, 2008). Psychological factors are stronger predictors of low back pain treatment outcomes than either physical examination findings or the severity or duration of pain. Psychosocial factors that may predict poorer low back pain outcomes include presence of depression, passive coping strategies, job dissatisfaction, higher disability levels, disputed compensation claims, and somatization.

---

**TABLE 54-6. Key aspects of evaluation and management of low back pain**

---

Most back pain (>70%–80%) improves in the first 2–6 weeks. Thus, a 4-week wait (i.e., a conservative approach) is warranted (even with sciatica) in the absence of red flags.

Red flags that may prompt earlier diagnostic testing or referral include the following:

- Cancer: history of cancer (strong predictor) or unexplained weight loss, failure to improve after 4 weeks, and age greater than 50 years (all weaker predictors)

---

*Note.* ESR=erythrocyte sedimentation rate; MRI=magnetic resonance imaging; NSAIDs=nonsteroidal anti-inflammatory drugs; TCAs=tricyclic antidepressants.

- Infection (vertebral): fever, intravenous drug use, recent infection (none well studied)
- Compression fracture: older age, osteoporosis, steroid use
- Cauda equina syndrome rare (0.04%); urinary retention 90% sensitive.

Physical examination focuses on a few cardinal neurological parts of the lower-body exam:

- Straight-leg raising (SLR) in which the hip is flexed while the knee remains extended. Ipsilateral-positive SLR is 91% sensitive but only 26% specific for radiculopathy, whereas a crossed-positive SLR (i.e., sciatica in the other leg) is only 29% sensitive but 88% specific.
- Lower-extremity motor and sensory exam:
  - Knee strength and reflexes (L4 nerve root); screen with squat and rise
  - Great toe and foot dorsiflexion strength (L5 nerve root); screen with heel walking
  - Foot plantar-flexion and ankle reflexes (S1 nerve root); screen with walking on toes

Diagnostic tests are needed in only a minority of cases (with red flags or persistent neurological signs).

- MRI is the preferred imaging study (less radiation and better visualization of soft tissue, vertebral marrow, and the spinal canal).
- With some weaker red flags (e.g., age >50 years), plain films and ESR may be obtained first and MRI obtained only if these tests are abnormal or symptoms persist.

Psychological factors are a stronger predictor of chronicity and functional outcomes such as disability than physical exam findings or the severity or duration of pain.

Treatment: No treatment for back pain has good-quality (grade A) evidence of substantial benefit. The following have fair-quality (grade B) evidence of moderate benefit or small benefit but no significant harm, costs, or burdens:

- Pharmacotherapy: acetaminophen, NSAIDs, TCAs, tramadol/opiates, benzodiazepines
- Nonpharmacological: chiropractic, acupuncture, massage, yoga, exercise, progressive relaxation, cognitive-behavioral therapy, intensive interdisciplinary rehabilitation

---

*Note.* ESR=erythrocyte sedimentation rate; MRI=magnetic resonance imaging; NSAIDs=nonsteroidal anti-inflammatory drugs; TCAs=tricyclic antidepressants.

Medications are the most frequently recommended intervention for low back pain. The most commonly prescribed medications for low back pain are NSAIDs, skeletal muscle relaxants, and opioid analgesics ([Chou and Huffman 2007a](#)). Benzodiazepines, systemic corticosteroids, antidepressant medications, and antiepileptic drugs are also prescribed. Frequently used over-the-counter medications include acetaminophen, aspirin, and certain NSAIDs. No treatments for back pain have grade A evidence supporting their use—that is, good-quality evidence of substantial benefits. [Table 54-6](#) summarizes treatments with grade B evidence. For pharmacotherapy, this includes acetaminophen, NSAIDs, tramadol, and TCAs. For all medications, the evidence of beneficial effects on functional outcomes is limited. Skeletal muscle relaxants, which may be beneficial for acute back pain, do not have established efficacy for chronic pain. Although systematic reviews of opioids for various chronic pain conditions have shown moderate benefits, the evidence for opioids specifically for low back pain is sparse and inconclusive ([Martell et al. 2007](#)). A prospective study found that early prescription of opioids for acute occupational low back

injury was associated with an increased risk of work disability at 1 year, even after adjustment for severity of pain, function, and initial injury ([Franklin et al. 2008](#)). A systematic review of 25 trials involving 2,206 patients found no benefits for either continuous or intermittent traction in the treatment of low back pain ([Clarke et al. 2007](#)). There is also good evidence that systemic corticosteroids are ineffective for low back pain with or without sciatica. One systematic review identified only 7 trials evaluating medications for sciatica ([Vroomen et al. 2000](#)). Two small trials suggest that gabapentin may be useful in the subset of patients with radiculopathy.

Ten trials were included in two systematic reviews of antidepressants ([Salerno et al. 2002](#); [Staiger et al. 2003](#)). In all of the trials, the duration of therapy ranged from 4 to 8 weeks. Antidepressants were consistently superior to placebo for pain relief, whereas the benefits in terms of functional outcomes were uncertain. The pooled effect size for pain relief was moderate (0.41). Indirect comparisons suggested modest benefits with TCAs but not with paroxetine or trazodone. A recent review of six trials of duloxetine in patients with back pain showed an analgesic benefit ([Pergolizzi et al. 2013](#)).

## Osteoarthritis

Osteoarthritis is one of the most common musculoskeletal pain disorders (along with low back pain and fibromyalgia) in both primary care and specialty settings. It typically increases with age (particularly after age 50 years), with the majority of individuals older than 65 years having at least one joint affected by osteoarthritis. Common joints involve the distal and proximal interphalangeal (but not metacarpal) joints of the fingers, the base of the thumb, the knees, the hips, and the cervical and lumbar regions of the spine. The shoulder and elbow are rarely involved. The most common finding on physical examination is an increase in joint size secondary to osteophyte formation. Plain radiographs are typically the only diagnostic test required to confirm the diagnosis of osteoarthritis, which is manifested by loss of joint space and/or osteophyte formation.

In contrast to the case in rheumatoid arthritis and other inflammatory types of arthritis, the structural changes in osteoarthritis are not amenable to specific disease-modifying treatments. Thus, the focus of treatment in osteoarthritis is reduction of pain and preservation of function. Acetaminophen and NSAIDs, which are inexpensive and available without a prescription, are the mainstays of pharmacotherapy. A systematic review of 13 trials in patients with osteoarthritis of the knee found that both aerobic exercise and home-based quadriceps-strengthening exercise reduced pain (effect sizes, 0.52 and 0.39, respectively) and disability (effect sizes, 0.46 and 0.32) ([Roddy et al. 2005](#)). Benefits of aerobic and strengthening exercises in osteoarthritis patients were confirmed in a second systematic review ([Brosseau et al. 2003](#)). For advanced disease with progressive pain and functional impairment, total hip arthroplasty and knee arthroplasty are effective. In contrast, a systematic review of 23 studies found inconclusive evidence for the benefits of arthroscopic lavage and/or debridement in knee osteoarthritis ([Samson et al. 2007](#)). The lack of efficacy for lavage, with or without intra-articular corticosteroids, was confirmed in a meta-analysis of six trials involving 855 patients ([Avouac et al. 2010](#)). Glucosamine, chondroitin, and intra-articular hyaluronic acid have been the most popular CAM treatments for osteoarthritis, but multiple meta-analyses and systematic reviews ([Table 54-7](#)) found insufficient evidence to support the efficacy of either glucosamine or chondroitin. In contrast, hyaluronic acid seems to be effective in knee osteoarthritis, although it does require intra-articular administration. It also seems to be similar in

efficacy to continuous NSAID therapy (Bannuru et al. 2014) and intra-articular corticosteroids (Bannuru et al. 2009).

**TABLE 54-7. Glucosamine, chondroitin, and hyaluronic acid for osteoarthritis (OA) summary of systematic reviews**

Treatment	Study	Condition	Review type	Benefits	Strength of evidence	Comments
Glucosamine	Vlad et al. 2007	Knee or hip OA	Meta-analysis (15 trials, 2,825 patients)	Not known	Moderate	Glucosamine hydrochloride (three trials) did not have a significant effect (0.06), glucosamine sulfate (three trials) (0.44). However, large heterogeneity among studies made conclusions about effectiveness uncertain.
Glucosamine	Wu et al. 2013	Knee or hip OA	Meta-analysis (19 trials, 3,195 patients)	No	Moderate	Neither glucosamine hydrochloride nor glucosamine sulphate had a significant effect (0.03 and 0.22, respectively) in trial weeks or 12 weeks.

*Note.* GAIT=Glucosamine-Chondroitin Arthritis Intervention Trial.

<b>Treatment</b>	<b>Study</b>	<b>Condition</b>	<b>Review type</b>	<b>Benefits</b>	<b>Strength of evidence</b>	<b>Comments</b>
Chondroitin	<a href="#">Reichenbach et al. 2007</a>	Knee or hip OA	Meta-analysis (20 trials, 3,846 patients)	No	Moderate	Minimal effect on symptoms. Only the large high quality trials which accounted for 40% of patients.
Glucosamine and/or chondroitin	<a href="#">Distler and Anguelouch 2006</a>	Knee or hip OA	Network meta-analysis (10 trials, 3,803 patients)	No	Moderate	Review of prior network analysis of large clinical trials concluded that neither glucosamine nor chondroitin were effective for OA.
Glucosamine and/or chondroitin	<a href="#">Wandel et al. 2010</a>	Knee or hip OA	Review of prior reviews	No	Moderate	All trials of patients with knee OA comparing glucosamine vs. placebo, chondroitin vs. placebo, and 1 trial comparing glucosamine vs. chondroitin vs. placebo. No effect on either joint space narrowing

---

*Note.* GAIT=Glucosamine-Chondroitin Arthritis Intervention Trial.

Treatment	Study	Condition	Review type	Benefits	Strength of evidence	Comments
Glucosamine and/or chondroitin	<a href="#">Samson et al. 2007</a>	Knee OA	Systematic (21 trials)	Not known	Moderate	Evidence small to moderate. The GAIT study included 1,583 patients and showed no difference from placebo.
Hyaluronic acid (intra-articular)	<a href="#">Arrich et al. 2005</a>	Knee OA	Meta-analysis (22 trials)	No	Moderate	Small but clinically insignificant effect on pain. Confirmed in four high quality studies.
Hyaluronic acid (intra-articular)	<a href="#">Samson et al. 2007</a>	Knee OA	Systematic (42 trials)	Not known	Moderate	Generally no modes of benefit compared with placebo but unclear clinical significance.
Hyaluronic acid (intra-articular)	<a href="#">Bannuru et al. 2011</a>	Knee OA	Meta-analysis (54 trials, 7,545 patients)	Yes	Moderate	Small to moderate effect sizes for pain at week 4 (0.31), week 8 (0.46), and week 24 (0.21).
Hyaluronic acid (intra-articular)	<a href="#">Miller and Block 2013</a>	Knee OA	Meta-analysis (29 trials, 4,866 patients)	Yes	Moderate	Moderate effect sizes (0.43) for knee pain over 4 weeks.

*Note.* GAIT=Glucosamine–Chondroitin Arthritis Intervention Trial.

[Avouac et al. \(2007\)](#) conducted a meta-analysis of trials evaluating opioid therapy in osteoarthritis patients. Of the 18 placebo-controlled trials, 13 assessed pain intensity for 2,438 participants receiving opioids and 1,295 receiving placebo. Six studies evaluated



stronger opioids (oxycodone in 4 studies, fentanyl and morphine in 1 study each), and 7 studies examined weaker opioids (tramadol in 4 studies, tramadol-acetaminophen combination in 2 studies, and codeine in 1 study). The median trial duration was 12 weeks. The pooled effect size for pain intensity was moderate, at  $-0.79$  (95% CI= $-0.98$  to  $-0.59$ ). Sensitivity analysis showed no changes in the conclusions by type of opioid studied, type of scale used to assess pain, or methodological quality of the study. Physical function was assessed in 5 trials, with 1,429 participants receiving opioids (tramadol-acetaminophen in 2 studies; morphine, tramadol, and codeine in 1 study each) and 595 receiving placebo. The median trial duration was 4 weeks. The pooled effect size for physical function was small, at  $-0.31$  (95% CI= $-0.39$  to  $-0.24$ ). Again, sensitivity analyses did not change the conclusions. The average treatment discontinuation rate for toxicity was 25% in the opioid group (31% for strong opioids and 19% for weak opioids) versus 7% in the placebo group.

In contrast to the many trials of antidepressants for neuropathic pain, fibromyalgia, and chronic low back pain, few studies have investigated antidepressants for the treatment of osteoarthritic pain. One exception is duloxetine, for which three trials in osteoarthritis have shown efficacy for pain ([Pergolizzi et al. 2013](#)). However, other studies have shown that when depression co-occurs with arthritis, it can explain as much of the variance in pain intensity as objective severity of the arthritis ([Katon et al. 2007](#)). Also, RCTs have shown that treatment of depression in arthritis patients may reduce pain as well as depression ([Kroenke et al. 2009a](#); [E.H. Lin et al. 2003](#)). Thus, while antidepressants cannot currently be recommended as a first-line treatment in osteoarthritis patients without depression, screening for and co-managing depression may benefit patients in their pain outcomes.

## Headache

Although there are less common and/or more serious causes of headache, most individuals with chronic headache have either migraine headache or tension-type headache (TTH). Up to one-third of the general population report TTH, and 10% experience migraine headaches ([Robbins and Lipton 2010](#)). However, more patients with migraine headache present to physicians for care. Contrary to public perceptions, sinus disease, hypertension, and eye strain are not common causes of headache.

Migraine is easier to diagnose in the presence of aura, which most commonly include a visual prodrome such as blind spots (scotomas), zigzag patterns (fortification spectra), or flashing lights (scintilla). However, aura occur in less than 20% of patients with migraine attacks.

Diagnostic criteria can differentiate migraine headache from TTH ([Toward Optimized Practice 2012](#)). Migraine without aura is diagnosed if at least two of the following are present: 1) nausea during the attack, 2) light sensitivity during the attack; and 3) some of the attacks interfere with the patient's activities. TTH is diagnosed if headaches are not associated with nausea and at least two of the following are present: 1) bilateral headache, 2) nonpulsating pain, 3) mild to moderate intensity, and 4) headache is not worsened by activity.

Some individuals with migraine or TTH develop chronic daily headache (CDH), defined as a headache frequency of  $\geq 15$  days a month for longer than 3 months. A common reversible cause of CDH is medication overuse headache (MOH), which can develop when analgesics are taken for headaches more than 2-3 days per week. Whereas all analgesics have the potential for MOH, the risk appears to be the highest with opioids or combination analgesics containing butalbital or caffeine, intermediate with triptans, and lowest with

NSAIDS. MOH often manifests as a headache that is present upon awakening and that responds to analgesics with only transient relief. This in turn can lead to a vicious circle of increased analgesic use.

Neuroimaging has a low yield in the evaluation of headaches. Even among selected patients with headache seen in tertiary referral centers, less than 1%–2% have abnormal imaging findings that influence treatment ([Clarke et al. 2010](#); [Dumas et al. 1994](#)). Factors that may justify an imaging study are focal neurological signs or symptoms, onset of headache after age 40 years, and severe or worsening headaches that do not respond to appropriate therapy.

An initial stepped-care approach to pharmacotherapy for migraine and TTH is summarized in [Table 54–8](#). Because migraine headache is both more disabling and more prevalent among patients who seek care, the amount of clinical trial evidence available, as well as the number of medications that have been well studied, is greater than for TTH. Treatment of less common types of headache (e.g., cluster headache) or chronic refractory headache probably warrants referral to a neurologist or other clinician specializing in headache management.

**TABLE 54–8. Stepped-care pharmacotherapy for headache**

Medication	Migraine	Tension type
Acute (abortive)		
Step 1	NSAID	Acetaminophen or NSAID
Step 2	Triptan	
Step 3	Opioid	
Prophylactic (preventive)		
Step 1	Beta-blocker	Amitriptyline or nortriptyline
Step 2	Topiramate	
Step 3	Divalproex	

*Note.* NSAID=nonsteroidal anti-inflammatory drug.

*Source.* Derived from [Becker et al. 2015](#); [Loder et al. 2012](#); [Silberstein et al. 2012](#).

## Algorithmic Approach to Treatment of Chronic Pain

This chapter has focused on the main classes of treatments for chronic pain, with a particular emphasis on pharmacotherapy. Five of the most common pain disorders have been discussed: neuropathic pain, fibromyalgia, low back pain, osteoarthritis, and headache. Based on our reviews within these parameters, an evidence-based stepped-care algorithm for treating pain is summarized in [Table 54–9](#), adapted from our previous review ([Kroenke et al. 2009b](#)) and tested (in an earlier version) in a clinical trial ([Kroenke et al. 2014](#)).

**TABLE 54–9. Evidence-based stepped-care analgesic algorithm by type of pain co**

Step	Medication	Dosing	Musculoskeletal <sup>a</sup>	Fibromyalgia	NeuropathicHe
<b>1</b>	<b>Simple analgesics</b>				
	Acetaminophen	650–1,000 mg every 6h (maximum of 3,000–4,000 mg/day, but only 2,000 mg/day if cirrhosis or $\geq 3$ alcoholic drinks/day)	+	+	+
	NSAIDs <sup>b,c</sup>				
	Naproxen	500 mg every 12h, or 500 mg in A.M. and then 250 bid (up to 1,000 mg/day)	+	+	+
	Ibuprofen	600 mg every 6h (maximum 2,400 mg/day)	+	+	+
	Salsalate	1,000 mg every 8h or 1,500 mg every 12h (up to 3,000 mg/day)	+	+	+

*Note.* bid=twice daily; hs=at bedtime; NSAID=nonsteroidal anti-inflammatory drug; q times daily; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; tid=three times daily.

++=U.S. Food and Drug Administration approved and/or strong evidence from 1 randomized controlled trials. +=Moderate evidence;  $\pm$ =Mixed (inconclusive) evidence.

<sup>a</sup>Includes back pain, osteoarthritis, and other localized joint or musculoskeletal pain.

<sup>b</sup>This is not a list of all drugs in this class.

<sup>c</sup>Consider trials of at least two NSAIDs; over-the-counter=naproxen, ibuprofen, ketoprofen.

<sup>d</sup>Triptans used for acute migraine treatment; other drugs used for migraine prevention.

Step	Medication	Dosing	Musculoskeletal <sup>a</sup>	Fibromyalgia	NeuropathicHe
	Meloxicam	7.5–15 mg/day (up to 15 mg/day)	+	+	+
	Etodolac	300 mg every 8h or 500 mg every 12h (maximum 1,000 mg/day)	+	+	+
	Diclofenac	50 mg every 8h (maximum 150 mg/day)	+	+	+
	Sulindac	150–200 mg bid (maximum 400 mg/day)	+	+	+
<b>2</b>	<b>TCAs<sup>b</sup></b>				
	Amitriptyline	Start at 10–25 mg; titrate to 100 mg		+	+
	Nortriptyline	Start at 10–25 mg; titrate to 100 mg		+	+
<b>2</b>	<b>Muscle relaxants<sup>b</sup></b>				

*Note.* bid=twice daily; hs=at bedtime; NSAID=nonsteroidal anti-inflammatory drug; q times daily; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; tid=three times daily.

++=U.S. Food and Drug Administration approved and/or strong evidence from 1 randomized controlled trials. +=Moderate evidence; ±=Mixed (inconclusive) evidence.

<sup>a</sup>Includes back pain, osteoarthritis, and other localized joint or musculoskeletal pain.

<sup>b</sup>This is not a list of all drugs in this class.

<sup>c</sup>Consider trials of at least two NSAIDs; over-the-counter=naproxen, ibuprofen, ketoprofen.

<sup>d</sup>Triptans used for acute migraine treatment; other drugs used for migraine prevention.

Step	Medication	Dosing	Musculoskeletal <sup>a</sup>	Fibromyalgia	NeuropathicHe
	Cyclobenzaprine	5-10 mg bid to tid (maximum 20-30 mg total daily dose)	+	±	
	Methocarbamol	Start at 500 mg qid; can increase to 1,000 mg qid	±	±	
	Tizanidine	Start at 2 mg tid; can increase to 6-8 mg tid			
<b>2</b>	<b>Gabapentoids</b>				
	Gabapentin	Start at 100 mg tid; titrate to 900-1,200 mg tid		±	++
	Pregabalin	Start at 75-100 mg bid; titrate to 450 mg/day total in bid doses		++	++
<b>2</b>	<b>SNRI antidepressants</b>				
	Venlafaxine	75 mg/day sustained release; titrate to 225 mg/day		±	±

*Note.* bid=twice daily; hs=at bedtime; NSAID=nonsteroidal anti-inflammatory drug; q times daily; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; tid=three times daily.

++=U.S. Food and Drug Administration approved and/or strong evidence from 1 randomized controlled trials. +=Moderate evidence; ±=Mixed (inconclusive) evidence.

<sup>a</sup>Includes back pain, osteoarthritis, and other localized joint or musculoskeletal pain.

<sup>b</sup>This is not a list of all drugs in this class.

<sup>c</sup>Consider trials of at least two NSAIDs; over-the-counter=naproxen, ibuprofen, ketoprofen.

<sup>d</sup>Triptans used for acute migraine treatment; other drugs used for migraine prevention.

Step	Medication	Dosing	Musculoskeletal <sup>a</sup>	Fibromyalgia	NeuropathicHe
	Duloxetine	Start at 30 mg/day; titrate to 60 mg/day	+	++	++
	Milnacipran	Start at 12.5 mg bid; titrate to 50 mg bid		++	
<b>3</b>	<b>Category IV controlled</b>				
	Tramadol	Start 25 mg bid or tid; titrate to maximum of 100 mg qid	+	+	+
<b>4</b>	<b>Category II opiates<sup>b</sup></b>				
	Hydrocodone	Start 5 mg bid to qid; try to keep ≤10-20 mg qid	±		±
	Oxycodone	Start 5 mg bid to qid; try to keep ≤10-20 mg qid (A sustained-released formulation is also available that can be given bid.)	±		±

*Note.* bid=twice daily; hs=at bedtime; NSAID=nonsteroidal anti-inflammatory drug; q times daily; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; tid=three times daily.

++=U.S. Food and Drug Administration approved and/or strong evidence from 1 randomized controlled trials. +=Moderate evidence; ±=Mixed (inconclusive) evidence.

<sup>a</sup>Includes back pain, osteoarthritis, and other localized joint or musculoskeletal pain.

<sup>b</sup>This is not a list of all drugs in this class.

<sup>c</sup>Consider trials of at least two NSAIDs; over-the-counter=naproxen, ibuprofen, ketoprofen.

<sup>d</sup>Triptans used for acute migraine treatment; other drugs used for migraine prevention.

Step	Medication	Dosing	Musculoskeletal <sup>a</sup>	Fibromyalgia	NeuropathicHe
	Morphine	15 mg bid sustained release; try to keep ≤60 mg bid	±		±
<b>A Migraine-specific agents<sup>b,d</sup></b>					
	Tryptans <sup>b</sup>				
	Sumatriptan	50-100 mg oral or 5- 20 mg nasal spray			
	Zolmitriptan	2.5-5.0 mg oral or nasal spray			
	Beta-blockers <sup>b</sup>				
	Propranolol	20-80 mg bid			
	Metoprolol	25-100 mg bid			
	Topiramate	Start at 25 mg hs to bid; titrate to 50 mg bid (or 100 mg hs)			
	Divalproex	Start at 250 mg bid; titrate to 500 mg bid			
<b>B Topical analgesics</b>					

*Note.* bid=twice daily; hs=at bedtime; NSAID=nonsteroidal anti-inflammatory drug; q times daily; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; tid=three times daily.

++=U.S. Food and Drug Administration approved and/or strong evidence from 1 randomized controlled trials. +=Moderate evidence; ±=Mixed (inconclusive) evidence.

<sup>a</sup>Includes back pain, osteoarthritis, and other localized joint or musculoskeletal pain.

<sup>b</sup>This is not a list of all drugs in this class.

<sup>c</sup>Consider trials of at least two NSAIDs; over-the-counter=naproxen, ibuprofen, ketoprofen.

<sup>d</sup>Tryptans used for acute migraine treatment; other drugs used for migraine prevention.

Step Medication	Dosing	Musculoskeletal <sup>a</sup>	Fibromyalgia	NeuropathicHe
Capsaicin	Apply 0.025%–0.075% cream 2–4 times/day over painful area	+		+
Lidocaine gel or patch	Gel or ointment 2–4 times/day or 5% patch (≤3 patches)	+		+
Salsalate/other NSAIDs	Apply 2–4 times/day over painful area	+		+

*Note.* bid=twice daily; hs=at bedtime; NSAID=nonsteroidal anti-inflammatory drug; q times daily; SNRI=serotonin-norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; tid=three times daily.

++=U.S. Food and Drug Administration approved and/or strong evidence from 1 randomized controlled trials. +=Moderate evidence; ±=Mixed (inconclusive) evidence.

<sup>a</sup>Includes back pain, osteoarthritis, and other localized joint or musculoskeletal pain.

<sup>b</sup>This is not a list of all drugs in this class.

<sup>c</sup>Consider trials of at least two NSAIDs; over-the-counter=naproxen, ibuprofen, ketoprofen.

<sup>d</sup>Triptans used for acute migraine treatment; other drugs used for migraine prevention.

## Other Issues

### Treatment of Pain Comorbid With Depression or Anxiety

As mentioned earlier, there is substantial evidence for a pain-depression dyad and probably a pain-depression-anxiety triad (see “Psychiatric Comorbidity”). The comorbidity among these disorders ranges from 30% to 60%, and they have reciprocal adverse effects on quality of life, disability, health care use, and treatment response. In particular, the presence of pain negatively affects depression outcomes, while depression in turn makes pain treatments less effective. Anxiety may have a similar effect, although the research in this area is less substantial than for depression.

Several trials have shown that depression treatment also benefits patients on pain outcomes, although the effect size for pain is only about half that for depression (Greco et al. 2004; Kroenke et al. 2009a; E.H. Lin et al. 2003). Other trials have demonstrated the



effectiveness of simultaneous treatment of chronic pain and comorbid depression ([Kroenke et al. 2009a, 2010](#)). Several suggestions may be considered. First, pain should be asked about when treating depressed or anxious patients, particularly in those who are not achieving remission or optimal responses. Likewise, psychiatric screening should be considered in patients with persistent pain, possibly with brief measures that screen for both depression and anxiety ([Kroenke et al. 2009c](#)). Second, it may be that antidepressant selection is important when pain is a major problem. For some types of pain conditions, TCAs and SNRI antidepressants appear to be more effective than SSRI or other antidepressants, although head-to-head trials are still few. Third, adding CBT, PSM programs, or other nonpharmacological treatments proven effective for pain could be considered. Fourth, optimizing analgesic management in patients with depression and pain, rather than simply focusing on depression medications, may be important. Increasingly, we may need to consider pain and depression as dual diagnoses, where attention to both is necessary to optimize patients' outcomes.

## Placebo Effect

As with other symptom-based conditions (e.g., depression, anxiety, somatoform disorders), pain has a placebo response in the 30%–40% range or higher. This can make it challenging to separate the specific effects of a pain treatment—medication or nonpharmacological—from placebo or other nonspecific effects. A network meta-analysis of 149 trials in adults with osteoarthritis showed that the effect size for intra-articular or topical placebo was greater than that for oral placebo ([Bannuru et al. 2015](#)). In the model accounting for differential effects, intra-articular and topical therapies were superior to oral treatments in reducing pain. When these differential effects were ignored, oral NSAIDs were superior. At the same time, the role of placebo effects on pain outcomes can be useful in clinical practice, including patient expectancy for an analgesic outcome and the clinical benefits of a positive therapeutic relationship. Pain is the most frequent reason for seeking CAM care ([Astin 1998](#)). Although evidence for several CAM treatments may still be lacking, their placebo effects coupled with frustration among many allopathic physicians and patients in the context of chronic pain may account for the popularity of CAM treatments for pain.

Experimental work has also revealed some interesting physiological effects of placebo. A meta-analysis of 12 studies (1,183 participants) was conducted to examine the effects of placebo and an opioid antagonist, naloxone, on pain ([Sauro and Greenberg 2005](#)). Placebo administration was associated with a decrease in self-reported pain, and a hidden or blind injection of naloxone reversed placebo-induced analgesia. An experimental study in 20 healthy subjects found that the placebo and nocebo effects (i.e., the therapeutic and adverse effects, respectively, of inert substances or sham procedures) are associated with opposite responses of dopaminergic and endogenous opioid neurotransmission in a distributed network of regions throughout the brain ([Scott et al. 2008](#)). The results support other literature showing that the belief in and expectation of analgesia induce discrete physiological changes, leading to relief from pain, and this response may be mediated by endogenous opioids.

Clinical ways to take advantage of the placebo effects of an analgesic are summarized by [Klinger et al. \(2014\)](#):

- **Enhancing expectations**—examples include 1) emphasis on positive drug effects and avoidance of an overemphasis on side effects; 2) explaining the mechanism of drug

action; 3) personal interaction rather than only written materials; and 4) explaining the course of drug action while avoiding unrealistic promises.

- **Enhancing learning components**—examples include 1) focusing on sensory aspects of a pain medicine such as its color or size to distinguish it from other medicines the patient may be taking; 2) association of analgesic medication with positive internal states and positive external conditions; 3) combining analgesic intake with other pain-relieving techniques; and 4) time-contingent (scheduled) rather than pain-contingent (intermittent) use of analgesics.

## Assessment and Monitoring of Pain

Inadequate pain assessment has been identified as a key barrier to appropriate pain management. Important initiatives have aimed to increase awareness of pain as a clinical problem by promoting better pain assessment. The U.S. Department of Veterans Affairs (VA) campaign promoting “pain as the fifth vital sign” requires all VA facilities to assess patients using a numeric rating scale (NRS) of 0–10 for current pain, where 0 is “no pain,” 5 is “moderate pain,” and 10 is “worst pain possible.” Even more far-reaching, the [Joint Commission on Accreditation of Healthcare Organizations \(2000\)](#) pain assessment and management standards, implemented in 2001, require accredited health care facilities to assess all patients for pain in both inpatient and ambulatory care settings. Although Joint Commission standards do not mandate a specific method of pain assessment, many organizations have responded by adopting use of an NRS of pain as the “fifth vital sign” ([Dahl 2002](#)). However, this movement has not led to clear improvements in the quality or outcomes of chronic pain management, and studies have shown that the NRS may not be the optimal measure for assessing and monitoring chronic pain in clinical practice ([Krebs et al. 2007](#); [Mularski et al. 2006](#)). An important limitation of single-item pain measurement is that it provides an overly simplified picture of a complex subjective experience.

Consensus recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) included four core chronic pain outcome domains for monitoring treatment response: pain intensity (i.e., severity), physical functioning (i.e., pain-specific disability), emotional functioning (largely depression), and patient-rated overall improvement ([Dworkin et al. 2008](#)). The first two domains are captured in the PEG pain scale, which has been validated and is based on three items from the Brief Pain Inventory (average Pain severity, interference with Enjoyment of life, and interference with General activities), shown in [Figure 54-1](#) ([Krebs et al. 2009, 2010](#)). For emotional functioning, a clinical or patient-rated assessment of depression is recommended. For overall improvement, the single-item Patient Global Impression of Change scale uses a seven-point rating scale with the options “very much improved,” “much improved,” “minimally improved,” “no change,” “minimally worse,” “much worse,” and “very much worse.”

**1. What number best describes your pain on average in the past week?**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

**2. What number best describes how, during the past week, pain has interfered with your general activity?**

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

**3. What number best describes how, during the past week, pain has interfered with your enjoyment of life?**

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

**FIGURE 54-1.** PEG three-item pain scale.

The PEG three-item pain scale—an ultrabrief measure for assessing and monitoring pain—is based on three items from the Brief Pain Inventory: average **P**ain severity, interference with **E**njoyment of life, and interference with **G**eneral activities.

## Gaps in Knowledge Base Regarding Treatment of Chronic Pain

There are several important gaps in our knowledge regarding treatment that in fact are probably not unique to chronic pain. First, there is a paucity of head-to-head trials, meaning that although we can draw conclusions about the effectiveness of a particular monotherapy compared with a placebo or minimal treatment, we have much less information about the comparative effectiveness of different treatments. Second, few trials have evaluated different strategies for choosing initial treatment, so that deciding between first-line and subsequent treatments is more a matter of expert consensus, clinician experience, and patient preferences. Third, evidence is sparse on the effectiveness of dual-medication or other combination therapy versus monotherapy or sequential treatment, even though patients are frequently prescribed more than one medication or treatment. Fourth, most treatment trials have been short-term, so evidence of benefits sustained beyond 4–12 weeks is often lacking; this is a critical gap given the fact that our focus is on the management of chronic pain.

Despite these gaps, substantial evidence has accumulated over the past several decades about what works and what does not work for treating chronic pain. Avoiding ineffective treatments and maximizing the use of treatments proven beneficial in clinical trials are

likely to produce better outcomes than have often been experienced by clinicians and patients in the management of chronic pain.

---

## References

---

- Aaron LA, Buchwald D: A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 134(9 Pt 2):868-881, 2001 11346323
- Abeles AM, Pillinger MH, Solitar BM, Abeles M: Narrative review: the pathophysiology of fibromyalgia. *Ann Intern Med* 146(10):726-734, 2007 17502633
- Ablin J, Fitzcharles MA, Buskila D, et al: Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. *Evid Based Complement Alternat Med* 2013(Nov):485272, 2013 24348701
- Adams EH, Breiner S, Cicero TJ, et al: A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. *J Pain Symptom Manage* 31(5):465-476, 2006 16716877
- Ahles TA, Wasson JH, Seville JL, et al: A controlled trial of methods for managing pain in primary care patients with or without co-occurring psychosocial problems. *Ann Fam Med* 4(4):341-350, 2006 16868238
- Allen LA, Escobar JI, Lehrer PM, et al: Psychosocial treatments for multiple unexplained physical symptoms: a review of the literature. *Psychosom Med* 64(6):939-950, 2002 12461199
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000
- Ang DC, Kroenke K, McHorney CA: Impact of pain severity and location on health-related quality of life. *Rheumatol Int* 26(6):567-572, 2006 16096793
- Angst MS, Clark JD: Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 104(3):570-587, 2006 16508405
- Antman EM, Bennett JS, Daugherty A, et al; American Heart Association: Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation* 115(12):1634-1642, 2007 17325246
- Arnold LM, Keck PE Jr, Welge JA: Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 41(2):104-113, 2000 10749947
- Arnow BA, Hunkeler EM, Blasey CM, et al: Comorbid depression, chronic pain, and disability in primary care. *Psychosom Med* 68(2):262-268, 2006 16554392
- Arrich J, Piribauer F, Mad P, et al: Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *CMAJ* 172(8): 1039-1043, 2005 15824412
- Astin JA: Why patients use alternative medicine: results of a national study. *JAMA* 279(19):1548-1553, 1998 9605899
- Attal N, Cruccu G, Haanpää M, et al; EFNS Task Force: EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 13(11):1153-1169, 2006 17038030
- Avouac J, Gossec L, Dougados M: Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 15(8):957-965, 2007 17398122
- Avouac J, Vicaut E, Bardin T, Richette P: Efficacy of joint lavage in knee osteoarthritis: meta-analysis of randomized controlled studies. *Rheumatology (Oxford)* 49(2): 334-340, 2010 19955221
- Bair MJ, Robinson RL, Katon W, Kroenke K: Depression and pain comorbidity: a literature review. *Arch Intern Med* 163(20): 2433-2445, 2003 14609780

- Bair MJ, Robinson RL, Eckert GJ, et al: Impact of pain on depression treatment response in primary care. *Psychosom Med* 66(1): 17-22, 2004 14747633
- Bair MJ, Wu J, Damush TM, et al: Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. *Psychosom Med* 70(8):890-897, 2008 18799425
- Bair MJ, Poleshuck EL, Wu J, et al: Anxiety but not social stressors predict 12-month depression and pain severity. *Clin J Pain* 29(2):95-101, 2013 23183264
- Ballantyne JC, Mao J: Opioid therapy for chronic pain. *N Engl J Med* 349(20):1943-1953, 2003 14614170
- Bannuru RR, Natov NS, Obadan IE, et al: Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum* 61(12):1704-1711, 2009 19950318
- Bannuru RR, Natov NS, Dasi UR, et al: Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis—meta-analysis. *Osteoarthritis Cartilage* 19(6):611-619, 2011 21443958
- Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE: Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum* 43(5):593-599, 2014 24216297
- Bannuru RR, McAlindon TE, Sullivan MC, et al: Effectiveness and implications of alternative placebo treatments: a systematic review and network meta-analysis of osteoarthritis trials. *Ann Intern Med* 163(5):365-372, 2015 26215539
- Barden J, Edwards JE, McQuay HJ, Andrew Moore R: Pain and analgesic response after third molar extraction and other postsurgical pain. *Pain* 107(1-2):86-90, 2004 14715393
- Basbaum A, Bushnell C, Devor M: Pain: basic mechanisms, in *Pain 2005—An Updated Review: Refresher Course Syllabus*. Edited by Justins DM. Seattle, WA, IASP Press, 2005, pp 3-18
- Becker WJ, Findlay T, Moga C, et al: Guideline for primary care management of headache in adults. *Can Fam Physician* 61(8): 670-679, 2015 26273080
- Bender JL, Radhakrishnan A, Diorio C, et al: Can pain be managed through the Internet? A systematic review of randomized controlled trials. *Pain* 152(8):1740-1750, 2011 21565446
- Bennett MI, Hughes N, Johnson MI: Methodological quality in randomised controlled trials of transcutaneous electric nerve stimulation for pain: low fidelity may explain negative findings. *Pain* 152(6): 1226-1232, 2011 21435786
- Bennett RM, Kamin M, Karim R, Rosenthal N: Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med* 114(7):537-545, 2003 12753877
- Biasi G, Manca S, Manganelli S, Marcolongo R: Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo. *Int J Clin Pharmacol Res* 18(1): 13-19, 1998 9604730
- Birse F, Derry S, Moore RA: Phenytoin for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* (5):CD009485, 2012 22592741
- Black DR, Sang CN: Advances and limitations in the evaluation of analgesic combination therapy. *Neurology* 65 (12 suppl 4): S3-S6, 2005 16385102
- Bourke JH, Langford RM, White PD: The common link between functional somatic syndromes may be central sensitisation. *J Psychosom Res* 78 (3):228-236, 2015 25598410
- Bradley JD, Brandt KD, Katz BP, et al: Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med* 325(2):87-91, 1991 2052056
- Bradley LA, Alberts KR: Psychological and behavioral approaches to pain management for patients with rheumatic disease. *Rheum Dis Clin North Am* 25(1):215-232, viii, 1999 10083965

- Brannan SK, Mallinckrodt CH, Brown EB, et al: Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. *J Psychiatr Res* 39(1):43-53, 2005 15504423
- Brecht S, Courtecuisse C, Debieuvre C, et al: Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. *J Clin Psychiatry* 68(11):1707-1716, 2007 18052564
- Breivik H: International Association for the Study of Pain: update on WHO-IASP activities. *J Pain Symptom Manage* 24(2): 97-101, 2002 12231125
- Bril V, England J, Franklin GM, et al; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation: Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 76(20): 1758-1765, 2011 21482920
- Brosseau L, MacLeay L, Robinson V, et al: Intensity of exercise for the treatment of osteoarthritis. *Cochrane Database Syst Rev* (2):CD004259, 2003 12804510
- Buntin-Mushock C, Phillip L, Moriyama K, Palmer PP: Age-dependent opioid escalation in chronic pain patients. *Anesth Analg* 100(6):1740-1745, 2005 15920207
- Burckhardt CS: Multidisciplinary approaches for management of fibromyalgia. *Curr Pharm Des* 12(1):59-66, 2006 16454725
- Busch AJ, Barber KA, Overend TJ, et al: Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev* (4):CD003786, 2007 17943797
- Carson S, Thakurta S, Low A, et al: Drug Class Review: Long-Acting Opioid Analgesics: Final Update 6 Report [Internet]. Portland, OR, Oregon Health & Science University, July 2011 21977550
- Chen KY, Chen L, Mao J: Buprenorphine-naloxone therapy in pain management. *Anesthesiology* 120(5):1262-1274, 2014 24509068
- Chong MS, Hester J: Diabetic painful neuropathy: current and future treatment options. *Drugs* 67(4):569-585, 2007 17352515
- Chou R, Huffman LH; American Pain Society; American College of Physicians: Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 147(7):505-514, 2007a 17909211
- Chou R, Huffman LH; American Pain Society; American College of Physicians: Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 147(7):492-504, 2007b 17909210
- Chou R, Peterson K: Drug class review on skeletal muscle relaxants. Portland, OR, Oregon Health and Science University, 2005. Final report. Available at: [http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/SMR\\_Final\\_Report\\_Update%2022.pdf](http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/SMR_Final_Report_Update%2022.pdf). Accessed December 16, 2008.
- Chou R, Helfand M, Peterson K, et al: Drug class review on cyclo-oxygenase (COX)-2 inhibitors and nonsteroidal antiinflammatory drugs (NSAIDs). Final report update 3. Portland, OR, Oregon Health and Science University, 2006. Available at: [http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/NSAIDS\\_Final\\_Report\\_Update%203.pdf](http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/NSAIDS_Final_Report_Update%203.pdf). Accessed December 16, 2008.
- Chou R, Norris SL, Carson S, et al: Drug class review on drugs for neuropathic pain. Final report. Portland, OR, Oregon Health and Science University, 2007a. Available at: [http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/NP\\_Final\\_Report\\_Original.pdf](http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/NP_Final_Report_Original.pdf). Accessed December 16, 2008.
- Chou R, Qaseem A, Snow V, et al; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society

- Low Back Pain Guidelines Panel: Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 147(7):478-491, 2007b 17909209
- Chou R, Deyo R, Devine B, et al: The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evidence Report/Technology Assessment No. 218. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality, September 2014
- Chou R, Hashimoto R, Friedly J, et al: Epidural corticosteroid injections for radiculopathy and spinal stenosis: a systematic review and meta-analysis. *Ann Intern Med* 163(5):373-381, 2015a 26302454
- Chou R, Turner JA, Devine EB, et al: The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 162(4):276-286, 2015b 25581257
- Clarke CE, Edwards J, Nicholl DJ, Sivaguru A: Imaging results in a consecutive series of 530 new patients in the Birmingham Headache Service. *J Neurol* 257(8):1274-1278, 2010 20198381
- Clarke JA, van Tulder MW, Blomberg SE, et al: Traction for low-back pain with or without sciatica. *Cochrane Database Syst Rev* (2):CD003010, 2007 17443521
- Clauw DJ: Fibromyalgia: update on mechanisms and management. *J Clin Rheumatol* 13(2):102-109, 2007 17414543
- Cohen J: Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ, Lawrence Erlbaum, 1998
- Cohen JL, Sauter SV, deVellis RF, deVellis BM: Evaluation of arthritis self-management courses led by laypersons and by professionals. *Arthritis Rheum* 29(3):388-393, 1986 3964314
- Corrigan R, Derry S, Wiffen PJ, Moore RA: Clonazepam for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* (5):CD009486, 2012 22592742
- Crawford C, Lee C, Buckenmaier C 3rd, et al; Active Self-Care Therapies for Pain (PACT) Working Group: The current state of the science for active self-care complementary and integrative medicine therapies in the management of chronic pain symptoms: lessons learned, directions for the future. *Pain Med* 15 (suppl 1):S104-S113, 2014 24734856
- Curatolo M, Bogduk N: Pharmacologic pain treatment of musculoskeletal disorders: current perspectives and future prospects. *Clin J Pain* 17(1):25-32, 2001 11289086
- Dahl JL: Working with regulators to improve the standard of care in pain management: the U.S. experience. *J Pain Symptom Manage* 24(2):136-146, 2002 12231131
- Damush TM, Weinberger M, Perkins SM, et al: Randomized trial of a self-management program for primary care patients with acute low back pain: short-term effects. *Arthritis Rheum* 49(2):179-186, 2003 12687508
- Daniell HW: Hypogonadism in men consuming sustained-action oral opioids. *J Pain* 3(5):377-384, 2002 14622741
- Daniell HW: Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain* 9(1):28-36, 2008 17936076
- Demyttenaere K, Bonnewyn A, Bruffaerts R, et al: Comorbid painful physical symptoms and depression: prevalence, work loss, and help seeking. *J Affect Disord* 92(2-3):185-193, 2006 16516977
- Derry S, Gill D, Phillips T, Moore RA: Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* (3):CD008244, 2012 22419330
- Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF: Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. *Can Fam Physician* 61(8):e372-e381, 2015 26505059
- DeVeugh-Geiss AM, West SL, Miller WC, et al: The adverse effects of comorbid pain on depression outcomes in primary care patients: results from the ARTIST trial. *Pain Med* 11(5):732-741, 2010 20353408



- Devulder J, Richarz U, Nataraja SH: Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Curr Med Res Opin* 21(10):1555-1568, 2005 16238895
- Dhanani NM, Caruso TJ, Carinci AJ: Complementary and alternative medicine for pain: an evidence-based review. *Curr Pain Headache Rep* 15(1):39-46, 2011 21063917
- Distler J, Anguelouch A: Evidence-based practice: review of clinical evidence on the efficacy of glucosamine and chondroitin in the treatment of osteoarthritis. *J Am Acad Nurse Pract* 18(10):487-493, 2006 16999714
- Dixon KE, Keefe FJ, Scipio CD, et al: Psychological interventions for arthritis pain management in adults: a meta-analysis. *Health Psychol* 26(3):241-250, 2007 17500610
- Doherty M, Hawkey C, Goulder M, et al: A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. *Ann Rheum Dis* 70(9):1534-1541, 2011 21804100
- Dowell D, Haegerich TM, Chou R; U.S. Centers for Disease Control and Prevention: CDC draft guideline for prescribing opioids for chronic pain—United States, 2016. Available at: <http://www.regulations.gov/contentStreamer?documentId=CDC-2015-0112-0002&>. Accessed February 17, 2016.
- Du S, Yuan C, Xiao X, et al: Self-management programs for chronic musculoskeletal pain conditions: a systematic review and meta-analysis. *Patient Educ Couns* 85(3):e299-e310, 2011 21458196
- Dumas MD, Pexman JH, Kreeft JH: Computed tomography evaluation of patients with chronic headache. *CMAJ* 151(10): 1447-1452, 1994 7954139
- Dworkin RH, O'Connor AB, Backonja M, et al: Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 132(3):237-251, 2007 17920770
- Dworkin RH, Turk DC, Wyrwich KW, et al: Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 9(2):105-121, 2008 18055266
- Eccles NK: A critical review of randomized controlled trials of static magnets for pain relief. *J Altern Complement Med* 11(3): 495-509, 2005 15992236
- Eccleston C, Fisher E, Craig L, et al: Psychological therapies (Internet-delivered) for the management of chronic pain in adults. *Cochrane Database Syst Rev* (2):CD010152, 2014 24574082
- Eisenberg E, McNicol E, Carr DB: Opioids for neuropathic pain. *Cochrane Database Syst Rev* (3):CD006146, 2006 16856116
- Ernst E, Lee MS, Choi TY: Acupuncture: does it alleviate pain and are there serious risks? A review of reviews. *Pain* 152(4): 755-764, 2011 21440191
- Finnerup NB, Attal N, Haroutounian S, et al: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 14(2):162-173, 2015 25575710
- Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS: Are opioid-dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review. *J Pain Symptom Manage* 25(6):559-577, 2003 12782437
- Franklin GM; American Academy of Neurology: Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology* 83(14): 1277-1284, 2014 25267983
- Franklin GM, Stover BD, Turner JA, et al; Disability Risk Identification Study Cohort: Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine* 33(2):199-204, 2008 18197107
- Freyenhagen R, Muth-Selbach U, Lipfert P, et al: The effect of mirtazapine in patients with chronic pain and concomitant depression. *Curr Med Res Opin* 22(2):257-264, 2006 16466597
- Fricton J, Velly A, Ouyang W, Look JO: Does exercise therapy improve headache? a systematic review with meta-analysis. *Curr Pain Headache Rep* 13(6):413-419, 2009 19889280



- Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E: Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ* 174(11):1589-1594, 2006 16717269
- Furlan AD, Yazdi F, Tsertsvadze A, et al: A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. *Evid Based Complement Alternat Med* 2012:953139, 2012 22203884
- Gallagher RM: Pain science and rational polypharmacy: an historical perspective. *Am J Phys Med Rehabil* 84 (3 suppl):S1-S3, 2005 15722779
- Gilron I, Bailey JM, Tu D, et al: Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 352(13):1324-1334, 2005 15800228
- Gilron I, Bailey JM, Tu D, et al: Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 374(9697):1252-1261, 2009 19796802
- Goldenberg DL, Burckhardt C, Crofford L: Management of fibromyalgia syndrome. *JAMA* 292(19):2388-2395, 2004 15547167
- Goldenberg DL, Clauw DJ, Palmer RE, Clair AJ: Opioid use in fibromyalgia: a cautionary tale. *Mayo Clin Proc* 91(5):640-648, 2016 26975749
- Gowans SE, deHueck A: Pool exercise for individuals with fibromyalgia. *Curr Opin Rheumatol* 19(2):168-173, 2007 17278933
- Greco T, Eckert G, Kroenke K: The outcome of physical symptoms with treatment of depression. *J Gen Intern Med* 19(8):813-818, 2004 15242465
- Gureje O, Von Korff M, Simon GE, Gater R: Persistent pain and well-being: a World Health Organization Study in Primary Care. *JAMA* 280(2):147-151, 1998 9669787
- Gureje O, Von Korff M, Kola L, et al: The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. *Pain* 135(1-2):82-91, 2008 17570586
- Häuser W, Bernardy K, Üçeyler N, Sommer C: Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain* 145(1-2):69-81, 2009 19539427
- Häuser W, Klose P, Langhorst J, et al: Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther* 12(3):R79, 2010 20459730
- Häuser W, Petzke F, Üçeyler N, Sommer C: Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology (Oxford)* 50(3):532-543, 2011 21078630
- Heit HA: Addiction, physical dependence, and tolerance: precise definitions to help clinicians evaluate and treat chronic pain patients. *J Pain Palliat Care Pharmacother* 17(1):15-29, 2003 14640337
- Henningsen P, Zimmermann T, Sattel H: Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. *Psychosom Med* 65(4):528-533, 2003 12883101
- Henningsen P, Zipfel S, Herzog W: Management of functional somatic syndromes. *Lancet* 369(9565):946-955, 2007 17368156
- Henschke N, Kuijpers T, Rubinstein SM, et al: Injection therapy and denervation procedures for chronic low-back pain: a systematic review. *Eur Spine J* 19(9):1425-1449, 2010 20424870
- Henschke N, Kamper SJ, Maher CG: The epidemiology and economic consequences of pain. *Mayo Clin Proc* 90(1):139-147, 2015 25572198
- Hill KP: Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA* 313(24):2474-2483, 2015 26103031
- Højsted J, Sjøgren P: An update on the role of opioids in the management of chronic pain of nonmalignant origin. *Curr Opin Anaesthesiol* 20(5):451-455, 2007 17873598

- Hollingshead J, Dühmke RM, Cornblath DR: Tramadol for neuropathic pain. *Cochrane Database Syst Rev* (3):CD003726, 2006 16856016
- Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education: *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC, National Academies Press, 2011. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK91497/>. Accessed February 24, 2016.
- International Association for the Study of Pain: IASP terminology. May 22, 2012. Updated from IASP Task Force on Taxonomy: Pain terms: a current list with definitions and notes on usage, in *Classification of Chronic Pain*, 2nd Edition. Edited by Merskey H, Bogduk N. Seattle, WA, IASP Press, 1994, pp 209-214. Available at: <http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576>. Accessed March 14, 2016.
- Jackson JL, O'Malley PG, Kroenke K: Antidepressants and cognitive-behavioral therapy for symptom syndromes. *CNS Spectr* 11(3):212-222, 2006 16575378
- Jensen MP, Patterson DR: Hypnotic approaches for chronic pain management: clinical implications of recent research findings. *Am Psychol* 69(2):167-177, 2014 24547802
- Jensen MK, Thomsen AB, Højsted J: 10-year follow-up of chronic non-malignant pain patients: opioid use, health related quality of life and health care utilization. *Eur J Pain* 10(5):423-433, 2006 16054407
- Joint Commission on Accreditation of Healthcare Organizations: *Pain Assessment and Management: An Organizational Approach*. Oakbrook Terrace, IL, JCAHO, 2000
- Joranson DE, Carrow GM, Ryan KM, et al: Pain management and prescription monitoring. *J Pain Symptom Manage* 23(3):231-238, 2002 11888721
- Jung AC, Staiger T, Sullivan M: The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 12(6):384-389, 1997 9192257
- Karjalainen K, Malmivaara A, van Tulder M, et al: Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. *Cochrane Database Syst Rev* (2):CD001984, 2000 10796458
- Karp JF, Scott J, Houck P, et al: Pain predicts longer time to remission during treatment of recurrent depression. *J Clin Psychiatry* 66(5):591-597, 2005 15889945
- Katon W, Lin EH, Kroenke K: The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 29(2):147-155, 2007 17336664
- Kelley GA, Kelley KS, Hootman JM, Jones DL: Effects of community-deliverable exercise on pain and physical function in adults with arthritis and other rheumatic diseases: a meta-analysis. *Arthritis Care Res (Hoboken)* 63(1):79-93, 2011 20824798
- Khoromi S, Cui L, Nackers L, Max MB: Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain* 130(1-2):66-75, 2007 17182183
- Klinger R, Colloca L, Bingel U, Flor H: Placebo analgesia: clinical applications. *Pain* 155(6):1055-1058, 2014 24333780
- Krebs EE, Carey TS, Weinberger M: Accuracy of the pain numeric rating scale as a screening test in primary care. *J Gen Intern Med* 22(10):1453-1458, 2007 17668269
- Krebs EE, Gaynes BN, Gartlehner G, et al: Treating the physical symptoms of depression with second-generation antidepressants: a systematic review and metaanalysis. *Psychosomatics* 49(3):191-198, 2008 18448772
- Krebs EE, Lorenz KA, Bair MJ, et al: Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *J Gen Intern Med* 24(6): 733-738, 2009 19418100
- Krebs EE, Bair MJ, Damush TM, et al: Comparative responsiveness of pain outcome measures among primary care patients with musculoskeletal pain. *Med Care* 48(11):1007-1014, 2010 20856144
- Kroenke K: The interface between physical and psychological symptoms. *Prim Care Companion J Clin Psychiatry* 5 (suppl 7): 11-18, 2003a

- Kroenke K: Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. *Int J Methods Psychiatr Res* 12(1):34-43, 2003b 12830308
- Kroenke K: Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. *Psychosom Med* 69(9): 881-888, 2007 18040099
- Kroenke K, Price RK: Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. *Arch Intern Med* 153(21):2474-2480, 1993 8215752
- Kroenke K, Swindle R: Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. *Psychother Psychosom* 69(4):205-215, 2000 10867588
- Kroenke K, Spitzer RL, Williams JBW, et al: Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Arch Fam Med* 3(9): 774-779, 1994 7987511
- Kroenke K, Jackson JL, Chamberlin J: Depressive and anxiety disorders in patients presenting with physical complaints: clinical predictors and outcome. *Am J Med* 103(5):339-347, 1997 9375700
- Kroenke K, Shen J, Oxman TE, et al: Impact of pain on the outcomes of depression treatment: results from the RESPECT trial. *Pain* 134(1-2):209-215, 2008 18022319
- Kroenke K, Bair MJ, Damush TM, et al: Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA* 301(20):2099-2110, 2009a 19470987
- Kroenke K, Krebs EE, Bair MJ: Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *Gen Hosp Psychiatry* 31(3):206-219, 2009b 19410099
- Kroenke K, Spitzer RL, Williams JBW, Löwe B: An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics* 50(6):613-621, 2009c 19996233
- Kroenke K, Theobald D, Wu J, et al: Effect of telecare management on pain and depression in patients with cancer: a randomized trial. *JAMA* 304(2):163-171, 2010 20628129
- Kroenke K, Krebs EE, Wu J, et al: Telecare collaborative management of chronic pain in primary care: a randomized clinical trial. *JAMA* 312(3):240-248, 2014 25027139
- Lee C, Straus WL, Balshaw R, et al: A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum* 51(5):746-754, 2004 15478167
- Lee J, Ellis B, Price C, Baranowski AP: Chronic widespread pain, including fibromyalgia: a pathway for care developed by the British Pain Society. *Br J Anaesth* 112(1): 16-24, 2014 24196696
- Lin EH, Katon W, Von Korff M, et al; IMPACT Investigators: Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA* 290(18):2428-2429, 2003 14612479
- Lin J, Zhang W, Jones A, Doherty M: Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ* 329(7461):324-329, 2004 15286056
- Loder E, Burch R, Rizzoli P: The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache* 52(6):930-945, 2012 22671714
- Lorig KR, Holman H: Self-management education: history, definition, outcomes, and mechanisms. *Ann Behav Med* 26(1):1-7, 2003 12867348
- Magni G, Marchetti M, Moreschi C, et al: Chronic musculoskeletal pain and depressive symptoms in the National Health and Nutrition Examination, I: epidemiologic follow-up study. *Pain* 53(2):163-168, 1993 8336986
- Manchikanti L, Benyamin RM, Falco FJ, et al: Do epidural injections provide short- and long-term relief for lumbar disc herniation? a systematic review. *Clin Orthop Relat Res* 473(6):1940-1956, 2015 24515404

- Manheimer E, White A, Berman B, et al: Meta-analysis: acupuncture for low back pain. *Ann Intern Med* 142(8):651-663, 2005 15838072
- Manheimer E, Linde K, Lao L, et al: Meta-analysis: acupuncture for osteoarthritis of the knee. *Ann Intern Med* 146(12):868-877, 2007 17577006
- Marangell LB, Clauw DJ, Choy E, et al: Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. *Pain* 152(1): 31-37, 2011 20598442
- Marks JL, van der Heijde DM, Colebatch AN, et al: Pain pharmacotherapy in patients with inflammatory arthritis and concurrent cardiovascular or renal disease: a Cochrane systematic review. *J Rheumatol Suppl* 90:81-84, 2012 22942334
- Martell BA, O'Connor PG, Kerns RD, et al: Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med* 146(2):116-127, 2007 17227935
- Mason L, Moore RA, Derry S, et al: Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 328(7446):991-994, 2004a 15033881
- Mason L, Moore RA, Edwards JE, et al: Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain. *BMJ* 328(7446):995-997, 2004b 15033879
- Mason L, Moore RA, Edwards JE, et al: Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskelet Disord* 5:28, 2004c 15317652
- Mavandadi S, Ten Have TR, Katz IR, et al: Effect of depression treatment on depressive symptoms in older adulthood: the moderating role of pain. *J Am Geriatr Soc* 55(2):202-211, 2007 17302656
- Max MB, Lynch SA, Muir J, et al: Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 326(19):1250-1256, 1992 1560801
- Mayhew E, Ernst E: Acupuncture for fibromyalgia—a systematic review of randomized clinical trials. *Rheumatology (Oxford)* 46(5):801-804, 2007 17189243
- McBeth J, Prescott G, Scotland G, et al: Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. *Arch Intern Med* 172(1):48-57, 2012 22082706
- McCarthy CJ, Callaghan MJ, Oldham JA: Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: a systematic review. *BMC Musculoskelet Disord* 7:51, 2006 16776826
- McWilliams LA, Cox BJ, Enns MW: Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain* 106(1-2):127-133, 2003 14581119
- Micca JL, Ruff D, Ahl J, Wohlreich MM: Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials. *BMC Musculoskelet Disord* 14(1):137, 2013 23590727
- Miller LE, Block JE: US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. *Clin Med Insights Arthritis Musculoskelet Disord* 6:57-63, 2013 24027421
- Moore RA, McQuay HJ: Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 7(5):R1046-R1051, 2005 16207320
- Moore RA, Straube S, Wiffen PJ, et al: Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* (3): CD007076, 2009 19588419
- Morley S, Williams A, Eccleston C: Examining the evidence about psychological treatments for chronic pain: time for a paradigm shift? *Pain* 154(10):1929-1931, 2013 23742793
- Moulin DE, Iezzi A, Amireh R, et al: Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 347(8995):143-147, 1996 8544547
- Mularski RA, White-Chu F, Overbay D, et al: Measuring pain as the 5th vital sign does not improve quality of pain management. *J Gen Intern Med* 21(6):607-612, 2006 16808744

- Murray CJ, Atkinson C, Bhalla K, et al; U.S. Burden of Disease Collaborators: The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA* 310(6):591–608, 2013 23842577
- Naugle KM, Fillingim RB, Riley JL 3rd: A meta-analytic review of the hypoalgesic effects of exercise. *J Pain* 13(12):1139–1150, 2012 23141188
- Nnoaham KE, Kumbang J: Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev* (3):CD003222, 2008 18646088
- Nuckols TK, Anderson L, Popescu I, et al: Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med* 160(1):38–47, 2014 24217469
- O’Connell NE, Wand BM, Marston L, et al: Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* (4):CD008208, 2014 24729198
- O’Malley PG, Jackson JL, Santoro J, et al: Antidepressant therapy for unexplained symptoms and symptom syndromes. *J Fam Pract* 48(12):980–990, 1999 10628579
- Ohayon MM, Schatzberg AF: Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry* 60(1):39–47, 2003 12511171
- Papakostas GI, Fava M: A meta-analysis of clinical trials comparing milnacipran, a serotonin-norepinephrine reuptake inhibitor, with a selective serotonin reuptake inhibitor for the treatment of major depressive disorder. *Eur Neuropsychopharmacol* 17(1):32–36, 2007 16762534
- Perahia DG, Pritchett YL, Desai D, Raskin J: Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? *Int Clin Psychopharmacol* 21(6):311–317, 2006 17012978
- Pergolizzi JV Jr, Raffa RB, Taylor R Jr, et al: A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract* 13(3):239–252, 2013 22716295
- Pittler MH, Brown EM, Ernst E: Static magnets for reducing pain: systematic review and meta-analysis of randomized trials. *CMAJ* 177(7):736–742, 2007 17893349
- Posadzki P, Ernst E: Guided imagery for musculoskeletal pain: a systematic review. *Clin J Pain* 27(7):648–653, 2011a 21430523
- Posadzki P, Ernst E: Osteopathy for musculoskeletal pain patients: a systematic review of randomized controlled trials. *Clin Rheumatol* 30(2):285–291, 2011b 21053038
- Posadzki P, Ernst E, Terry R, Lee MS: Is yoga effective for pain? A systematic review of randomized clinical trials. *Complement Ther Med* 19(5):281–287, 2011 21944658
- Posadzki P, Lewandowski W, Terry R, et al: Guided imagery for non-musculoskeletal pain: a systematic review of randomized clinical trials. *J Pain Symptom Manage* 44(1):95–104, 2012 22672919
- Quilici S, Chancellor J, Löthgren M, et al: Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol* 9:6, 2009 19208243
- Raine R, Haines A, Sensky T, et al: Systematic review of mental health interventions for patients with common somatic symptoms: can research evidence from secondary care be extrapolated to primary care? *BMJ* 325(7372):1082–1085, 2002 12424170
- Rauenzahn S, Del Fabbro E: Opioid management of pain: the impact of the prescription opioid abuse epidemic. *Curr Opin Support Palliat Care* 8(3):273–278, 2014 25004173
- Reichenbach S, Sterchi R, Scherer M, et al: Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 146(8):580–590, 2007 17438317
- Reiner K, Tibi L, Lipsitz JD: Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain Med* 14(2):230–242, 2013 23240921
- Reuben DB, Alvanzo AA, Ashikaga T, et al: National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. *Ann Intern Med* 162(4):295–300, 2015 25581341

- Robbins MS, Lipton RB: The epidemiology of primary headache disorders. *Semin Neurol* 30(2):107-119, 2010 20352581
- Roddy E, Zhang W, Doherty M: Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. *Ann Rheum Dis* 64(4):544-548, 2005 15769914
- Rooks DS, Gautam S, Romeling M, et al: Group exercise, education, and combination self-management in women with fibromyalgia: a randomized trial. *Arch Intern Med* 167(20):2192-2200, 2007 17998491
- Rowbotham MC, Reisner LA, Davies PS, Fields HL: Treatment response in antidepressant-naïve postherpetic neuralgia patients: double-blind, randomized trial. *J Pain* 6(11):741-746, 2005 16275598
- Rubinstein SM, van Middelkoop M, Kuijpers T, et al: A systematic review on the effectiveness of complementary and alternative medicine for chronic non-specific low-back pain. *Eur Spine J* 19(8):1213-1228, 2010 20229280
- Russell IJ, Kamin M, Bennett RM, et al: Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol* 6(5):250-257, 2000 19078481
- Salerno SM, Browning R, Jackson JL: The effect of antidepressant treatment on chronic back pain: a meta-analysis. *Arch Intern Med* 162(1):19-24, 2002 11784215
- Samson DJ, Grant MD, Ratko TA, et al: Treatment of primary and secondary osteoarthritis of the knee. *Evid Rep Technol Assess (Full Rep)* 157(157):1-157, 2007 18088162
- Sandoval JA, Furlan AD, Mailis-Gagnon A: Oral methadone for chronic noncancer pain: a systematic literature review of reasons for administration, prescription patterns, effectiveness, and side effects. *Clin J Pain* 21(6):503-512, 2005 16215336
- Sauro MD, Greenberg RP: Endogenous opiates and the placebo effect: a meta-analytic review. *J Psychosom Res* 58(2):115-120, 2005 15820838
- Savage SR, Joranson DE, Covington EC, et al: Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Manage* 26(1): 655-667, 2003 12850648
- Schappert SM; National Center for Health Statistics: National Ambulatory Medical Care Survey: 1989 summary. *Vital Health Stat* 13(110):1-80, 1992 1376543
- Schug SA: Clinical pharmacology of non-opioid and opioid analgesics, in *Pain 2005—An Updated Review: Refresher Course Syllabus*. Edited by Justins DM. Seattle, WA, IASP Press, 2005, pp 31-40
- Scott DJ, Stohler CS, Egnatuk CM, et al: Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 65(2):220-231, 2008 18250260
- Sharma M, Haider T: Yoga as an alternative and complementary treatment for patients with low back pain a systematic review. *J Evidence-Based Complementary & Alternative Medicine..* 18:23-28, 2013
- Shneker BF, McAuley JW: Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 39(12):2029-2037, 2005 16288079
- Silberstein SD, Holland S, Freitag F, et al; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society: Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 78(17):1337-1345, 2012 22529202
- Sim J, Adams N: Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia. *Clin J Pain* 18(5):324-336, 2002 12218504
- Skljarevski V, Liu P, Zhang S, et al: Efficacy and safety of duloxetine in patients with chronic low back pain who used versus did not use concomitant nonsteroidal anti-inflammatory drugs or acetaminophen: a post hoc pooled analysis of 2 randomized, placebo-controlled trials. *Pain Res Treat* 2012(Mar):296710, 2012 22550577
- Smith HS: Taxonomy of pain syndromes, in *The Neurological Basis of Pain*. Edited by Pappagallo M. New York, McGraw-Hill, 2005, pp 289-300

- Staiger TO, Gaster B, Sullivan MD, Deyo RA: Systematic review of antidepressants in the treatment of chronic low back pain. *Spine* 28(22):2540-2545, 2003 14624092
- Sternbach RA: Pain and "hassles" in the United States: findings of the Nuprin pain report. *Pain* 27(1):69-80, 1986 3785965
- Tan G, Craine MH, Bair MJ, et al: Efficacy of selected complementary and alternative medicine interventions for chronic pain. *J Rehabil Res Dev* 44(2):195-222, 2007 17551873
- Thaler KJ, Morgan LC, Van Noord M, et al: Comparative effectiveness of second-generation antidepressants for accompanying anxiety, insomnia, and pain in depressed patients: a systematic review. *Depress Anxiety* 29(6):495-505, 2012 22553134
- Thielke SM, Fan MY, Sullivan M, Unützer J: Pain limits the effectiveness of collaborative care for depression. *Am J Geriatr Psychiatry* 15(8):699-707, 2007 17670998
- Toward Optimized Practice: Guideline for primary care management of headache in adults. Edmonton (AB), Canada, Toward Optimized Practice, July 2012. Available at: [www.topalbertadoctors.org/cpgs/10065](http://www.topalbertadoctors.org/cpgs/10065). Accessed March 8, 2017.
- Towheed TE, Maxwell L, Judd MG, et al: Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* (1):CD004257, 2006 16437479
- Tremont-Lukats IW, Challapalli V, McNicol ED, et al: Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. *Anesth Analg* 101(6):1738-1749, 2005 16301253
- Underwood M, Ashby D, Cross P, et al; TOIB study team: Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. *BMJ* 336(7636): 138-142, 2008 18056743
- van Koulil S, Effting M, Kraaimaat FW, et al: Cognitive-behavioural therapies and exercise programmes for patients with fibromyalgia: state of the art and future directions. *Ann Rheum Dis* 66(5):571-581, 2007 16916856
- van Middelkoop M, Rubinstein SM, Kuijpers T, et al: A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J* 20(1):19-39, 2011 20640863
- VanderWeide LA, Smith SM, Trinkley KE: A systematic review of the efficacy of venlafaxine for the treatment of fibromyalgia. *J Clin Pharm Ther* 40(1):1-6, 2015 25294655
- Veehof MM, Oskam MJ, Schreurs KMG, Bohlmeijer ET: Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *Pain* 152(3):533-542, 2011 21251756
- Verhaak PF, Kerssens JJ, Dekker J, et al: Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain* 77(3):231-239, 1998 9808348
- Vlad SC, LaValley MP, McAlindon TE, Felson DT: Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis Rheum* 56(7):2267-2277, 2007 17599746
- Von Korff M, Moore JC: Stepped care for back pain: activating approaches for primary care. *Ann Intern Med* 134(9 Pt 2):911-917, 2001 11346328
- Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA: Conservative treatment of sciatica: a systematic review. *J Spinal Disord* 13(6):463-469, 2000 11132976
- Wandel S, Jüni P, Tendal B, et al: Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 341:c4675, 2010 20847017
- Warsi A, LaValley MP, Wang PS, et al: Arthritis self-management education programs: a meta-analysis of the effect on pain and disability. *Arthritis Rheum* 48(8):2207-2213, 2003 12905474
- Wasan AD, Correll DJ, Kissin I, et al: Iatrogenic addiction in patients treated for acute or subacute pain: a systematic review. *J Opioid Manag* 2(1):16-22, 2006 17319113
- Watkins PB, Kaplowitz N, Slaterry JT, et al: Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA* 296(1):87-93, 2006 16820551

- Watson CP, Vernich L, Chipman M, Reed K: Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology* 51(4):1166-1171, 1998 9781549
- Wegman A, van der Windt D, van Tulder M, et al: Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. *J Rheumatol* 6(11): 741-746, 2004 14760807
- Weimer MB, Chou R: Research gaps on methadone harms and comparative harms: findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence clinical practice guideline. *J Pain* 15(4):366-376, 2014 24685460
- Weinstein JN, Tosteson TD, Lurie JD, et al: Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. *JAMA* 296(20):2441-2450, 2006 17119140
- Weinstein JN, Tosteson TD, Lurie JD, et al; SPORT Investigators: Surgical versus nonsurgical therapy for lumbar spinal stenosis. *N Engl J Med* 358(8):794-810, 2008 18287602
- White A, Foster NE, Cummings M, Barlas P: Acupuncture treatment for chronic knee pain: a systematic review. *Rheumatology (Oxford)* 46(3):384-390, 2007 17215263
- White KP, Nielson WR, Harth M, et al: Does the label "fibromyalgia" alter health status, function, and health service utilization? A prospective, within-group comparison in a community cohort of adults with chronic widespread pain. *Arthritis Rheum* 47(3):260-265, 2002 12115155
- Wiffen PJ, McQuay HJ, Edwards JE, Moore RA: Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev* (3): CD005452, 2005a 16034978
- Wiffen PJ, McQuay HJ, Moore RA: Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev* (3):CD005451, 2005b 16034977
- Williams CM, Maher CG, Latimer J, et al: Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 384(9954):1586-1596, 2014 25064594
- Wolfe F, Clauw DJ, Fitzcharles MA, et al: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 62(5):600-610, 2010 20461783
- Wren AA, Wright MA, Carson JW, Keefe FJ: Yoga for persistent pain: new findings and directions for an ancient practice. *Pain* 152(3):477-480, 2011 21247696
- Wu D, Huang Y, Gu Y, Fan W: Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-controlled trials. *Int J Clin Pract* 67(6):585-594, 2013 23679910
- Zeng C, Li H, Yang T, et al: Electrical stimulation for pain relief in knee osteoarthritis: systematic review and network meta-analysis. *Osteoarthritis Cartilage* 23(2):189-202, 2015 25497083



## CHAPTER 55

# Treatment of Child and Adolescent Disorders

Karen Dineen Wagner, M.D., Ph.D.

Steven R. Pliszka, M.D.

This chapter focuses on the use of psychopharmacology for treating psychiatric disorders in children and adolescents. It is important for clinicians to be aware of the evidence base for the use of psychotropic medications in children and adolescents. In this chapter, data from the literature, with a focus on controlled studies, are presented. On the basis of these findings, clinical recommendations regarding pharmacotherapy for childhood psychiatric disorders are offered. The appendix and tables at the end of this chapter contain specific information about dosages, monitoring, and adverse effects of psychotropic medications in children.

---

# Psychotropic Medication for Children and Adolescents

---

## Evaluation

Prior to the initiation of psychotropic medication for children and adolescents, a comprehensive evaluation is necessary to ensure the accuracy of the diagnosis. A thorough history and careful attention to the clinical presentation are central components of the evaluation. The clinician should interview the child and parents separately so that both may have the opportunity to freely express their concerns. Extended-family members, school personnel, and school records are other potential sources of information.

Clinicians must be skilled at differential diagnosis of childhood disorders, given that there is a significant overlap of symptoms among these disorders. Knowledge of commonly occurring comorbid disorders is also necessary. Medical conditions should be considered within the differential diagnosis and adequately assessed.

Disorder-specific rating scales at baseline and during the course of treatment may be useful in assisting with the measurement of clinical outcome.

## Clinical Issues Affecting Response to Pharmacotherapy

Whenever a child fails to respond to initial pharmacotherapy, several clinical issues should be

addressed before initiating alternative or adjunctive medication.

## **Diagnostic Accuracy**

The diagnosis should be reassessed. Often there is symptomatic overlap among disorders that may lead to misdiagnosis. For example, symptoms of excessive energy and distractibility are common features of both attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder.

## **Comorbid Disorders**

Unrecognized comorbid disorders may adversely affect treatment outcome. As an example, comorbid ADHD may lower response rates in the treatment of bipolar disorder ([Pavuluri et al. 2006](#)).

## **Psychosocial Factors**

Child abuse, domestic violence, family conflict, parental psychopathology, and bullying by peers may lead to symptoms that mimic or exacerbate a preexisting psychiatric disorder.

## **Medication Compliance**

Some children and adolescents are reluctant to take medication because of such reasons as denial of illness, perceived stigma, and side effects. For increased medication compliance, the child or adolescent, as well as the parents, must understand the youth's disorder, course of illness, and goals of treatment. It is important for parents to participate in monitoring their child's medication compliance.

## Nonpharmacological Treatment

Psychotherapy may be beneficial, either alone or in conjunction with medication. Specific psychotherapies have been found to be effective in the treatment of some childhood disorders. For example, cognitive-behavioral therapy (CBT) and interpersonal therapy have demonstrated efficacy in the treatment of adolescents with depression ([Zhou et al. 2015](#)). Similarly, CBT is commonly used for the treatment of childhood anxiety disorders ([Roblek and Piacentini 2005](#)). Behavior therapy has led to improvement in symptoms of ADHD for children ([Pelham et al. 1998](#)). Adjunctive psychoeducation with medication treatment has shown benefit in the treatment of children with bipolar disorder ([Fristad et al. 2003](#)). Social skills training can be a useful component of treatment in autism spectrum disorder ([Krasny et al. 2003](#)).

## Informed Consent

Informed consent is necessary prior to prescribing psychotropic medication to any patient, but it is particularly important in pediatric psychopharmacology because few medications have been approved by the U.S. Food and Drug Administration (FDA) for young populations. There are five recommended components of informed consent for prescribing psychotropic medications to children and adolescents ([Popper 1987](#)). The child's parent(s) and the child or adolescent should be provided with the following information:

1. The purpose (benefits) of the treatment
2. A description of the treatment process

3. An explanation of the risks of the treatment, including risks that would ordinarily be described by the psychiatrist and risks that would be relevant to making the decision
4. A statement of alternative treatments, including nontreatment
5. A statement that there may be unknown risks associated with these medications (this is particularly essential for children due to the paucity of information on the potential long-term effects of psychotropic medications)

## Evidence Base

It is important for clinicians to be aware of the evidence base for medication treatment of each childhood psychiatric disorder. Clinical treatment guidelines generally rely on the strength of the available data in determining first-line agents. In most cases, clinicians should select a medication within the group of first-line agents when initiating medication treatment with a child. Additional factors that will dictate medication choice are prior medication history, medical history, side-effect profile of the drug, and adolescent and parent preferences.

---

## Major Depressive Disorder

---

The lifetime prevalence of major depression or dysthymia in adolescents is 11.7% ([Merikangas et al. 2010](#)). DSM-5 ([American Psychiatric Association 2013](#)) criteria are used to establish a diagnosis of major depression in children and adolescents. The mean length of an episode of major

depression in youth ranges from 8 to 13 months, and relapse rates range from 30% to 70% ([Birmaher et al. 2002](#)). There is increasing evidence for the continuity of depression from youth into adulthood ([Melvin et al. 2013](#)).

## Selective Serotonin Reuptake Inhibitors

For the acute and maintenance treatment of major depression in children and adolescents, the FDA has approved two selective serotonin reuptake inhibitor (SSRI) medications: fluoxetine for patients ages 8 years and older and escitalopram for patients ages 12 years and older. Other SSRIs that have been studied in controlled trials for children and adolescents with major depression include citalopram, sertraline, and paroxetine.

### Fluoxetine

There have been three positive controlled medication trials of fluoxetine in the treatment of major depression in children and adolescents. In the first study, 96 child and adolescent outpatients (ages 8–17 years) with major depression were randomly assigned to fluoxetine 20 mg/day or placebo for an 8-week trial ([Emslie et al. 1997](#)). The fluoxetine group, with 27 youths (56%) much or very much improved, showed statistically significantly greater improvement in Clinical Global Impression (CGI) Scale scores than the placebo group, with 16 youths (33%) much or very much improved. Medication side effects leading to discontinuation in the study were manic symptoms in three patients and severe rash in one patient.

In a double-blind, placebo-controlled multicenter study of fluoxetine, 219 child and adolescent outpatients (ages 8–17 years) with major depression were randomly assigned to fluoxetine 20 mg/day or placebo for an 8-week trial ([Emslie et al. 2002](#)). Improvement in depression was statistically significantly greater for the fluoxetine group, as assessed by means of the Children's Depression Rating Scale—Revised (CDRS-R), than for the placebo group. Fifty-two percent of patients treated with fluoxetine were rated as much or very much improved, compared with 37% of patients treated with placebo. Headache was the only side effect that was reported more frequently in the group treated with fluoxetine than in the group treated with placebo.

In a multicenter trial of 439 adolescent outpatients with a diagnosis of major depression ([March et al. 2004](#)), patients were randomly assigned to 12 weeks of fluoxetine (10–40 mg/day), fluoxetine (10–40 mg/day) with CBT, CBT alone, or placebo. Compared with placebo, the combination of fluoxetine with CBT was significantly superior, according to changes in CDRS-R scores. Combination treatment with fluoxetine and CBT was significantly superior to treatment with fluoxetine alone or CBT alone. Fluoxetine monotherapy was superior to CBT. Response rates (defined as CGI ratings of much or very much improved), were 71% for fluoxetine–CBT combination therapy, 61% for fluoxetine, 43% for CBT, and 35% for placebo.

## **Escitalopram**

There have been two controlled trials of escitalopram in the treatment of youth with depression, one positive and one negative. The efficacy of escitalopram in adolescents was demonstrated in a double-blind, placebo-controlled

multicenter trial of 157 adolescents with major depression ([Emslie et al. 2009](#)). Patients were randomly assigned to escitalopram (dosage range=10-20 mg/day) or placebo for an 8-week trial. The group treated with escitalopram showed statistically significantly greater improvement in depression (CDRS-R scores) than the placebo group. Sixty-four percent of escitalopram-treated patients were much or very much improved, compared with 53% of placebo-treated patients. In a study that included 264 children and adolescents with major depression ([Wagner et al. 2006a](#)), there was no significant improvement on CDRS-R scores at endpoint between escitalopram and placebo. The most common adverse events with escitalopram were headache, abdominal pain, nausea, insomnia, and menstrual cramps.

## Citalopram

There have been two controlled trials of citalopram in the treatment of depression in youth, one with positive and one with negative results. The efficacy of citalopram was demonstrated in a double-blind, placebo-controlled multicenter trial of 174 outpatient children and adolescents (ages 7-17 years) with major depression ([Wagner et al. 2004b](#)). Patients were randomly assigned to receive citalopram (dosage range=20-40 mg/day; mean daily dosage=23 mg for children, 24 mg for adolescents) or placebo for an 8-week trial. Compared with the placebo group, the citalopram group showed statistically significantly greater improvement in depression (CDRS-R scores). The most frequent adverse events were headache, nausea, rhinitis, abdominal pain, and influenza-like symptoms. A European double-blind, placebo-controlled multicenter study ([von Knorring et al. 2006](#)) of citalopram in 224 adolescents with major depression failed to show



superiority of citalopram to placebo on the primary efficacy measures, the Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present Episode Version (Kiddie-SADS-P) and the Montgomery-Åsberg Depression Rating Scale (MADRS). The most commonly reported adverse events were headache, nausea, and vomiting.

## Sertraline

The efficacy of sertraline was assessed in two identical double-blind, placebo-controlled multicenter studies of 376 outpatient children and adolescents with major depression ([Wagner et al. 2003a](#)). Patients were randomly assigned to sertraline (dosage range=50–200 mg/day; mean daily dosage=131 mg) or placebo for a 10-week trial. Compared with the placebo group, the group receiving sertraline showed a statistically significantly greater improvement in depression (CDRS-R scores). Response rates (decrease  $\geq 40\%$  in baseline CDRS-R scores) were 69% in the group treated with sertraline and 59% in the group treated with placebo. The most common side effects in the group treated with sertraline were headache, nausea, insomnia, upper respiratory tract infection, abdominal pain, and diarrhea.

Sertraline, CBT, and combined CBT plus sertraline were compared in the treatment of 73 adolescents with depressive disorders ([Melvin et al. 2006](#)). All treatments resulted in statistically significant improvement on all outcome measures; there were no significant advantages of combined treatment.

In the Adolescent Depression and Psychotherapy Trial (ADAPT; [Goodyer et al. 2008](#)), 208 adolescents with major depression were randomly assigned to receive an SSRI alone or an SSRI plus CBT for 12 weeks. No significant

differences were found between the groups; 44% of the SSRI-alone group and 42% of the SSRI-plus-CBT group were much or very much improved on the CGI Improvement subscale (CGI-I).

## Paroxetine

There have been three double-blind, placebo-controlled trials of paroxetine for treatment of depression in children and adolescents, all of which had negative findings on the primary outcome measure. In a study of 275 adolescent outpatients (ages 12-18 years) with major depression, patients were randomly assigned to paroxetine (dosage range=20-40 mg/day; mean daily dosage=28 mg), imipramine (dosage range=200-300 mg/day; mean daily dosage=205 mg), or placebo for an 8-week trial ([Keller et al. 2001](#)). There was no statistically significant difference among the treatment groups on the primary efficacy measure of reduction in total score on the Hamilton Rating Scale for Depression (Ham-D). The most common side effects reported for paroxetine were headache, nausea, dizziness, dry mouth, and somnolence.

Two hundred six children and adolescents (ages 7-17 years) with major depression were included in an 8-week double-blind, placebo-controlled, randomized multicenter study of paroxetine treatment ([Emslie et al. 2006](#)). There was no statistically significant difference between patients treated with paroxetine and patients given placebo on change from baseline in CDRS-R total score at endpoint. Adverse events reported for paroxetine with an incidence of >5% and at least twice that of placebo were dizziness, cough, dyspepsia, and vomiting.

A 12-week international placebo-controlled multicenter trial of paroxetine in 286 adolescents with major depression

failed to show superiority for paroxetine compared with placebo on change from baseline in MADRS or Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Lifetime Version (Kiddie-SADS-L) total score ([Berard et al. 2006](#)).

## Other Antidepressants

### Venlafaxine

Two double-blind, placebo-controlled multicenter studies have evaluated the efficacy of venlafaxine extended release (XR) in the treatment of major depression in 165 and 169 child and adolescent outpatients, respectively ([Emslie et al. 2007](#)). Patients were randomly assigned to venlafaxine XR (37.5–225 mg/day; flexible dosage based on body weight) for 8-week trials. Both studies were negative on the primary outcome measure of change from baseline to endpoint in the CDRS-R scores. The most common adverse events were anorexia and abdominal pain ([Emslie et al. 2007](#)).

### Nefazodone

There have been two double-blind, placebo-controlled multicenter trials of nefazodone in the treatment of major depression in youth ([Rynn et al. 2002](#); [U.S. Food and Drug Administration 2004b](#)). These studies failed to find statistically significant improvement in baseline-to-endpoint CDRS-R scores between the nefazodone-treated group and the placebo-treated group. The most common adverse events with nefazodone were headache, abdominal pain, nausea, vomiting, somnolence, and dizziness.

## Bupropion

There are no controlled trials of bupropion for the treatment of pediatric depression.

In an 8-week study of bupropion sustained release (dosage range=100-400 mg/day; mean daily dosage=362 mg) for treating 11 adolescents with major depression, 8 adolescents (79%) showed a 50% reduction in depression scores from baseline ([Glod et al. 2000](#)). Bupropion sustained release was assessed in an 8-week open study for the treatment of comorbid depression and ADHD in 24 adolescents ([Daviss et al. 2001](#)). Global improvement was reported in 14 subjects (58%) for both depression and ADHD and in 7 subjects (29%) for depression only. Common side effects were headache, nausea, rash, and irritability.

## Mirtazapine

There have been two double-blind, placebo-controlled multicenter trials of mirtazapine in the treatment of child and adolescent outpatients with major depression. In these studies, mirtazapine was not superior to placebo on the primary efficacy measure of change from baseline to endpoint in CDRS-R scores ([U.S. Food and Drug Administration 2004b](#)).

## Duloxetine

There have been two failed 10-week trials of duloxetine in the treatment of children and adolescents with major depression ([Atkinson et al. 2014](#); [Emslie et al. 2014](#)). Duloxetine and fluoxetine were not superior to placebo on the primary efficacy measure of change from baseline to endpoint in CDRS-R scores. The most common adverse

events were nausea, vomiting, nasopharyngitis, upper abdominal pain, headache, and somnolence.

### **Desvenlafaxine Succinate Sustained Release**

The efficacy of desvenlafaxine sustained release (SR) for the treatment of major depression in 340 children and adolescents (ages 7–17 years) was assessed in a double-blind, placebo-controlled trial ([Pfizer 2015](#)). The study had three treatment arms: desvenlafaxine SR, fluoxetine, and placebo. This was a failed study; neither desvenlafaxine SR nor fluoxetine was significantly superior to placebo.

### **Selegiline Transdermal System**

In a placebo-controlled trial of 308 adolescents with major depression, selegiline transdermal system was not superior to placebo on the primary efficacy measure of change from baseline to endpoint in CDRS-R scores ([DelBello et al. 2014](#)). The most common adverse events for selegiline were application site reactions, headaches, and nausea.

## **Suicidality and Black Box Warning**

In a combined analysis of 24 short-term placebo-controlled trials of antidepressant medications in child and adolescent major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders, the rates of suicidality (suicidal thinking and behavior) were 4% in patients given medication and 2% in patients given placebo. There were no suicides in any of the clinical trials. The FDA directed manufacturers to add a black box warning to the health professional label of antidepressant medications to describe the increased risk of suicidal thoughts and

behavior in children and adolescents being treated with antidepressant medications and to emphasize the need for close monitoring of patients taking the medications ([U.S. Food and Drug Administration 2004a](#)). Parents and patients should be advised of the black box warning for antidepressant medication.

In a subsequent meta-analysis of 27 trials of antidepressants in pediatric major depression, the rates of suicidal ideation and attempts were 3% in the youth treated with antidepressants and 2% in the youth who received placebo ([Bridge et al. 2007](#)). The investigators reported that the number needed to treat was 10, whereas the number needed to harm was 112, and therefore the benefits of antidepressants outweigh the potential risk from suicidal ideation or attempt.

A number of studies, in both the United States and Europe, have failed to demonstrate an association between antidepressant use and youth suicide ([Gibbons et al. 2006](#); [Markowitz and Cuellar 2007](#); [Simon et al. 2006](#); [Søndergård et al. 2006](#)). It is noteworthy that the suicide rate in youth increased following the addition of the black box warning on antidepressants ([Hamilton et al. 2007](#)). The FDA advisory has been associated with significant decreases in the rates of diagnosis and treatment of pediatric depression ([Libby et al. 2007](#)). The risk of deliberate self-harm was found to be higher in youth whose treatment was initiated with high-dosage SSRIs than in those whose treatment began with modal-dosage SSRIs ([Miller et al. 2014](#)).

## Treatment-Resistant Depression

In the National Institute of Mental Health (NIMH)-funded multisite Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial ([Brent et al. 2008](#)), 334 adolescents with SSRI-resistant depression were randomly assigned to one of four treatments for 12 weeks: 1) switch to an alternate SSRI (paroxetine, citalopram, or fluoxetine), 2) switch to an alternate SSRI plus CBT, 3) switch to venlafaxine, or 4) switch to venlafaxine plus CBT. CBT plus a medication switch (to venlafaxine or to an alternate SSRI) produced the highest rate of response (54.8%). Response rates (CGI-I score  $\leq 2$  and CDRS-R  $\geq 50\%$  reduction) were similar for switching to an alternate SSRI and switching to venlafaxine (47% and 48.2%, respectively). Skin problems and increases in diastolic blood pressure and pulse were more frequently experienced during venlafaxine treatment than during SSRI treatment.

## Clinical Recommendations for Major Depressive Disorder

An evidence-based consensus medication algorithm for the treatment of childhood major depression is available (Texas Children's Medication Algorithm Project [TMAP]; [Hughes et al. 2007](#)). Based on research evidence and panel discussion, four stages of medication treatment are identified:

- Stage 1: SSRI
- Stage 2: Alternate SSRI
- Stage 2A (if partial response to SSRI): SSRI+lithium, bupropion, or mirtazapine
- Stage 3: Different class of antidepressant medication (venlafaxine, bupropion, mirtazapine, duloxetine)

- Stage 4: Reassessment, treatment guidance

An additional recommendation is that antidepressants should be continued for 6–12 months after symptom remission. At the time of discontinuation of an antidepressant, the dosage should be tapered slowly (i.e., no more than 25% per week). The typical tapering and discontinuation period is 2–3 months.

---

## Bipolar Disorder

---

The prevalence of bipolar disorder in a community sample of adolescents was found to be 1% ([Merikangas et al. 2010](#)). Although DSM-5 criteria are used to diagnose bipolar disorder in youth, the clinical features in children may differ from those in adolescents and adults. Children with bipolar disorder frequently exhibit mixed mania and rapid cycling ([B. Geller et al. 2000](#)). One-year recovery rates of 87% and relapse rates of 64% have been reported in children with bipolar disorder ([B. Geller et al. 2004](#)).

Six medications have FDA approval for the acute treatment of bipolar I disorder, mixed or manic episode, in youth: lithium ( $\geq 12$  years old), aripiprazole ( $\geq 10$  years old), asenapine ( $\geq 10$  years old), olanzapine ( $\geq 13$  years old), risperidone ( $\geq 10$  years old), and quetiapine ( $\geq 10$  years old). Ziprasidone has been studied for the treatment of bipolar disorder in youth, but it does not have FDA approval for that indication.

## Lithium



The efficacy of lithium for the treatment of bipolar I disorder, manic or mixed episode, was assessed in an 8-week double-blind, placebo-controlled trial involving 81 youths (ages 7–17 years) ([Findling et al. 2015b](#)). The mean lithium serum level at endpoint was 0.98 mEq/L. Lithium was superior to placebo on the primary outcome measure of change in Young Mania Rating Scale (YMRS) score from baseline to endpoint. On CGI-I scores, 47% of lithium-treated and 21% of placebo-treated patients were much or very much improved. The most common adverse events with lithium were vomiting, nausea, and headache. There was a statistically significant increase in thyrotropin concentration with lithium.

In an NIMH-funded study, 153 children and adolescents with bipolar I disorder, mixed or manic episode, were randomly assigned to treatment with lithium, divalproex, or placebo in an 8-week trial ([Kowatch et al. 2007](#)). Target lithium serum levels were 0.8–1.2 mEq/L. Lithium was not significantly superior to placebo.

There is one small double-blind, placebo-controlled study of lithium treatment for adolescent bipolar disorder and DSM-III-R ([American Psychiatric Association 1984](#))-defined substance dependence ([B. Geller et al. 1998](#)). Twenty-five adolescent outpatients were randomly assigned to either lithium (mean serum level=0.97 mEq/L) or placebo for a 6-week trial. There was significantly greater improvement in global functioning with lithium than with placebo. Side effects in the group treated with lithium were polyuria, thirst, nausea, vomiting, and dizziness.

## Atypical Antipsychotics

## Aripiprazole

The efficacy of aripiprazole was assessed in a 4-week double-blind, placebo-controlled trial that included 296 youths with bipolar I disorder, mixed or manic episode ([Findling et al. 2009](#)). Both low-dosage aripiprazole (10 mg/day) and high-dosage aripiprazole (30 mg/day) were significantly superior to placebo in reduction of YMRS scores. The response rate ( $\geq 50\%$  reduction in YMRS score) was 44.8% for low-dosage aripiprazole, 63.6% for high-dosage aripiprazole, and 26.1% for placebo. The most common adverse events with aripiprazole were somnolence, extrapyramidal side effects (EPS), and tremor, which were more frequent in the high-dosage aripiprazole group.

## Asenapine

The efficacy of asenapine was evaluated in a 3-week, double-blind, placebo-controlled trial of 403 youths (ages 10–17 years) with bipolar I disorder, mixed or manic episode ([Actavis 2017](#)). Dosages ranged from 2.5 to 10 mg twice daily. Asenapine was significantly superior to placebo on outcome measures of change in YMRS and CGI Bipolar (CGI-BP) Severity of Illness scores from baseline to endpoint. The most common adverse events were somnolence, dizziness, oral hypoesthesia, headache, fatigue, and increased appetite.

## Olanzapine

There is one reported double-blind, placebo-controlled multicenter study of olanzapine (2.5–20 mg/day) in the treatment of adolescent outpatients with bipolar I disorder, mixed or manic episode ([Tohen et al. 2007](#)). Adolescents

were randomly assigned to receive olanzapine ( $n=107$ ) or placebo ( $n=54$ ) for 3 weeks. Response rates (defined as  $\geq 50\%$  decrease in YMRS score) were significantly greater for the olanzapine group (44.8%) than for the placebo group (18.5%). Remission rates (defined as YMRS score  $<12$ ) were significantly greater for the olanzapine group (35.2%) than for the placebo group (11.1%). Adverse effects in the olanzapine group were hyperprolactinemia, weight gain (mean=3.7 kg), somnolence, and sedation.

## Risperidone

In a 3-week double-blind, placebo-controlled trial, the efficacy of risperidone was assessed in 169 children and adolescents with bipolar I disorder, manic or mixed episode ([Haas et al. 2009](#)). Both low-dosage risperidone (0.5–2.5 mg/day) and high-dosage risperidone (3–6 mg/day) were significantly superior to placebo in reduction of YMRS scores. The response rate ( $\geq 50\%$  reduction in baseline YMRS score) was 59% for low-dosage risperidone and 63% for high-dosage risperidone, compared with a placebo response rate of 26%. The most common adverse events with risperidone were somnolence, headache, and fatigue. EPS were more frequent in the high-dosage risperidone group than in the low-dosage group.

## Quetiapine

In a 3-week double-blind, placebo-controlled trial, the efficacy of quetiapine was assessed in 277 youths with bipolar I disorder, manic or mixed episode ([DelBello et al. 2007](#)). Both low-dosage quetiapine (400 mg/day) and high-dosage quetiapine (600 mg/day) were significantly superior to placebo in reduction of YMRS scores. The response rate

( $\geq 50\%$  reduction in baseline YMRS score) was 64% for low-dosage quetiapine, 58% for high-dosage quetiapine, and 37% for placebo. The most common adverse events with quetiapine were somnolence, sedation, dizziness, and headache.

## **Ziprasidone**

The efficacy of ziprasidone was assessed in a 4-week double-blind, placebo-controlled trial that included 150 youths with bipolar I disorder, manic or mixed episode ([DelBello et al. 2008](#)). Ziprasidone dosages ranged from 80 to 160 mg/day. Ziprasidone was significantly superior to placebo in reduction of YMRS scores. The response rate ( $\geq 50\%$  reduction in YMRS score) was 62% for ziprasidone and 35% for placebo. The most common side effects with ziprasidone were sedation, somnolence, nausea, fatigue, and dizziness.

# **Anticonvulsants**

## **Divalproex**

A 4-week double-blind, placebo-controlled multicenter trial of 150 youths (ages 10–17 years) with bipolar I disorder, mixed or manic episode, did not show a significant difference in YMRS scores from baseline to endpoint for those patients given divalproex extended release (ER) and those given placebo ([Wagner et al. 2009](#)). The mean modal dose of divalproex ER was 1,286 mg. There were no statistically significant differences in adverse-event incidents between the divalproex ER and placebo groups.

Gastrointestinal symptoms were more commonly reported in divalproex ER than in placebo groups.

## **Carbamazepine**

In an open-label study of carbamazepine ER for 137 youths (ages 10–17 years) with bipolar I disorder, mixed or manic episode, there was a statistically significant reduction in scores on the YMRS from baseline to endpoint ([Findling and Ginsberg 2014](#)). At endpoint, the most prevalent dosage of carbamazepine ER was 1,200 mg/day. The most common adverse events were rash, decreased white blood cell count, nausea, and vomiting.

## **Oxcarbazepine**

The only double-blind, placebo-controlled multicenter trial of oxcarbazepine for the treatment of children and adolescents with bipolar I disorder, current episode mixed or manic, failed to show superiority of oxcarbazepine over placebo. The researchers randomly assigned 116 youths (ages 7–18 years) to receive oxcarbazepine (mean dosage=1,515 mg/day) or placebo for a 7-week trial ([Wagner et al. 2006b](#)). There was no significant difference in YMRS scores at endpoint between the oxcarbazepine and placebo groups. The most common side effects in the oxcarbazepine-treated patients were dizziness, nausea, somnolence, diplopia, fatigue, and rash.

## **Topiramate**

A double-blind, randomized, placebo-controlled multicenter study assessing the efficacy of topiramate treatment in children and adolescents with acute mania was designed as a 200-patient study but was terminated after randomization

of 56 patients (ages 6–17 years) when adult mania trials failed to show efficacy ([DelBello et al. 2005](#)). Dosages were titrated to 400 mg/day (mean dosage=278 mg/day). Over a 4-week period, no significant difference was found between the topiramate and placebo groups. The most common adverse events in the topiramate group included decreased appetite, nausea, diarrhea, paresthesias, and somnolence.

## Lamotrigine

In a 12-week open-label trial, the efficacy of lamotrigine was assessed in 30 children and adolescents with bipolar spectrum disorders ([Biederman et al. 2010](#)). The mean lamotrigine dosage at endpoint was 160.7 mg/day. Significant improvement in mean YMRS scores was reported; however, only about half the participants completed the trial, and seven participants discontinued lamotrigine because of rash.

## Comparator Studies

The Treatment of Early Age Mania (TEAM) study compared the effectiveness of risperidone, lithium, and divalproex in the treatment of 279 youths (ages 6–15 years) with bipolar I disorder, manic or mixed episode ([B. Geller et al. 2012](#)). Response was defined as a CGI-BP-Improvement Mania score of 2 or lower. The mean lithium level was 1.09 mEq/L, the mean divalproex level was 113.6 µg/mL, and the mean risperidone dosage was 2.57 mg/day. The risperidone response rate (68.5%) was significantly higher than response rates for lithium (35.6%) and divalproex (24%). There was no significant difference between lithium and divalproex response rates. Increased weight gain, body

mass index (BMI), and prolactin levels occurred significantly more frequently with risperidone than with lithium or divalproex.

Similarly, a comparator analysis of the efficacy of antipsychotics and mood stabilizers for the treatment of pediatric bipolar disorder showed significantly greater improvement in YMRS scores for patients given antipsychotics than for those given mood stabilizers ([Correll et al. 2010](#)). Effect sizes were 0.65 for antipsychotics and 0.24 for mood stabilizers.

The comparative efficacy of lithium, divalproex, and carbamazepine was assessed in a 6-week randomized open-label trial involving 42 children and adolescents with bipolar disorder ([Kowatch et al. 2000b](#)). There were no significant differences in response rates ( $\geq 50\%$  reduction in YMRS score) among the groups given lithium (38%), divalproex (53%), and carbamazepine (38%).

The comparative efficacy of risperidone and divalproex was assessed in an 8-week double-blind, randomized trial in 66 children and adolescents with bipolar disorder ([Pavuluri et al. 2010](#)). Significantly higher response rates ( $\geq 50\%$  reduction in YMRS) were found for risperidone (78.1%) than for divalproex (45.5%), and improvement was more rapid in risperidone-treated patients than in divalproex-treated patients.

The comparative efficacy of quetiapine and divalproex was assessed in a 4-week double-blind, placebo-controlled trial involving 50 adolescents with bipolar I disorder, manic or mixed episode ([DelBello et al. 2006](#)). No significant group differences were found in YMRS scores during the trial.

In an 8-week open-label trial, the efficacies of olanzapine and risperidone were compared in preschool-age children

with bipolar disorder ([Biederman et al. 2005](#)). There were no significant differences in response rates between risperidone (69%) and olanzapine (53%).

In a 6-week placebo-controlled trial of valproic acid versus risperidone for children (ages 3–7 years) with bipolar disorder, manic, mixed or hypomanic episode, risperidone was superior to placebo on reduction in YMRS scores from baseline to endpoint. There was no significant difference found between valproic acid and placebo ([Kowatch et al. 2015](#)).

## Combination Treatment

Some children with bipolar disorder may not respond to initial monotherapy treatment or may need combination treatment over the course of the illness. For example, in a study by [Kowatch et al. \(2000a\)](#), following acute 6-week treatment with one mood stabilizer, 20 of 35 youths (58%) required additional psychotropic medication over the next 16 weeks. The response rate to combination treatment with two mood stabilizers was high (80%) for those youths who did not respond to monotherapy.

The FDA has approved the use of quetiapine or aripiprazole as an adjunct to lithium or valproate treatment in children ages 10 years and older with bipolar I disorder, mixed or manic episode.

The effectiveness of combination treatment with lithium and divalproex was assessed in an open trial ([Findling et al. 2003](#)). Ninety youths (ages 5–17 years) with bipolar I or II disorder were treated for up to 20 weeks with divalproex (mean blood level=79.8 µg/mL) and lithium (mean blood level=0.9 mmol/L). The clinical remission rate (defined as



contiguous weekly ratings of YMRS scores  $\leq 12.5$ , CDRS-R scores  $\leq 40$ , Children's Global Assessment Scale [CGAS] scores  $\geq 51$ , clinical stability, and no mood cycling) was 42%.

The efficacy of risperidone in combination with lithium or divalproex was assessed in a 6-month open-label trial ([Pavuluri et al. 2004](#)). Thirty-seven youths (ages 5–18 years) with bipolar I disorder, manic or mixed episode, received either risperidone (mean dosage=0.75 mg/day) plus divalproex (mean serum level=106  $\mu\text{g/mL}$ ) or risperidone (mean dosage=0.70 mg/day) plus lithium (mean serum level=0.9 mEq/L). Response rates ( $\geq 50\%$  reduction in baseline YMRS scores) were similar for both combinations: 80% for divalproex plus risperidone, and 82.4% for lithium plus risperidone. There were no significant differences between the groups in safety and tolerability.

Risperidone augmentation for lithium nonresponders was assessed in a 1-year open-label study ([Pavuluri et al. 2006](#)). Twenty-one of 38 youths (ages 4–17 years) who failed to respond to lithium monotherapy or relapsed after initial response were given risperidone (mean dosage=0.99 mg/day) for 11 months. Response rates in the lithium plus risperidone group were 85.7%.

In a double-blind, placebo-controlled study of quetiapine, 30 adolescents with bipolar disorder received divalproex (20 mg/kg) and were randomly assigned to adjunctive quetiapine (mean daily dosage=432 mg) or placebo for 6 weeks ([DelBello et al. 2002](#)). Response rates ( $\geq 50\%$  reduction in baseline YMRS score) were significantly higher in the group receiving divalproex and quetiapine (87%) than in the group receiving divalproex and placebo (53%).

## Maintenance Treatment

Sixty youths who had responded to a combination of lithium and divalproex in a 20-week trial were randomly assigned in a double-blind trial to either lithium or divalproex for 18 months ([Findling et al. 2005](#)). There was no significant difference in the time to relapse between the groups (median days: divalproex 112, lithium 114).

## Clinical Recommendations for Bipolar Disorder

Treatment guidelines were developed by expert consensus and review of the available treatment literature for children and adolescents (ages 6–17 years) with bipolar I disorder, manic or mixed episode ([Kowatch et al. 2005](#)). Six stages were identified:

- Stage 1: Monotherapy with mood stabilizer or atypical antipsychotic
- Stage 2: Switch monotherapy agent (drug class not tried in stage 1)
- Stage 3: Switch monotherapy agent (drug class not tried in stage 1 or 2) OR combination treatment (2 agents)
- Stage 4: Combination treatment (2 agents) OR combination treatment (3 agents)
- Stage 5: Alternative monotherapy (drugs not tried in stages 1, 2, 3)
- Stage 6: Electroconvulsive therapy (adolescents) or clozapine

If a child fails to respond to treatment in one stage, the clinician should move to the next stage of treatment. For treatment of bipolar I disorder, manic or mixed episode

with psychosis, the recommendation for initial treatment is a mood stabilizer plus an atypical antipsychotic. A minimum of 4–6 weeks at therapeutic blood levels and/or adequate dosages for each medication is recommended. Following sustained remission of at least 12–24 months, medication taper should be considered.

---

## Anxiety Disorders

---

DSM-5 anxiety disorders include generalized anxiety disorder, social anxiety disorder, panic disorder, selective mutism, agoraphobia, specific phobia, and separation anxiety disorder. Obsessive-compulsive disorder and posttraumatic stress disorder are now in separate DSM-5 categories (Obsessive-Compulsive and Related Disorders and Trauma- and Stressor-Related Disorders, respectively).

### Generalized Anxiety Disorder

The prevalence of generalized anxiety disorder (GAD) in children and adolescents is estimated to range from 2.9% to 7.3% ([Anderson et al. 1987](#); [Kashani and Orvaschel 1988](#); [Merikangas et al. 2010](#)). Children with GAD have excessive anxiety and worry about several events or activities (e.g., school performance), have difficulty controlling the worry, and have at least one associated symptom, such as restlessness, fatigue, concentration difficulties, irritability, muscle tension, and sleep disturbance ([American Psychiatric Association 2013](#)). The course of GAD in youth tends to be chronic ([Keller et al. 1992](#)).

## Duloxetine

Duloxetine has been approved by the FDA for the treatment of GAD in youths ages 7–17 years.

The efficacy of duloxetine was assessed in a 10-week double-blind, placebo-controlled trial for 272 youths (ages 7–17 years) with GAD ([Strawn et al. 2015](#)). Duloxetine was flexibly dosed from 30 to 120 mg/day. The primary efficacy measure was the Pediatric Anxiety Rating Scale (PARS). Duloxetine was significantly superior to placebo on improvement in PARS scores from baseline to endpoint. Response (defined as 50% improvement on PARS severity for GAD) and remission (defined as a PARS severity for GAD  $\leq 8$ ) were significantly greater for the duloxetine group (59% and 50%, respectively) than the placebo group (42% and 34%, respectively). Adverse events reported with significantly greater frequency for the duloxetine group than for the placebo group were nausea, vomiting, decreased appetite, oropharyngeal pain, dizziness, cough, and palpitations.

## Venlafaxine

The efficacy of venlafaxine XR in children and adolescents with GAD ( $N=320$ ) was evaluated in two double-blind, placebo-controlled trials ([Rynn et al. 2007](#)). Venlafaxine was given at dosages up to 225 mg/day. In one study, venlafaxine XR was superior to placebo on primary and secondary measures; however, in the other study, the results were negative.

## Sertraline

Twenty-two children and adolescents (ages 5–17 years) with GAD were randomly assigned to sertraline or placebo

in a 9-week double-blind trial ([Rynn et al. 2001](#)). The maximum dosage of sertraline was 50 mg/day. Significant differences in favor of sertraline over placebo were observed on the Hamilton Anxiety Scale (Ham-A) scores and on CGI Severity of Illness (CGI-S) and CGI-I ratings. Side effects found to be more common (but not statistically significantly so) with sertraline than with placebo were dry mouth, drowsiness, leg spasm, and restlessness.

## **Buspirone**

The efficacy of buspirone was evaluated for 559 youths (ages 6–17 years) with GAD who participated in a 6-week randomized placebo-controlled trial ([Bristol-Myers Squibb 2010](#)). Buspirone dosages ranged from 15 to 60 mg/day. There was no statistically significant difference in outcome between buspirone and placebo.

# **Social Anxiety Disorder (Social Phobia)**

The prevalence of social anxiety disorder (social phobia) in adolescents is reported to be 9.1% ([Merikangas et al. 2010](#)). The DSM-5 diagnostic criteria for social anxiety disorder are the same for children and adolescents as for adults. Social anxiety disorder in youth is a chronic condition, and it increases the risk of depression ([Stein et al. 2001](#)).

## **Selective Serotonin Reuptake Inhibitors**

**Paroxetine.** The efficacy and safety of paroxetine were evaluated in a 16-week double-blind, placebo-controlled

multicenter trial in 322 outpatient children and adolescents (ages 8–17 years) with social anxiety disorder ([Wagner et al. 2004a](#)). Paroxetine was significantly superior to placebo, with rates of response (defined as CGI-I score=1 or 2) of 77.6% and 38.3%, respectively. Side effects more common with paroxetine than with placebo were insomnia, decreased appetite, and vomiting.

**Fluoxetine.** The efficacy of fluoxetine was evaluated in a 12-week randomized trial of fluoxetine (up to 40 mg/day), Social Effectiveness Therapy for Children (SET-C), and placebo for 80 youths (ages 7–17 years) with social anxiety disorder ([Beidel et al. 2007](#)). Both fluoxetine and SET-C were superior to placebo in reducing social stress and behavioral avoidance and increasing general functioning.

**Sertraline.** Fourteen outpatient children and adolescents (ages 10–17 years) with a diagnosis of social anxiety disorder received sertraline (dosage range=100–200 mg/day; mean daily dosage=123 mg) in an 8-week open trial ([Compton et al. 2001](#)). Five of the patients (36%) were much or very much improved, and four of the patients (29%) had a partial response by the end of the 8-week trial. Sertraline was well tolerated, and no patient developed significant behavioral disinhibition or mania ([Compton et al. 2001](#)).

**Escitalopram.** Twenty children with social anxiety disorder participated in a 12-week open-label study of escitalopram ([Isolan et al. 2007](#)). Sixty-five percent of participants were much or very much improved.

**Citalopram.** [Chavira and Stein \(2002\)](#) investigated the effectiveness of a combined psychoeducational and

pharmacological treatment program for youth with social anxiety disorder. Twelve children and adolescents (ages 8–17 years) with social anxiety disorder received citalopram (mean daily dosage=35 mg) and eight 15-minute counseling sessions over a 12-week period. On the basis of clinical global ratings of change, five of the patients (41.7%) were very much improved, and five of the patients (41.7%) were much improved.

## **Venlafaxine**

In a 16-week double-blind, placebo-controlled trial, 293 children and adolescents with social anxiety disorder were randomly assigned to venlafaxine XR (dosage range=37.5–225 mg) or placebo ([March et al. 2007](#)). Venlafaxine XR was significantly superior to placebo in reducing ratings of social anxiety. Response rates (CGI-I score  $\leq 2$ ) were 56% for the venlafaxine XR group and 37% for the placebo group.

## **Panic Disorder**

The prevalence of panic disorder in children and adolescents ranges from 0.6% to 5.0% in the community and from 0.2% to 9.6% in clinical settings ([Masi et al. 2001](#)). The DSM-5 diagnostic criteria for panic disorder in children and adolescents are the same as those for adults. Panic disorder in youth is a chronic condition, and there is continuity between pediatric and adult panic disorder ([Biederman et al. 1997](#)).

## **Selective Serotonin Reuptake Inhibitors**

In an open-label trial, 12 children and adolescents (ages 7–17 years) with panic disorder were treated with an SSRI for 6–8 weeks ([Renaud et al. 1999](#)). Mean daily dosages of SSRIs were fluoxetine 34 mg, paroxetine 20 mg, and sertraline 125 mg. Adjunctive benzodiazepines were used for 8 patients. Seventy-five percent of patients showed much to very much clinical improvement while receiving treatment with SSRIs. At the end of the trial, 8 patients (67%) no longer fulfilled panic disorder criteria.

**Paroxetine.** A chart review was conducted of 18 child and adolescent outpatients (ages 7–16 years) with a diagnosis of panic disorder who received monotherapy with paroxetine (dosage range=10–40 mg/day; mean daily dosage=23 mg) ([Masi et al. 2001](#)). The mean paroxetine treatment duration was 11.7 months. Fifteen patients (83%) had a CGI score of much or very much improved. The most common side effects were nausea, tension-agitation, sedation, insomnia, palpitations, and headache.

**Citalopram.** Three youths (ages 9, 13, and 16 years) with panic disorder and school phobia were treated with citalopram (up to 20 mg/day) over an 8- to 15-month period. All patients experienced resolution of panic attacks during the course of citalopram treatment ([Lepola et al. 1996](#)).

## **Benzodiazepines**

In a 2-week open trial, four adolescents with panic disorder were treated with clonazepam (0.5 mg twice daily). A significant reduction in panic attacks (from 3 attacks per week to 0.25 per week) was reported ([Kutcher and MacKenzie 1988](#)).



# Mixed Anxiety Disorders

## Selective Serotonin Reuptake Inhibitors

**Fluvoxamine.** One hundred twenty-eight outpatient children and adolescents (ages 6–17 years) with GAD, social anxiety disorder, or separation anxiety disorder (who had received 3 weeks of open treatment with supportive psychoeducational therapy without improvement) were randomly assigned to fluvoxamine (up to 300 mg) or placebo for an 8-week trial ([Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001](#)). The group treated with fluvoxamine had a significantly greater reduction in scores on the PARS than did the group treated with placebo. The response rate (CGI-I score  $\leq 3$ ) was 76% in the group being treated with fluvoxamine and 29% in the group receiving placebo. After completion of the 8-week placebo-controlled study, the 128 patients entered a 6-month open-label treatment phase ([Walkup et al. 2002](#)). Anxiety symptoms remained low in 33 of 35 of the subjects (94%) who initially responded to fluvoxamine. Of 14 fluvoxamine nonresponders switched to fluoxetine, anxiety symptoms significantly improved in 10 patients (71%). Among 48 placebo nonresponders, 27 (56%) showed significant improvement in anxiety on fluvoxamine.

**Fluoxetine.** Seventy-four youths (ages 7–17 years) with GAD, separation anxiety disorder, and/or social phobia were randomly assigned to fluoxetine (20 mg/day) or to placebo for 12 weeks ([Birmaher et al. 2003](#)). Sixty-one percent of fluoxetine-treated patients and 35% of placebo-treated patients were much or very much improved.

Fluoxetine's efficacy in long-term treatment of children with GAD, separation anxiety disorder, and/or social phobia was assessed in a 1-year open treatment ([Clark et al. 2005](#)) following the acute-phase study ([Birmaher et al. 2003](#)). Compared with youth taking no medication, those taking fluoxetine ( $n=42$ ) showed significantly superior outcome in anxiety measures.

The comparative efficacy of fluoxetine and clomipramine was evaluated in a 12-week double-blind, randomized, placebo-controlled trial for 36 youths (ages 7-17 years) with GAD, separation anxiety, and/or social anxiety disorder ([da Costa et al. 2013](#)). Although all groups showed significant improvement, no significant difference was found between fluoxetine and placebo or between clomipramine and placebo.

**Sertraline.** The comparative efficacy of sertraline, CBT, sertraline plus CBT, and placebo was evaluated in a 12-week randomized controlled trial (the Child Anxiety Multimodal Study [CAMS]) involving 488 children and adolescents with a diagnosis of GAD, separation anxiety disorder, or social phobia ([Walkup et al. 2008](#)). Combination treatment was significantly superior to sertraline alone or CBT alone. Rates of response (CGI-I score  $\leq 2$ ) were 80.7% for combined treatment, 59.7% for CBT, and 54.9% for sertraline. All treatments were significantly superior to placebo (23.7%).

Long-term outcomes from the CAMS study have been reported ([Piacentini et al. 2014](#)). At 24 and 36 weeks, most ( $\geq 80\%$ ) of the acute responders maintained a positive response. Combination treatment maintained an advantage over CBT and sertraline alone.

# Clinical Recommendations for Anxiety Disorders

In regard to childhood anxiety disorders, SSRIs are the first-line treatment ([Reinblatt and Walkup 2005](#)). Duloxetine and venlafaxine also have demonstrated efficacy for the treatment of childhood GAD. Other treatment options include buspirone, tricyclic antidepressants, and benzodiazepines ([Bernstein et al. 1996](#)). However, benzodiazepines should be used only on a short-term basis (i.e., weeks) because of the potential for abuse and dependence in youth ([Riddle et al. 1999](#)).

---

## Obsessive-Compulsive Disorder

---

OCD has a prevalence rate of 2%–4% in youth ([Douglass et al. 1995](#); [Zohar 1999](#)). The DSM-5 criteria for OCD are the same in children and adults. The course of OCD in youth is chronic.

## Serotonin Reuptake Inhibitors

Four medications have received FDA approval for the treatment of OCD in children and adolescents: sertraline ( $\geq 6$  years old), fluoxetine ( $\geq 7$  years old), fluvoxamine ( $\geq 7$  years old), and clomipramine ( $\geq 10$  years old). Citalopram and paroxetine have been studied for treatment of OCD in youth but do not have FDA approval.

### Sertraline

In a double-blind, placebo-controlled multicenter study, 187 children and adolescents (ages 6–17 years) with OCD were randomly assigned to sertraline or placebo ([March et al. 1998](#)). Sertraline dosages were titrated to a maximum of 200 mg/day during the first 4 weeks of the trial, and these dosages were maintained for an additional 8 weeks. The mean dosage of sertraline was 167 mg/day at endpoint. Compared with patients receiving placebo, patients receiving sertraline showed significantly greater improvement on the CY-BOCS, the NIMH Global Obsessive Compulsive Rating Scale (NIMH GOCS), and the CGI-S and CGI-I subscales. Forty-two percent of patients in the sertraline group and 26% of patients in the placebo group were rated as very much or much improved. Side effects of insomnia, nausea, agitation, and tremor occurred significantly more often in the group receiving sertraline than in the group receiving placebo.

In an assessment of the long-term safety and effectiveness of sertraline for pediatric OCD, 137 patients who completed the 12-week double-blind, placebo-controlled sertraline study ([March et al. 1998](#)) were given open-label sertraline (mean dosage=120 mg/day) in a 52-week extension study. Significant improvement was found on CY-BOCS, NIMH GOCS, and CGI scores. Rates of response (defined as >25% decrease in CY-BOCS and a CGI-I score of 1 or 2) were 72% for children and 61% for adolescents ([Cook et al. 2001](#)). Full remission (defined as a CY-BOCS score <8) was achieved in 47% of patients, and an additional 25% achieved partial remission (CY-BOCS score >8 but <15) ([Wagner et al. 2003b](#)). The most common side effects were headache, nausea, diarrhea, somnolence, abdominal pain, hyperkinesias, nervousness, dyspepsia, and vomiting.

The relative and combined efficacy of sertraline and CBT was assessed in a 12-week trial for 112 children and adolescents (ages 7–17 years) with OCD ([Pediatric OCD Treatment Study \[POTS\] Team 2004](#)). Patients were randomly assigned to sertraline, CBT, combined sertraline and CBT, or placebo. Combined treatment was significantly superior to CBT alone and sertraline alone, which did not differ from each other.

The efficacy of sequential sertraline and CBT compared with CBT and placebo was assessed in an 18-week trial for 47 youths (ages 7–17 years) with OCD ([Storch et al. 2013](#)). No significant difference was found between the groups on improvement in OCD symptoms.

## **Fluoxetine**

The safety and efficacy of fluoxetine were assessed in a 13-week double-blind, placebo-controlled multicenter trial ([D.A. Geller et al. 2001](#)). One hundred three children and adolescents (ages 7–17 years) with OCD were randomly assigned in a 2:1 ratio to either fluoxetine (dosage range=10–60 mg/day; mean daily dosage=24.6 mg) or placebo. The group treated with fluoxetine showed a statistically significant reduction in OCD severity compared with the group treated with placebo, as determined by changes in CY-BOCS scores. Rates of response (defined as >40% reduction in CY-BOCS score) were 49% in the fluoxetine group and 25% in the placebo group. There were no significant differences in treatment-emergent adverse events between the fluoxetine and placebo groups.

Fluoxetine was compared with placebo in a controlled trial in 43 children and adolescents with OCD ([Liebowitz et al. 2002](#)). After 16 (but not 8) weeks of treatment, the

fluoxetine group had significantly lower CY-BOCS scores than the placebo group.

## **Fluvoxamine**

The safety and efficacy of fluvoxamine were evaluated in a double-blind, placebo-controlled multicenter study ([Riddle et al. 2001](#)). One hundred twenty outpatient children and adolescents (ages 8-17 years) with OCD were randomly assigned to receive fluvoxamine (dosage range=50-200 mg/day; mean daily dosage=165 mg) or placebo for a 10-week trial. Patients who did not respond after 6 weeks could discontinue the double-blind phase and enter an open-label trial of fluvoxamine. Mean scores on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) were significantly different for the fluvoxamine and the placebo groups at weeks 1, 2, 3, 4, 6, and 10. Response rates (>25% reduction in CY-BOCS scores) were 42% in the group being treated with placebo. Adverse events occurring at a placebo-adjusted frequency of greater than 10% were insomnia and asthenia.

In an assessment of the safety and effectiveness of fluvoxamine in the long-term treatment of pediatric OCD, 99 patients who completed the acute double-blind, placebo-controlled fluvoxamine study by [Riddle et al. \(2001\)](#) participated in a 1-year open-label extension study ([Walkup et al. 1998](#)). Fluvoxamine dosages were titrated to 200 mg/day over the first 4 weeks. Patients experienced a 42% reduction in CY-BOCS scores by the end of long-term treatment. Clinical improvement plateaued at about 6 months of treatment. The most common side effects of fluvoxamine were insomnia, asthenia, nausea, hyperkinesias, and nervousness.

## Clomipramine

Clomipramine has been shown to be efficacious in the treatment of pediatric OCD in two double-blind, placebo-controlled trials. In the first study ([Flament et al. 1985](#)), 19 children (ages 10–18 years) with OCD were randomly assigned to clomipramine (dosage range=100–200 mg/day; mean daily dosage=141 mg) or placebo for 5 weeks. Significant improvement in observed and self-reported obsessions and compulsions was found for patients who received clomipramine. The most common side effects with clomipramine were tremor, dry mouth, dizziness, and constipation. One patient had a grand mal seizure.

In an 8-week double-blind, placebo-controlled multicenter study of 60 children and adolescents (ages 10–17 years) with OCD, it was found that patients who received clomipramine (up to 200 mg/day) had significantly greater reductions in scores on the CY-BOCS than the placebo group (37% and 8%, respectively). Forty-seven patients continued in a 1-year open-label extension trial, and effectiveness was maintained with long-term treatment. The most frequent side effects with clomipramine were dry mouth, somnolence, dizziness, fatigue, tremor, headache, constipation, and anorexia ([DeVeugh-Geiss et al. 1992](#)).

## Citalopram

Twenty-three child and adolescent outpatients (ages 9–18 years) with OCD were administered open-label citalopram (dosage range=10–40 mg/day; mean daily dosage=37 mg) in a 10-week trial ([Thomsen 1997](#)). There was a statistically significant improvement in CY-BOCS scores from baseline to endpoint. Adverse effects were minimal and transient.



In an 8-week open-label citalopram study of 15 youths (ages 6–17 years) with OCD, 14 patients showed significant improvement in CY-BOCS scores from baseline to endpoint ([Mukaddes and Abali 2003](#)).

In a long-term open study of 30 adolescents with OCD, citalopram (dosage range=20–70 mg/day; mean daily dosage=46.5 mg) was administered for 1–2 years ([Thomsen et al. 2001](#)). There was a significant reduction in CY-BOCS scores from baseline to assessment at 2 years. No serious adverse events were reported, and the most common side effects were sedation, sexual dysfunction, and weight gain.

## **Paroxetine**

The efficacy and safety of paroxetine were assessed in a double-blind, placebo-controlled multicenter study of 203 outpatient children and adolescents (ages 7–17 years) with OCD ([D.A. Geller et al. 2004](#)). Patients were randomly assigned to paroxetine (dosage range=10–50 mg/day; mean daily dosage=23 mg) or placebo for a 10-week trial. There was a statistically significant greater reduction in CY-BOCS scores from baseline to endpoint in patients treated with paroxetine than in patients treated with placebo. Response rates (>25% reduction in CY-BOCS scores) were 64.9% in the paroxetine-treated patients and 41.2% in the placebo-treated patients. The most common adverse effects in the paroxetine group were headache, abdominal pain, nausea, respiratory disorder, somnolence, hyperkinesias, and trauma.

The efficacy of paroxetine in 335 outpatients (ages 7–17 years) with OCD was assessed in a 16-week open-label multicenter study of paroxetine (10–60 mg/day), followed by double-blind randomization of responders to paroxetine or placebo for an additional 16 weeks ([Emslie et al. 2000](#)).



No significant differences in response rates were found between the group receiving paroxetine and the group receiving placebo in the randomization phase.

## Atypical Antipsychotic Augmentation

Adjunctive risperidone ( $\leq 2$  mg daily) was investigated in an open trial for 17 adolescents with OCD who failed to respond to two serotonin reuptake inhibitor monotherapy trials. A significant reduction in CY-BOCS scores was reported ([Thomsen 2004](#)).

Aripiprazole augmentation of CBT was found to be effective in the case of an adolescent who had a partial response to combined CBT and sertraline ([Storch et al. 2008](#)).

In a naturalistic sample of 220 children and adolescents with OCD, 43 children were treated with an atypical antipsychotic as an augmenting agent ([Masi et al. 2009](#)). Twenty-five of these youths (58.1%) responded to treatment.

The efficacy of aripiprazole augmentation of an SSRI was assessed in 39 youths with OCD who had not responded to two trials with SSRI monotherapy ([Masi et al. 2010](#)). Fifty-nine percent of the youths responded to treatment.

## Other Agents

### D-Cycloserine

Augmentation of CBT with D-cycloserine was evaluated in a double-blind, placebo-controlled trial for 30 youths (ages 8–

17 years) with OCD. No significant differences were found between treatment groups ([Storch et al. 2010](#)).

D-Cycloserine-augmented CBT was assessed in a double-blind, placebo-controlled pilot trial for 17 youths with difficult-to-treat OCD ([Farrell et al. 2013](#)). The augmented CBT resulted in greater improvement in OCD symptoms than CBT plus placebo.

## **Riluzole**

Sixty children and adolescents with treatment-resistant OCD participated in a 12-week double-blind, placebo-controlled trial of add-on riluzole or placebo with current treatment ([Grant et al. 2014](#)). The riluzole final dosage was 100 mg/day. All participants significantly improved on CY-BOCS ratings, and there was no significant difference between riluzole and placebo on any outcome measures. Adverse events reported for patients given riluzole included one case of pancreatitis and five instances of slight increase with transaminases.

## **N-Acetylcysteine**

The authors of a case report ([Yazici and Percinel 2014](#)) and a case series ([Yazici and Percinel 2015](#)) describe the use of N-acetylcysteine (NAC) augmentation for treatment-resistant OCD in children and adolescents. NAC dosages were initiated at 600 mg/day and increased up to 2,400–3,000 mg/day. Improvement in OCD symptoms was found in some cases.

# **Clinical Recommendations for Obsessive-Compulsive Disorder**

SSRIs are the medication treatment of choice for OCD in children and adolescents ([American Academy of Child and Adolescent Psychiatry 2012](#)). Clomipramine is also effective in the treatment of this disorder; however, it is not a first-line treatment because of its adverse-event profile. A 12-week trial at an adequate dosage is indicated to determine whether a child with OCD will respond to an SSRI. If a child fails to respond to one SSRI, switching to another SSRI is a reasonable strategy. Clomipramine, either as monotherapy or as augmentation of an SSRI, may be a third treatment option. Other possible SSRI augmentation strategies are clonazepam and atypical antipsychotics; however, these agents have not received systematic study. Some children may require long-term medication maintenance; however, it is reasonable to attempt medication discontinuation 1 year after symptom stabilization. Medication should be tapered gradually to assess for relapse. Two or three relapses should lead to long-term treatment.

---

## Posttraumatic Stress Disorder

---

The prevalence of posttraumatic stress disorder (PTSD) in adolescents is reported to be 5% ([Merikangas et al. 2010](#)). The criteria for diagnosing PTSD in children older than age 6 years are the same as those used for adults ([American Psychiatric Association 2013](#)). PTSD symptoms in children tend to vary over time, and although the disorder is chronic, the course is prolonged with greater severity of the stressor ([Clarke et al. 1993](#)).

# Sertraline

The efficacy of sertraline was evaluated in a 10-week double-blind, placebo-controlled trial in 131 children and adolescents with PTSD ([Robb et al. 2010](#)). Sertraline dosages ranged from 50 to 200 mg/day. There was no difference between sertraline-treated patients and placebo-treated patients in scores on the primary outcome measure, the University of California, Los Angeles Post-Traumatic Stress Disorder Index for DSM-IV (UCLA PTSD-I).

The benefit of adding sertraline versus placebo to trauma-focused CBT was assessed in a controlled 12-week trial ([Cohen et al. 2007](#)). Although both groups showed significant improvement in symptoms of PTSD, there was no significant advantage from adding sertraline rather than placebo to CBT.

# Citalopram

Eight adolescents with PTSD received citalopram in a fixed daily dosage of 20 mg in a 12-week open-label study ([Seedat et al. 2001](#)). Core PTSD symptoms of reexperiencing, avoidance, and hyperarousal showed statistically significant improvement at week 12, with a 38% reduction in total score on the Clinician-Administered PTSD Scale—Child and Adolescent Version (CAPS-CA). Citalopram was well tolerated, and the most common side effects were increased sweating, nausea, headache, and tiredness.

In a larger 8-week open trial, [Seedat et al. \(2002\)](#) treated 24 children and adolescents with citalopram (dosage range=20–40 mg/day; mean daily dosage=20 mg). Both the children and the adolescents had a significant reduction in

CAPS-CA scores at endpoint. Common side effects of citalopram were drowsiness, headache, nausea, and increased sweating.

## Guanfacine

The effectiveness of guanfacine extended release (GXR) was assessed in an 8-week open-label trial for 19 youths (ages 6–18 years) with current traumatic stress symptoms ([Connor et al. 2013](#)). GXR dosages ranged from 1 to 4 mg/day. On parent report, symptom clusters of reexperiencing, avoidance, and overarousal significantly improved.

## Clonidine

Seven preschool children (ages 3–6 years) with a diagnosis of PTSD received open treatment with clonidine at a dosage range of 0.05–0.15 mg/day ([Harmon and Riggs 1996](#)). To decrease sedation, oral clonidine was subsequently converted to a clonidine patch. The majority of children showed at least moderate improvements in hyperarousal, hypervigilance, insomnia, nightmares, and mood lability.

## Carbamazepine

Twenty-eight children and adolescents (ages 8–17 years) with a diagnosis of PTSD received carbamazepine (dosage range=300–1,200 mg/day) for an average of 35 days. Twenty-two patients (78%) became asymptomatic, and the

remaining six patients were significantly improved during the course of treatment ([Looff et al. 1995](#)).

## Propranolol

The efficacy of propranolol initiated within 12 hours after emergency department admission in preventing PTSD in 29 injured youths was assessed in a 10-day double-blind, placebo-controlled trial ([Nugent et al. 2010](#)). There was no significant difference between the propranolol and placebo groups on PTSD symptoms at 6 weeks.

Eleven children (ages 6–12 years) with a diagnosis of PTSD participated in an off-on-off medication design of 4 weeks of propranolol treatment ([Famularo et al. 1988](#)). Propranolol was initiated at 0.8 mg/kg/day and titrated to a maximum of 2.5 mg/kg/day. A significant improvement in PTSD symptoms was found during the treatment period. Side effects included sedation and mildly lowered blood pressure and pulse.

## Prazosin

In case studies ([Oluwabusi et al. 2012](#); [Strawn and Keeshin 2011](#); [Strawn et al. 2009](#)), prazosin 1–3 mg/day was reported to decrease symptoms of PTSD in children and adolescents.

## D-Cycloserine

In a controlled trial, 57 youths (ages 7–18 years) with PTSD were randomly assigned to receive D-cycloserine and CBT

or placebo and CBT ([Scheeringa and Weems 2014](#)). Although both groups had significant reductions in PTSD symptoms, there was no significant difference between the groups.

## Risperidone

In case reports and a small open-label trial, risperidone has shown some benefit in reducing symptoms of PTSD in children and adolescents ([Horrigan and Barnhill 1997](#); [Keeshin and Strawn 2009](#); [Meighen et al. 2007](#)).

## Quetiapine

In a case series, six adolescents with PTSD reported improvement in symptoms after 6 weeks of low-dosage (50–200 mg/day) quetiapine ([Stathis et al. 2005](#)).

## Clinical Recommendations for Posttraumatic Stress Disorder

For childhood trauma- and stressor-related disorders, SSRIs are the first-line treatment ([Reinblatt and Walkup 2005](#)). Other possible medications for PTSD are  $\alpha$ - and  $\beta$ -adrenergic blocking agents, non-SSRI antidepressants, and mood-stabilizing agents ([Cohen et al. 2010](#)).

---

## Attention-Deficit/Hyperactivity Disorder

---

The prevalence of ADHD in children and adolescents is estimated to range from 5% to 12%, whereas about 4% of adults in the general population meet criteria for ADHD ([Kessler et al. 2006](#)). In addition to demonstrating the core behavioral features of inattention, hyperactivity, and impulsivity, children with ADHD often have significant impairment in social and academic functioning ([Barkley 2005](#)). Of all of the childhood psychiatric disorders, ADHD has the greatest number of pharmacological treatment studies.

## Psychostimulants

The classes of psychostimulants include methylphenidate, dexamethylphenidate, dextroamphetamine, mixed amphetamine salts, and L-lysine-D-amphetamine (lisdexamfetamine). By the 1980s, there were already hundreds of randomized controlled trials showing the efficacy of stimulants in the treatment of ADHD in school-age children ([Greenhill et al. 1999](#)). [Arnold \(2000\)](#) reviewed studies in which subjects underwent a trial of both amphetamine and methylphenidate. This review suggested that approximately 41% of subjects with ADHD responded equally to methylphenidate and amphetamine, whereas 44% responded preferentially to one of the classes of stimulants. This finding suggests that the initial response rate to stimulants may be as high as 85% if both stimulants are tried (in contrast to the finding of 65%–75% response when only one stimulant is tried). In contrast, placebo response rates in stimulant trials are rarely above 20%–30%, making the effect size of the stimulants (0.8–1.0) one



of the largest among all the psychotropics. At present, however, no method is available to predict which stimulant will produce the best response in a given patient. The past decade has seen the emergence of the long-acting stimulants; studies of these agents have been the focus of major reviews ([Biederman and Spencer 2008](#); [Pliszka and AACAP Work Group on Quality Issues 2007](#)).

Initial research with stimulants was carried out in school-age children, but more recent controlled trials of stimulants have focused on adolescents ([Spencer et al. 2006b](#); [Wilens et al. 2006a](#)) and adults ([Biederman et al. 2006a](#); [Weisler et al. 2006](#)). These studies show that older individuals' rates of response to stimulants are similar to those of children, with adequate response for most subjects being obtained with 70–100 mg/day of methylphenidate or 40–60 mg/day of amphetamine.

Preschoolers with ADHD have also been the focus of investigation. In the NIMH Preschool ADHD Treatment Study (PATs), 183 children (ages 3–5 years) underwent an open-label trial of methylphenidate, with 165 of these subjects subsequently randomly assigned to a double-blind, placebo-controlled crossover trial of methylphenidate lasting 6 weeks ([Greenhill et al. 2006](#); [Wigal et al. 2006](#)). The mean optimal dosage of methylphenidate was found to be  $0.7 \pm 0.4$  mg/kg/day, which is lower than the mean of 1.0 mg/kg/day found to be optimal in school-age children. Eleven percent of subjects discontinued methylphenidate because of adverse events. Compared with school-age children, the preschool group showed a higher rate of emotional adverse events, including crabbiness, irritability, and proneness to crying. The conclusion was that the dosage of methylphenidate (or any stimulant) should be

titrated more conservatively in preschoolers than in school-age patients, and lower mean dosages may be effective.

The appendix at the end of this chapter shows the recommended dosage ranges for these agents. The appendix also discusses adverse events, particularly growth suppression, that occur with psychostimulants.

## Atomoxetine

Atomoxetine is a noradrenergic reuptake inhibitor that has indirect effects on dopamine reuptake in the cortex but not in the striatum ([Bymaster et al. 2002](#)). Numerous double-blind, placebo-controlled trials have demonstrated the medication's efficacy in the treatment of ADHD in children, adolescents, and adults ([Michelson et al. 2001, 2002, 2003](#)). Given its pharmacokinetic half-life of 5 hours, it is generally dosed twice a day. Although open trials comparing methylphenidate with atomoxetine showed the two agents to have similar efficacy ([Kratochvil et al. 2002](#)), double-blind, placebo-controlled trials comparing atomoxetine with amphetamine ([Biederman et al. 2006b](#); [Wigal et al. 2005](#)) and methylphenidate ([Newcorn et al. 2008](#)) have shown the stimulants to be more efficacious.

Atomoxetine is effective in treating ADHD in patients with comorbid tics and may also reduce tics ([Allen et al. 2005](#)). It is also useful in children with ADHD who have comorbid anxiety, showing effectiveness in treating anxiety and inattention ([Sumner et al. 2005](#)). Atomoxetine is well tolerated in long-term use. In a global multicenter study, 416 children and adolescents who responded to an initial 12-week open-label period of treatment with atomoxetine were randomly assigned to continued atomoxetine

treatment or placebo for 9 months under double-blind conditions. Relapse (defined as a return to 90% of baseline symptom severity) occurred significantly less often with atomoxetine (22.3%) than with placebo (37.9%) ([Michelson et al. 2001](#)). Data from 13 (6 double-blind, 7 open-label) atomoxetine studies were pooled for youths (ages 12–18 years) with ADHD ([Wilens et al. 2006b](#)). Of the 601 atomoxetine-treated subjects in this meta-analysis, 537 (89.4%) completed 3 months of acute treatment. At the time of the article's publication, 259 subjects (48.4%) were continuing atomoxetine treatment; 219 of these subjects had completed at least 2 years of treatment. Symptoms remained improved for up to 24 months without dosage escalation. During the 2-year treatment period, 99 subjects (16.5%) discontinued treatment due to lack of effectiveness, and 31 subjects (5.2%) discontinued treatment due to adverse events. No clinically significant abnormalities in height, weight, blood pressure, pulse, mean laboratory values, or electrocardiography parameters were found.

## Clonidine

A review of the literature from 1980 to 1999 found 39 studies regarding the use of clonidine for symptoms of childhood ADHD, and 11 of these studies had sufficient data to be included in a meta-analysis ([Connor et al. 1999](#)). Of the 150 subjects in these studies, 42 received clonidine for ADHD, and the others received clonidine for ADHD comorbid with tic disorders ( $n=67$ ), developmental disorders ( $n=15$ ), or conduct disorders ( $n=26$ ). The mean daily dosage of clonidine was 0.18 mg, and the average length of treatment was 10.9 weeks. Clonidine showed a

moderate effect size of 0.58 on symptoms of ADHD, which is smaller than the effect size (0.82) reported for stimulant treatment of ADHD ([Swanson et al. 1995b](#)).

An extended-release (ER) form of clonidine was more recently developed, and this formulation was evaluated in an 8-week double-blind, placebo-controlled trial ([Jain et al. 2011](#)) in which patients ( $N=236$ ) were randomly assigned to receive clonidine ER 0.2 mg/day, clonidine ER 0.4 mg/day, or placebo. Improvement in ADHD symptoms was significantly greater in the clonidine groups relative to the placebo group, with this difference apparent at week 2 and greatest at week 5. Somnolence was the most common side effect, and the rate of withdrawal due to adverse events was higher in the clonidine ER 0.4-mg/day group than in the other groups. There were no serious adverse events, and bradycardia was the most common cardiovascular side effect.

Clonidine ER has been added to stimulant medication in an effort to improve the initial stimulant response in the treatment of ADHD ([Kollins et al. 2011](#)). Children and adolescents with ADHD who had an inadequate response to their initial stimulant regimen ( $n=198$ ) were randomized to receive placebo or clonidine extended release added to their stable stimulant dosage for 8 weeks. Clonidine ER was flexibly dosed. At weeks 4 and 5, of the patients within the group receiving clonidine ER plus stimulant, 3%, 15%, 68%, and 14% received clonidine ER 0.1 mg/day, 0.2 mg/day, 0.3 mg/day, and 0.4 mg/day, respectively. Reduction in ADHD Rating Scale IV (ADHD-RS-IV) scores was greater for the group receiving clonidine ER than for the group receiving placebo in weeks 2–7 but not at week 8. Oddly, although addition of clonidine ER to amphetamine led to significantly

greater improvement, addition to methylphenidate did not. No serious adverse events were reported.

## Guanfacine

In a study by [Hunt et al. \(1995\)](#), 13 children and adolescents with ADHD received guanfacine (mean daily dosage=3.2 mg) for 1 month. Significant improvements in hyperactivity and inattention were found. In an 8-week double-blind, placebo-controlled trial, 34 children and adolescents (ages 7–14 years) with ADHD and tic disorder were randomly assigned to receive guanfacine (dosage range=1.5–3.0 mg/day) or placebo ([Scahill et al. 2001](#)). A 37% improvement in ADHD symptoms was reported for children treated with guanfacine, compared with an 8% improvement for children who received placebo. The most common side effects of guanfacine were sedation and dry mouth. There were no significant changes in pulse or blood pressure with guanfacine treatment.

An extended-release formulation of guanfacine (GXR) is also used for the treatment of ADHD ([Biederman et al. 2008](#); [Sallee et al. 2009](#)). In a double-blind, placebo-controlled Phase III multicenter trial ([Melmed et al. 2006](#)), children and adolescents ages 6–17 years were randomly assigned to placebo or 2 mg, 3 mg, or 4 mg/day of GXR. All three dosages of GXR were superior to placebo in reducing symptoms of ADHD. The most commonly reported side effects of GXR were headache, somnolence, and fatigue. No serious adverse events were reported. In healthy young adults (ages 19–24 years), abrupt discontinuation of 4 mg/day of GXR did not lead to increases in blood pressure

or electrocardiogram (ECG) abnormalities ([Kisicki et al. 2006](#)).

GXR has also been assessed as add-on therapy when children with ADHD have only a partial response to stimulants ([Wilens et al. 2012](#)). In a 9-week double-blind, placebo-controlled dosage optimization study, patients ( $N=461$ ) continued their stable dosage of psychostimulant given in the morning and were randomized to receive GXR in the morning (GXR AM), GXR in the evening (GXR PM), or placebo. At endpoint, compared with the group receiving placebo plus psychostimulant, each guanfacine treatment group showed significantly greater improvement from baseline on ADHD-RS-IV total scores. Results did not differ between the GXR AM and GXR PM groups in either efficacy or adverse events. There were no serious or unexpected adverse events.

## Clinical Recommendations for Attention-Deficit/Hyperactivity Disorder

Based on the strength of clinical trial data, stimulants should be regarded as the first line for treatment of ADHD, and generally a different stimulant class should be used if the first stimulant prescribed has failed. Either atomoxetine or guanfacine is an appropriate second-line agent. Stimulants have been combined with atomoxetine in an open trial, with results suggesting that the two agents are superior to atomoxetine alone ([Wilens et al. 2009](#)). Placebo-controlled studies have shown that the addition of either guanfacine ([Wilens et al. 2012](#)) or clonidine ([Kollins et al.](#)

[2011](#)) can further reduce symptoms of ADHD after a partial response to psychostimulants. Thus,  $\alpha_2$ -adrenergic receptor agonists are increasingly used in this adjunctive role.

The stages of pharmacological treatment of ADHD can be summarized as follows:

- Stage 1: Psychostimulant
- Stage 2: Alternative psychostimulant
- Stage 3: Atomoxetine or  $\alpha_2$  agonist
- Stage 4: Combination of  $\alpha_2$  agonist or atomoxetine with stimulant

---

## Disruptive Behavior Disorders and Aggression

---

Oppositional defiant disorder (ODD) and conduct disorder (CD) are highly comorbid with ADHD, particularly in younger children ([Pliszka et al. 1999](#)). ODD and CD are *syndromes*, whereas aggression is a *symptom*. Although many children and adolescents with CD are aggressive, a child can meet criteria for CD without being aggressive. Also, aggression may present as a problematic symptom in children with depression, psychosis, or bipolar disorder without the child meeting criteria for CD. Thus, the clinician must be clear whether the target of treatment is the syndrome of ODD or CD or the symptom of aggression, because studies have addressed the problems separately. Treatments for ADHD have been used to target ODD and CD, whereas mood stabilizers and antipsychotics have been used in patients with severe aggressive outbursts, regardless of diagnosis ([Pappadopulos et al. 2006](#)).

# Oppositional Defiant Disorder and Conduct Disorder

## Psychostimulants

In a 5-week double-blind, placebo-controlled trial of methylphenidate in 84 youths (ages 6–15 years) with CD (with and without ADHD), ratings of antisocial behaviors specific to CD were significantly reduced by methylphenidate treatment (up to 60 mg/day) ([Klein et al. 1997](#)). The severity of the ADHD did not affect the response of CD symptoms in the stimulant study. Since that study, multiple double-blind, placebo-controlled trials have shown that ODD responds to stimulant medication, yielding an effect size similar to that for the ADHD symptoms ([Spencer et al. 2006a](#)).

## Atomoxetine

Children and adolescents (ages 8–18 years) with ADHD were treated for approximately 8 weeks with placebo or atomoxetine under randomized, double-blind conditions. Of the 293 subjects, 39% were diagnosed with comorbid ODD and 61% were not ([Newcorn et al. 2005](#)). Treatment group differences and differences between patients with and without comorbid ODD were examined post hoc for changes on numerous clinical measures. Treatment response was similar in youth with and without ODD, although the comorbid group may require higher dosages to achieve response than those with ADHD alone.

In general, a child with ODD or CD should be treated with a stimulant or atomoxetine before proceeding to the use of other psychotropic agents. The use of more potent agents



(mood stabilizers, antipsychotics) is generally reserved for those with severe aggression, and then only after a behavioral treatment has failed.

## Aggression

### Psychostimulants

In a meta-analysis of the literature from 1970 to 2001 that examined 28 studies to determine the effect size for stimulants on overt and covert aggression-related behaviors in children with ADHD, it was found that the mean effect size for aggressive behaviors was similar to that for core behaviors of ADHD ([Connor et al. 2002](#)).

### Risperidone

A significant body of research has accumulated showing the effectiveness of risperidone in the treatment of aggression, although most of these studies involve patients with subaverage intelligence ([Snyder et al. 2002](#)); 80% of subjects had comorbid ADHD. Risperidone dosages ranged from 0.02 to 0.06 mg/kg/day. The risperidone-treated subjects showed a significant ( $P<0.001$ ) reduction (47.3%) in conduct problems compared with placebo-treated subjects (20.9%). The effect of risperidone was unaffected by diagnosis, presence versus absence of ADHD, psychostimulant use, and IQ status. Risperidone produced no changes in the cognitive variables, and the most common side effects were somnolence, headache, appetite increase, and dyspepsia. Somnolence did not predict response of aggressive symptoms. Side effects related to EPS were reported in 7 (13.2%) and 3 (5.3%) of the

subjects in the risperidone and placebo groups, respectively ( $P=0.245$ ).

Other double-blind, placebo-controlled trials of risperidone in children and adolescents with disruptive behavior disorders (and subaverage IQ) have yielded similar results, with no negative trials reported ([Aman et al. 2002](#); [Buitelaar et al. 2001](#); [LeBlanc et al. 2005](#)). Weight gain was a significant side effect in these studies, but there has not been evidence of adverse neuropsychological effects ([Günther et al. 2006](#)). Addition of risperidone to a stimulant does not appear to increase rates of side effects and enhances treatment of hyperactivity ([Aman et al. 2004](#)). Indeed, adding risperidone to a stimulant to control aggression has become a common practice, although a controlled study showed that aggression was equally reduced when either placebo or risperidone was added to psychostimulant medication ([Armenteros et al. 2007](#)). The sample in this study was small ( $N=25$ ), but the study should caution clinicians that aggression can respond to psychosocial events, such as the expectations of a study.

[Pandina et al. \(2006\)](#) wrote a full review of all studies of risperidone in the treatment of childhood aggression. This review pooled adverse-event data from these studies, showing the most common side effects of risperidone to be somnolence (33%), weight gain (20%), hyperprolactinemia (10.2%), and fatigue (10%). In the pooled studies, there was an excess mean weight gain (over normal growth) of  $6.0 \pm 7$  kg after 35–43 weeks of treatment. Of the 688 patients, 651 were free of dyskinetic movements at baseline, and only 1 patient developed new dyskinetic movements during the follow-up period (these symptoms resolved even though risperidone was continued). There was no worsening of dyskinetic movements in those patients with such

preexisting symptoms. Rates of EPS were low throughout the long-term follow-up period. It should be noted that the dosages of risperidone used in these studies were quite low (1–2 mg/day); thus, these results may not apply to dosages in the 6-mg/day range.

[Aman et al. \(2014\)](#) tested the efficacy of adding risperidone to concurrent psychostimulant treatment and parent training (PT) in behavior management in children with ADHD and severe comorbid aggression. Children ages 6–12 years (mean age 8.89 years) with severe physical aggression were randomly assigned to a 9-week trial of PT, stimulant, and placebo (basic treatment;  $n=84$ ) or of PT, stimulant, and risperidone (augmented treatment;  $n=84$ ). Children received a psychostimulant for 3 weeks, titrated for optimal effect, while parents received PT. If there was room for improvement at the end of week 3, placebo or risperidone was added for an additional 3 weeks. Both groups showed substantial reductions in aggressive behavior during the first 3 weeks of stimulant plus PT treatment. In the second phase, the risperidone group showed significantly greater reduction in rating scale measures of aggressive behavior, but CGI-I scores did not discriminate the groups. Adverse events were as expected, with the risperidone group experiencing greater weight gain and increases in serum lipid and prolactin levels than the placebo group. The study clearly showed the need to adequately treat ADHD in the aggressive child before prescribing second-generation antipsychotics.

## **Other Atypical Antipsychotics**

There have been only small open trials and case reports of the use of quetiapine, aripiprazole, olanzapine, and ziprasidone in the treatment of aggression ([Findling et al.](#)

2006; Hazaray et al. 2004; Khan and Mican 2006; Rugino and Janvier 2005; Staller 2004; Stephens et al. 2004; Valicenti-McDermott and Demb 2006). In most of these studies, children had primary psychiatric diagnoses other than ODD or CD, such as mood disorders or developmental disorders.

## Lithium

The efficacy of lithium in the treatment of CD in youth has been demonstrated in three double-blind, placebo-controlled studies. Haloperidol, lithium, and placebo were compared in a double-blind, randomized trial in 61 hospitalized children (ages 5–12 years) with aggression and CD (Campbell et al. 1984). The optimal dosages of haloperidol ranged from 1 to 6 mg/day; the optimal dosages of lithium ranged from 500 to 2,000 mg/day. Both haloperidol and lithium were found to be significantly superior to placebo in reducing aggression. However, there were more adverse effects associated with haloperidol than with lithium, including excessive sedation, acute dystonic reaction, and drooling. Stomachache, headache, and tremor were more common with lithium than with haloperidol.

In a subsequent study, Campbell et al. (1995) conducted a 6-week double-blind, placebo-controlled trial of lithium treatment for 50 hospitalized children (ages 5–12 years) with aggression and CD. The mean optimal daily dosage of lithium was 1,248 mg, and the mean serum level was 1.12 mEq/L. Lithium was significantly superior to placebo in reducing aggression. The most common lithium side effects were stomachache, nausea, vomiting, headache, tremor, and urinary frequency.

Eighty-six inpatients (ages 10–17 years) with CD were randomly assigned to treatment with lithium (mean daily dosage=1,425 mg; mean serum level=1.07 mmol/L) or placebo in a 4-week double-blind trial. Aggression ratings decreased significantly for the group treated with lithium, compared with the group treated with placebo. More than 50% of patients in the lithium group experienced nausea, vomiting, and urinary frequency ([Malone et al. 2000](#)).

In contrast, [Rifkin et al. \(1997\)](#) found no significant differences between lithium and placebo in aggression ratings in a 2-week double-blind study of 33 inpatients with CD. The short duration of treatment may have accounted for the lack of efficacy, suggesting that a 4- to 6-week trial is necessary to show response.

Severe mood dysregulation, referred to in DSM-5 as disruptive mood dysregulation disorder, is often characterized by severe aggressive outbursts. [Dickstein et al. \(2009\)](#) studied the effect of lithium in youths (ages 7–17 years) with severe mood dysregulation who were tapered off their medications. Those who continued to have significant mood dysregulation after a 2-week single-blind placebo run-in were randomized to a 6-week double-blind trial of either lithium ( $n=14$ ) or placebo ( $n=11$ ). Interestingly, 20 of 45 youths (45%) with severe mood dysregulation were not randomized due to significant clinical improvement during the placebo run-in. Among randomized patients, there were no significant between-group differences in any clinical measures. The placebo group showed no improvement at all (a true negative trial), with no evidence that an increase in sample size would have changed the results.

## **Divalproex**

Twenty outpatient children and adolescents (ages 10–18 years) with CD or ODD were randomly assigned to divalproex (dosage range=750–1,500 mg/day; mean blood level=82 µg/mL) or placebo in a 6-week double-blind, placebo-controlled crossover study. Of the 15 patients who completed both phases, 12 (80%) had a statistically significant superior response to divalproex. Increased appetite was the only significant side effect ([Donovan et al. 2000](#)). [Steiner et al. \(2003\)](#) randomly assigned 71 adolescents with CD in a residential facility for juvenile offenders to two groups, which received either a therapeutic dosage or a low dosage of divalproex for 7 weeks; both subjects and outcome raters were blind to treatment status. Reduction in aggression severity ( $P=0.02$ ), improvement in impulse control ( $P<0.05$ ), and global improvement ( $P=0.0008$ ) were greater in the group with therapeutic divalproex levels than in the low-dosage condition. As reported in another article from the same study, serum level and “immature defenses” (as assessed by the Weinberger Adjustment Inventory) predicted response to divalproex, but psychiatric comorbidity did not ([Saxena et al. 2005](#)).

[Blader et al. \(2009\)](#) treated 74 children with ADHD and aggression with open stimulant treatment during a lead-in phase that averaged 5 weeks. Children whose aggressive behavior persisted at the conclusion of the lead-in phase ( $n=30$ ) were randomly assigned to receive double-blind, flexibly dosed divalproex or a placebo adjunctive to stimulant for 8 weeks. Families received weekly behavioral therapy throughout the trial. A significantly higher proportion of the children randomly assigned to divalproex met remission criteria (8 of 14; 57%) than of those randomly assigned to placebo (2 of 13; 15%).

## Clonidine

Clonidine has often been combined with stimulants to treat comorbid aggression in children with ADHD. In a 2-month randomized comparison of clonidine, methylphenidate, and clonidine combined with methylphenidate in the treatment of 24 children and adolescents (ages 6–16 years) with ADHD and CD or ODD, it was found that all three treatment groups showed significant improvement in oppositional and CD symptoms ([Connor et al. 2000](#)). No significant ECG changes were noted.

Children (ages 6–14 years) with ADHD currently taking methylphenidate were randomly assigned to receive clonidine syrup 0.10–0.20 mg/day ( $n=37$ ) or placebo ( $n=29$ ) for 6 weeks ([Hazell and Stuart 2003](#)). Analysis showed that significantly more clonidine-treated children than control subjects were responders on the Conduct subscale (21 of 37 vs. 6 of 29;  $P<0.01$ ) of the parent-report Conners Behavior Checklist, but not on the Hyperactive Index subscale (13 of 37 vs. 5 of 29). Compared with placebo, clonidine was associated with a greater reduction in systolic blood pressure measured standing and with transient sedation and dizziness. Clonidine-treated individuals had a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared with placebo. The findings supported the use of clonidine in combination with psychostimulant medication to reduce conduct symptoms associated with ADHD.

## Clinical Recommendations for Disruptive Behavior Disorders and

# Aggression

The Center for the Advancement of Children's Mental Health at Columbia University joined with the New York State Office of Mental Health to develop guidelines for treatment of aggression, which led to the Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY; [Pappadopulos et al. 2003](#); [Schur et al. 2003](#)). These recommendations call first for a thorough psychiatric evaluation of the child with severe aggression. Next, a psychosocial intervention should be used first when the aggression is the primary problem, such as in ODD, CD, or intermittent explosive disorder. The clinician should then treat any primary condition, such as ADHD, psychosis, or mood disorder that may be causing or contributing to the aggression. If the aggression does not respond to these steps, then an atypical antipsychotic should be used. Different atypical antipsychotics should be tried as monotherapy before moving to polypharmacy (e.g., adding a classic mood stabilizer such as lithium or divalproex to the antipsychotic). Monitoring of weight and laboratory measures of glucose, cholesterol, and triglycerides is mandatory ([Correll and Carlson 2006](#)).

$\alpha_2$ -Adrenergic receptor agonists may be used in children with milder aggression or temper outbursts because the effect size of these medications on aggression is more modest ([Hazell and Stuart 2003](#)).

---

## Tourette Syndrome

---



The prevalence of Tourette syndrome is estimated to be 0.7% in children ([Comings et al. 1990](#)). Tourette syndrome is characterized by multiple motor tics and by one or more vocal tics that occur frequently for longer than 1 year. More commonly children suffer from chronic motor or vocal tics, but treatment is the same as for Tourette syndrome. A meta-analysis has been performed examining the effects of  $\alpha_2$ -adrenergic receptor agonists and antipsychotics in the pharmacological treatment of tics ([Weisman et al. 2013](#)).

## Alpha-2-Adrenergic Receptor Agonists

[Weisman et al. \(2013\)](#) identified six placebo-controlled studies examining the effect of clonidine ([Du et al. 2008](#); [Leckman et al. 1991](#); [Singer et al. 1995](#); [Tourette's Syndrome Study Group 2002](#)) or guanfacine ([Cummings et al. 2002](#); [Scahill et al. 2001](#)) in patients with tics. A meta-analysis demonstrated a significant effect of an  $\alpha_2$  agonist relative to placebo, with a standardized mean difference of 0.31 (95% confidence interval [CI], 0.15-0.48). This is a fairly modest effect. Of note, the analysis showed that clonidine had a significantly larger effect against tics when patients had comorbid ADHD than when patients did not have ADHD.

## Antipsychotics

[Weisman et al. \(2013\)](#) reviewed five placebo-controlled studies of haloperidol and pimozide ([Sallee et al. 1997](#); [Shapiro et al. 1989](#)), ziprasidone ([Sallee et al. 2000](#)), and

risperidone ([Dion et al. 2002](#); [Scahill et al. 2003](#)). Two studies directly compared haloperidol and risperidone without a placebo control ([Bruggeman et al. 2001](#); [Gilbert et al. 2004](#)), one study compared risperidone and clonidine ([Gaffney et al. 2002](#)), and one study compared haloperidol and the clonidine patch ([Kang et al. 2009](#)). However, the [Kang et al. \(2009\)](#) study, unlike the others, was not blinded. In the meta-analysis, all antipsychotics were superior to placebo, with a standardized mean difference of 0.61 (95% CI, 0.36-0.86). There was no difference between the various antipsychotic agents with regard to their efficacy for reducing tics. [Gaffney et al. \(2002\)](#) found clonidine and risperidone to be equivalent in efficacy. Studies of aripiprazole were not included in the [Weisman et al. \(2013\)](#) meta-analysis.

[Murphy et al. \(2005\)](#) reported six cases of children and adolescents (age range= 8-19 years; mean age=12.1 years) who had comorbid tic disorder and OCD and were treated with aripiprazole (mean dosage=11.7 mg/day; range=5-20 mg/day) for 12 weeks. The subjects experienced a mean reduction of 56% in the severity of their tics as assessed by the Yale Global Tic Severity Scale (YGTSS). Similarly, [Yoo et al. \(2006\)](#) treated 15 children and adolescents who had tic disorder with aripiprazole (mean dosage=10.89 mg/day; range=12.5-15 mg/day) and reported a mean reduction of 40% in YGTSS scores; side effects were minimal. Two subjects experienced nausea, one experienced weight gain, and one experienced sedation. The sedation responded to dosage reduction.

In a case series, 11 consecutive patients with Tourette syndrome (mean age=7 years; age range=7-50 years) were treated with aripiprazole; the symptoms of the majority of these patients had been refractory to previous

treatments with other antipsychotics ([Davies et al. 2006](#)). Ten of the 11 patients who were treated with aripiprazole improved, although to variable degrees. In the majority of patients, response was sustained with aripiprazole dosages ranging from 10 to 20 mg/day. Side effects were mild and transient.

[Zheng et al. \(2016\)](#) reviewed six studies of the treatment of tics with aripiprazole. This study included two randomized controlled trials, but in these studies aripiprazole was compared only with tiapride, an antipsychotic not available in the United States. The other four were open trials. The review found aripiprazole to be well tolerated and effective in reducing tics relative to baseline levels.

## Clinical Recommendations for Tourette Syndrome

If a tic is not severe or socially impairing, observation may be in order because tics typically wax and wane; in general, tics improve over time ([Leckman 2002](#)). Often, psychosocial treatment such as habit reversal training is highly effective at reducing tics ([Piacentini and Chang 2006](#)). If conservative treatment fails, use of an  $\alpha_2$  agonist would be desirable, due to the risk of weight gain and dyslipidemia with atypical antipsychotics. The atypical antipsychotics are preferred to typical antipsychotics because the latter have lower efficacy and a higher risk of tardive dyskinesia. Haloperidol and pimozide should be used only as a last resort when several atypical agents have failed.

In children with comorbid ADHD, a stimulant can be used, but a nonstimulant is indicated if the stimulant exacerbates

tics ([Pliszka et al. 2006a](#)). Stimulants often must be combined with  $\alpha_2$  agonists or antipsychotics to control both the ADHD and the tics ([Pliszka et al. 2006a](#); [Tourette's Syndrome Study Group 2002](#)).

---

## Schizophrenia

---

Cases of schizophrenia in children younger than age 13 years are very rare; however, the prevalence rises in adolescence, with peak onset between ages 15 and 30 years ([McClellan and Werry 2001](#)). The clinical features of the disorder are similar in youth and adults, and the same DSM-5 criteria are used to establish a diagnosis. The outcome of childhood-onset schizophrenia is reported to be poor ([Eggers and Bunk 1997](#)).

## Atypical Antipsychotics

Five atypical antipsychotics have FDA approval for the treatment of schizophrenia in adolescents: olanzapine (for ages  $\geq 13$  years), risperidone ( $\geq 13$  years), aripiprazole ( $\geq 13$  years), quetiapine ( $\geq 13$  years), and paliperidone ER ( $\geq 12$  years). Ziprasidone, asenapine, and clozapine have been studied for treatment of schizophrenia in youth but do not have FDA approval.

### Olanzapine

In a double-blind, placebo-controlled multicenter study of olanzapine (mean dosage=11.1 mg/day) for the treatment of adolescents with schizophrenia ([Kryzhanovskaya et al. 2009](#)), 107 adolescents were randomly assigned to receive

olanzapine ( $n=72$ ) or placebo ( $n=35$ ) for a 6-week trial. Olanzapine-treated adolescents had significant improvements on the Brief Psychiatric Rating Scale for Children (BPRS-C) and on CGI-S scores compared with the placebo group. There was no significant difference in response rate (defined as a  $\geq 30\%$  decrease in BPRS-C and a CGI-S score  $\leq 3$ ) between the olanzapine (37.5%) and placebo (25.7%) groups. Significantly more olanzapine-treated adolescents had high aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), and prolactin levels, as well as low bilirubin levels and hematocrit values, during treatment. There was a significant increase in fasting triglycerides at endpoint in the olanzapine-treated adolescents. Early response at 2 and 3 weeks has been shown to predict ultimate response and remission at week 6 ([Stentebjerg-Olesen et al. 2015](#)).

## Risperidone

Positive findings were reported in a double-blind, placebo-controlled multicenter trial of risperidone in the treatment of adolescents with schizophrenia ([Haas et al. 2007](#)). One hundred sixty adolescents were randomly assigned to risperidone 1–3 mg/day ( $n=55$ ), risperidone 4–6 mg/day ( $n=51$ ), or placebo ( $n=54$ ) for a 6-week trial. Both dosage ranges of risperidone were significantly superior to placebo on the primary efficacy measure, the Positive and Negative Syndrome Scale (PANSS) total change score at endpoint. The most common adverse events in the risperidone 1- to 3-mg/day group were somnolence (24%), agitation (15%), and headache (13%). EPS (16%), dizziness (14%), and hypertonia (14%) were the most common adverse events in

the risperidone 4- to 6-mg/day group. The investigators concluded that the overall risk-benefit ratio favored the lower dosage range of risperidone.

## **Aripiprazole**

In a large double-blind, placebo-controlled multicenter trial of aripiprazole for the treatment of schizophrenia in adolescents ([Findling et al. 2008](#)), 302 adolescents were randomly assigned to receive aripiprazole 10 mg/day, aripiprazole 30 mg/day (after 5- or 11-day titration), or placebo over a 6-week period. Both dosages of aripiprazole showed statistically significant differences from placebo on the PANSS total score at week 6. The most common adverse events associated with aripiprazole were EPS, somnolence, and tremor. Early response to aripiprazole at weeks 2 and 3 has been shown to predict later response and remission ([Correll et al. 2013](#)).

## **Quetiapine**

The efficacy of quetiapine in the treatment of schizophrenia in adolescents was evaluated in a 6-week double-blind, placebo-controlled trial in which subjects ( $N=222$ ) were randomly assigned to quetiapine 400 mg/day, quetiapine 800 mg/day, or placebo ([Findling et al. 2012](#)). Both quetiapine dosages were significantly superior to placebo in reduction of total PANSS scores. The most common adverse events with quetiapine were somnolence, headache, and dizziness. Mean changes in body weight, total cholesterol, and total triglycerides were greater in the quetiapine group than the placebo group.

## **Paliperidone Extended Release**

Paliperidone ER was evaluated in a 6-week double-blind, placebo-controlled trial in 201 adolescents (ages 12–17 years) with schizophrenia ([Singh et al. 2011](#)). Paliperidone ER fixed dosing was weight based; youth weighing 29 kg to less than 51 kg received 1.5 mg, 3 mg, or 6 mg/day, whereas patients weighing at least 51 kg received 1.5 mg, 6 mg, or 12 mg/day. With weight-based treatment, only the medium dosage range (3–6 mg/day) showed significant improvement compared with placebo. The fixed dosages of 3 mg/day, 6 mg/day, and 12 mg/day were also superior to placebo. Somnolence, akathisia, insomnia, headache, and tremor were the most common adverse events in the paliperidone ER group.

The long-term safety of paliperidone ER was evaluated in a 2-year open-label study for 400 adolescents with schizophrenia ([Savitz et al. 2015](#)). The most frequently reported treatment-emergent adverse events were increased weight, headache, insomnia, nasopharyngitis, akathisia, schizophrenia exacerbation, and tremor. There were no clinically significant changes in weight or BMI. Hyperprolactinemia was found in 56% of patients, and 9.3% had prolactin-related adverse events. The most common EPS-related adverse events were parkinsonism (15.5%) and hyperkinesia (13.8%).

## **Ziprasidone**

The efficacy of ziprasidone was evaluated in a 6-week double-blind, placebo-controlled trial for 283 adolescents ages 13–17 years with schizophrenia ([Findling et al. 2013](#)). Ziprasidone was flexibly dosed (40–160 mg/day). There was no significant difference between ziprasidone and placebo on change from baseline to endpoint on the BPRS-Anchored. The most common adverse events in the

ziprasidone group were somnolence and EPS. During the 26-week open-label follow-up, there were no clinically significant changes in metabolic indices and laboratory measures.

## Asenapine

The efficacy of asenapine was assessed in an 8-week double-blind, placebo-controlled trial for adolescents ages 12–17 years with schizophrenia ([Findling et al. 2015a](#)). Asenapine dosing was 2.5 mg bid or 5 mg bid. Asenapine was not significantly superior to placebo on the primary efficacy measure of change from baseline to endpoint on the PANSS total score. Weight gain  $\geq 7\%$ , somnolence, sedation, and hypersomnia were more common in the asenapine group than the placebo group. Adverse events of akathisia, fasting glucose elevation, and EPS were more common in the asenapine 5 mg bid group than the placebo group. Those youth who showed improvement during the acute phase maintained improvement in the 26-week open-label extension.

## Clozapine

A 6-week double-blind, placebo-controlled comparison of clozapine and haloperidol was conducted in 21 children and adolescents (ages 6–18 years) with schizophrenia ([Kumra et al. 1996](#)). Clozapine (mean dosage=176 mg/day; range=25–525 mg/day) was significantly superior to haloperidol (mean dosage=16 mg/day; range=7–27 mg/day) in reducing positive and negative symptoms of schizophrenia. Clozapine improved interpersonal functioning and enabled patients to live in a less restrictive setting. Side effects, however, were significant with



clozapine. One patient had a seizure, and three patients were given anticonvulsants after they became more irritable and aggressive and experienced epileptiform changes on electroencephalogram (EEG). Mild to moderate neutropenia, weight gain, and sinus tachycardia were the other major side effects.

## Comparison of Atypical Antipsychotics

In a 12-week open-label trial, risperidone (mean dosage=1.6 mg/day) was compared with olanzapine (mean dosage=8.2 mg/day) in the treatment of 25 children with schizophrenia ([Mozes et al. 2006](#)). Both treatment groups showed similar significant improvement as measured by PANSS total and subscale scores.

In an 8-week double-blind study, 50 children and adolescents (ages 8–19 years) with psychotic disorders were randomly assigned to receive risperidone (mean dosage=4 mg/day), olanzapine (mean dosage=12.3 mg/day), or haloperidol (mean dosage=5 mg/day) ([Sikich et al. 2004](#)). Eighty-eight percent of patients treated with olanzapine, 74% treated with risperidone, and 53% treated with haloperidol met response criteria (CGI-I scores of much or very much improved and at least a 20% reduction in BPRS-C total score).

Clozapine was compared with olanzapine in an 8-week double-blind randomized trial ([Shaw et al. 2006](#)). Twenty-five youths (ages 7–16 years) with schizophrenia that was resistant to treatment with at least two antipsychotics participated in the trial. Clozapine (mean dosage=327 mg/day) showed significant improvement on all outcome

measures, whereas olanzapine (mean dosage=19.1 mg/day) showed improvement on some outcome measures. Improvement in negative symptoms was significantly greater for the clozapine group.

In an 8-week double-blind trial comparing olanzapine and risperidone against the typical antipsychotic molindone in 116 children and adolescents with early-onset schizophrenia or schizoaffective disorder ([Sikich et al. 2008](#)), no significant differences were observed in rates of response (CGI-I score  $\leq 2$ , and  $\geq 20\%$  reduction in PANSS total score) among the treatment groups (risperidone 46%, olanzapine 34%, and molindone 50%). Significantly greater weight gain occurred with olanzapine and risperidone than with molindone.

A double-blind maintenance study followed this acute controlled trial in children and adolescents with early-onset schizophrenia or schizoaffective disorder ([Findling et al. 2010](#)). Of the 54 youths eligible for the maintenance phase, 14 (26%) completed 44 weeks of treatment. No significant differences were found among olanzapine, risperidone, and molindone in reduction of symptoms or time to discontinuation.

In an 8-week double-blind trial comparing paliperidone ER and aripiprazole in 228 adolescents with schizophrenia ([Savitz et al. 2015](#)), there was no significant difference between the paliperidone ER group and the aripiprazole group on change in PANSS scores from baseline to endpoint. Both medication groups showed improvement in symptoms and functional outcomes.

## Typical Antipsychotics

## Haloperidol

Haloperidol has been compared with placebo and other typical antipsychotics in controlled trials in youth. In a 10-week double-blind, placebo-controlled crossover study, the safety and efficacy of haloperidol were assessed in 12 hospitalized children (ages 5–12 years) with schizophrenia. Haloperidol (optimal dosage range=0.5–3.5 mg/day) was significantly superior to placebo in improving overall clinical functioning and reducing ideas of reference, delusions, and hallucinations. Common side effects were acute dystonic reaction, drowsiness, and dizziness ([Spencer et al. 1992](#)).

Haloperidol and loxapine were compared in a 4-week double-blind, placebo-controlled study of 75 adolescent inpatients with schizophrenia. Both haloperidol and loxapine were significantly superior to placebo, and there was no significant difference in efficacy between the two medications. Response rates (based on CGI-I scores) were 87.5% for loxapine, 70% for haloperidol, and 36.4% for placebo. Common side effects were sedation, EPS, and somnolence ([Pool et al. 1976](#)).

## Thiothixene

Thiothixene was compared with thioridazine in a 6-week single-blind study in 21 adolescent inpatients with schizophrenia. Thiothixene (optimal mean dosage=16.2 mg/day) and thioridazine (optimal mean dosage=178 mg/day) were equally effective in controlling symptoms, although most of the adolescents continued to be quite impaired. Thiothixene was less sedating than thioridazine ([Realmuto et al. 1984](#)). Thiothixene was also compared with trifluoperazine in an 8-week double-blind study of 16

children (ages 8–15 years) with schizophrenia ([Wolpert et al. 1967](#)). The effects of both medications were similar in terms of decreasing avoidance behavior, reducing stereotypic behavior, and increasing peer socialization.

## Clinical Recommendations for Schizophrenia

Both typical and atypical antipsychotics have demonstrated effectiveness in the treatment of schizophrenia in youth, although the sample sizes have been small in the trials of typical antipsychotics. Because fewer EPS and instances of tardive dyskinesia have been reported with atypical antipsychotics, it would be reasonable to initiate treatment with an atypical antipsychotic for a child with schizophrenia. It is important to monitor weight and metabolic parameters for children who receive atypical antipsychotics. Clozapine should be considered for treatment-resistant schizophrenia ([McClellan et al. 2013](#)).

Antipsychotics should be administered at adequate dosages for a period of 6 weeks to assess efficacy. If there is no response or if intolerable side effects occur, a trial of a different antipsychotic should be initiated ([American Academy of Child and Adolescent Psychiatry 2012](#)).

No data are available to guide maintenance treatment. Because the majority of youth will have a second psychotic episode within 5–7 years of stabilization, there is a significant risk of relapse with medication withdrawal ([Kumra 2000](#)). Maintenance treatment should be provided to most youth with schizophrenia to improve functioning and prevent relapse ([American Academy of Child and Adolescent Psychiatry 2012](#)). The aim is to use the lowest

effective dosage of medication to reduce the risk of adverse events. For those youth with prolonged remission, it may be possible to discontinue medication, but long-term monitoring will be necessary because of possible reemergence of psychotic symptoms.

---

## Autism Spectrum Disorder

---

Autism spectrum disorder is a new DSM-5 disorder that encompasses the previous DSM-IV ([American Psychiatric Association 1994](#)) categories of autistic disorder (autism), Asperger's disorder, and pervasive developmental disorder not otherwise specified. Symptoms of autism spectrum disorder represent a continuum of mild to severe impairments in two core domains: 1) deficits in social communication and social interaction and 2) restricted repetitive patterns of behavior, interests, and activities ([American Psychiatric Association 2013](#)). Associated behavioral features include hyperactivity, stereotypies, attentional problems, self-injurious behavior, aggression, mood lability, anxiety, obsessions, and compulsions. Autism spectrum disorder is estimated to have a prevalence of up to 18.7 per 10,000 population ([Howlin 2000](#)). The majority of children with the disorder will continue to have significant social and communication impairments throughout adulthood ([Buitelaar and Willemsen-Swinkels 2000](#)).

## Atypical Antipsychotics

For the treatment of irritability associated with autism spectrum disorder, the FDA has approved risperidone (for patients  $\geq 5$  years old) and aripiprazole ( $\geq 6$  years old). Olanzapine, quetiapine, and ziprasidone have been studied for autism spectrum disorders but do not have FDA approval for use in youth.

## Risperidone

One hundred one children (ages 5–17 years) with DSM-IV-defined autistic disorder participated in an 8-week double-blind, placebo-controlled trial of risperidone (dosage range=0.5–3.5 mg/day; mean dosage=1.8 mg/day) ([McCracken et al. 2002](#)). A significantly greater positive response (defined as a 25% decrease on the irritability subscale of the Aberrant Behavior Checklist [ABC] and a rating of much or very much improved on the CGI-I) was found for the risperidone group (69%) than the placebo group (12%). Adverse events of increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group. Mean weight gain was 2.7 kg in the risperidone group and 0.8 kg in the placebo group. An 18-month follow-up showed that the majority of subjects who responded to risperidone during intermediate-length treatment continued to show improvement ([McDougle et al. 2005](#)).

In a 24-month follow-up of 84 of these youths, there was continued improvement in maladaptive behavior from baseline ([Aman et al. 2015](#)). Social skills improved and irritability decreased for those youths who were taking risperidone at follow-up. Risperidone treatment was associated with enuresis, excessive appetite, and weight gain.

In an 8-week double-blind, placebo-controlled trial, 79 children (ages 5-12 years) with a DSM-IV diagnosis of autistic or other pervasive developmental disorder were randomly assigned to receive either placebo or risperidone (mean dosage=1.5 mg/day). Risperidone-treated patients exhibited a 64% improvement over baseline irritability, compared with a 30.7% improvement in subjects receiving placebo ([Shea et al. 2004](#)).

In a 6-month placebo-controlled study of 40 children (ages 2-9 years) with autism, risperidone (1 mg/day) decreased aggressiveness, hyperactivity, and irritability and improved social responsiveness and nonverbal communication. Appetite increase, weight gain, sedation, and transient dyskinesias were reported in the risperidone-treated children ([Nagaraj et al. 2006](#)).

The long-term effects of risperidone were assessed in youths (ages 5-17 years) with autism spectrum disorder ([Troost et al. 2005](#)). Twenty-four youths received risperidone for 6 months, followed by a double-blind discontinuation to placebo or continued risperidone. Risperidone was superior to placebo in preventing relapse, with relapse rates of 25% and 75%, respectively.

In a double-blind, placebo-controlled risperidone dosing study for 96 youths (ages 5-17 years), high-dosage risperidone (1.25 mg/day for youths weighing 20 to <45 kg; 1.75 mg/day for youths weighing  $\geq$ 45 kg) was significantly superior to placebo in baseline-to-endpoint change in score on the ABC Irritability subscale ([Kent et al. 2013b](#)). There was no significant difference, however, between scores of patients given low-dosage risperidone (0.125 mg/day for youths weighing 20 to <45 kg; 0.175 mg/day for youths weighing  $\geq$ 45 kg) and scores of patients given placebo. In an open-label extension study with flexibly dosed

risperidone, all groups showed additional improvement in efficacy scores ([Kent et al. 2013a](#)).

The comparative efficacy of risperidone and haloperidol was assessed in an 8-week double-blind trial that included 30 children and adolescents with DSM-IV autistic disorder ([Miral et al. 2008](#)). Risperidone produced significantly greater reductions in scores on the ABC as well as on other scales used to assess symptoms of autism. An open-label continuation study ([Gencer et al. 2008](#)) of this controlled trial showed that risperidone-treated patients had greater improvement than haloperidol-treated patients on CGI ratings and on the ABC.

In a 24-week randomized trial, combined treatment of risperidone and PT was compared with risperidone alone for the treatment of severe behavioral problems in 124 children with autism spectrum disorder ([Scahill et al. 2012](#)). Combined treatment was superior to medication alone in reduction of noncompliant behavior as assessed by the Home Situation Questionnaire (HSQ). In a 1-year follow-up, there was no significant difference between treatment groups on noncompliant behavior ([Arnold et al. 2012](#)).

## **Aripiprazole**

The efficacy of aripiprazole in the treatment of irritability was evaluated in 218 children and adolescents with DSM-IV autistic disorder in an 8-week double-blind, placebo-controlled trial ([Marcus et al. 2009](#)). Aripiprazole dosages were 5, 10, or 15 mg/day. Compared with placebo, all aripiprazole dosages produced significantly greater improvement on mean scores on the ABC Irritability subscale. The most common adverse events were sedation, tremor, and somnolence. The efficacy of aripiprazole was assessed in another 8-week double-blind, placebo-



controlled trial that included 98 children and adolescents with DSM-IV autistic disorder ([Owen et al. 2009](#)). Aripiprazole dosages were 5, 10, or 15 mg/day. Significantly greater improvements in mean scores on the ABC Irritability subscale were seen with aripiprazole versus placebo. Rates of EPS-related adverse events were 14.9% with aripiprazole and 8% with placebo.

Long-term maintenance treatment with aripiprazole was examined in a double-blind, placebo-controlled relapse-prevention trial for 86 youths with autism spectrum disorder ([Findling et al. 2014](#)). There was no statistically significant difference in time to relapse between aripiprazole and placebo. Relapse rates at week 16 were 35% for the aripiprazole group and 52% for the placebo group.

The efficacy of aripiprazole and risperidone were compared in a 2-month randomized, double-blind trial that included 59 children and adolescents with autism spectrum disorder ([Ghanizadeh et al. 2014](#)). Both aripiprazole and risperidone groups had lower scores on the ABC; there was no statistically significant difference between these medications.

## **Olanzapine**

The efficacy of olanzapine was evaluated in an 8-week double-blind, placebo-controlled trial that included 11 children and adolescents with pervasive developmental disorders ([Hollander et al. 2006](#)). Rates of response (CGI-I score  $\leq 2$ ) were 50% for olanzapine-treated patients and 20% for placebo-treated patients. Olanzapine-treated patients experienced significantly greater weight gain (mean 7.5 lbs for olanzapine vs. 1.5 lbs for placebo-treated patients).

In a 12-week open-label study of olanzapine (mean dosage=7.8 mg/day) in eight patients (ages 5-42 years) with DSM-IV autistic disorder or pervasive developmental disorder not otherwise specified, the six patients who completed the trial showed much or very much global improvement ([Potenza et al. 1999](#)). Significant improvements were found in hyperactivity, social relatedness, affectual responses, sensory responses, language usage, self-injurious behavior, aggression, irritability, anxiety, and depression. The most significant adverse effects were increased appetite and weight gain in six patients and sedation in three patients.

In a 3-month open study of olanzapine (dosage range=1.25-20 mg/day) in 25 subjects (ages 6-16 years) with pervasive developmental disorder, significant global improvement was reported. The most common side effect was weight gain (mean=4.8 kg) ([Kemner et al. 2002](#)).

Olanzapine was compared with haloperidol in a 6-week open trial in 12 children (ages 4-11 years) with DSM-IV autistic disorder ([Malone et al. 2001](#)). Both the olanzapine treatment (mean dosage=7.9 mg/day) and the haloperidol treatment (mean dosage=1.4 mg/day) reduced symptoms of social withdrawal and stereotypies and improved speech and object relations.

## Quetiapine

The effectiveness of quetiapine (dosage range=100-350 mg/day) was assessed in a 16-week open-label trial in six children with DSM-IV autistic disorder ([Martin et al. 1999](#)). No significant behavioral improvements were found from baseline to endpoint.

In a 12-week open-label study of quetiapine in nine adolescents (mean age=14.6 years) with DSM-IV autistic

disorder, only two patients were much or very much improved at study endpoint ([Findling et al. 2004](#)).

## **Ziprasidone**

The efficacy of ziprasidone was evaluated in a 6-week open-label study in 12 adolescents with autism ([Malone et al. 2007](#)). Ziprasidone dosages ranged from 20 mg/day to 160 mg/day (mean dosage=98.3 mg/day). Of the 12 patients, 9 (75%) were considered treatment responders (based on CGI-I scores  $\leq 2$ ). The mean change in QTc from baseline to endpoint was 14.7, which was a statistically significant increase. There was no significant weight change.

The efficacy and safety of ziprasidone in children, adolescents, and young adults with autism were evaluated in an open-label study in which 12 patients (ages 8–20 years) were treated with ziprasidone (mean daily dosage=59.23 mg) for at least 6 weeks ([McDougale et al. 2002](#)). Fifty percent of patients were responders based on a CGI rating of much improved or very much improved. Transient sedation was the most common side effect.

# **Typical Antipsychotics**

## **Haloperidol**

Haloperidol has been the most widely studied typical antipsychotic for the treatment of autism in children and adolescents. In double-blind, placebo-controlled studies, haloperidol has been shown to be significantly superior to placebo in reducing maladaptive behaviors and facilitating learning on discrimination tasks ([Campbell et al. 1982](#)); in increasing retention of discrimination learning and

decreasing maladaptive behaviors in the classroom ([Anderson et al. 1984](#)); in decreasing occurrence of stereotypies and increasing orienting reactions of children ([Cohen et al. 1980](#)); and in decreasing hyperactivity, temper tantrums, withdrawal, and stereotypies and increasing relatedness ([Anderson et al. 1989](#)). Optimal dosages of haloperidol in these studies ranged from 0.25 to 4 mg/day. The most common side effects were sedation, increased irritability, and acute dystonic reactions. Weight gain was modest (0.2 kg) in autistic children who received haloperidol 0.25–3.5 mg/day for a 6-month period ([Silva et al. 1993](#)).

The long-term efficacy of haloperidol was assessed in 48 children (ages 2–8 years) with autism who received haloperidol for 6 months ([Perry et al. 1989](#)). Haloperidol remained effective throughout the 6-month treatment period, and it was equally effective whether it was given continuously or on a discontinuous schedule consisting of 5 days on haloperidol and 2 days on placebo. Children who had symptoms of irritability, angry and labile affect, and uncooperativeness were the best responders to haloperidol.

## Serotonin Reuptake Inhibitors

### Fluoxetine

The efficacy of liquid fluoxetine in treating repetitive behaviors in autism was assessed in 45 children and adolescents with autism spectrum disorder. Subjects were randomly assigned to two 8-week acute phases in a double-blind crossover study ([Hollander et al. 2005](#)). Low-dosage liquid fluoxetine (mean dosage=9.9 mg/day) was superior to placebo in reducing repetitive behaviors.

In an open study of fluoxetine (dosage range=20 mg every other day to 80 mg/day) in 23 patients (ages 7-28 years) with autistic disorder, 15 patients (65%) experienced significant clinical global improvement ([Cook et al. 1992](#)). The most common side effects were restlessness, hyperactivity, agitation, decreased appetite, and insomnia.

## **Fluvoxamine**

A double-blind, placebo-controlled study of fluvoxamine treatment (mean dosage=106.9 mg/day) in 34 children and adolescents with DSM-IV autistic disorder did not find significant clinical improvement with fluvoxamine ([McDougle et al. 2000](#)).

## **Sertraline**

Open-label sertraline (dosage range=25-50 mg/day) was administered to nine children with DSM-IV autistic disorder ([Steingard et al. 1997](#)). Eight of the nine patients showed clinically significant improvement in ability to tolerate changes in their routine or environment without displaying symptoms of anxiety, irritability, or agitation.

## **Citalopram**

The efficacy of citalopram was evaluated for treatment of repetitive behavior in children with autism spectrum disorder ([King et al. 2009](#)). One hundred forty-nine children and adolescents with autism spectrum disorder were randomly assigned to receive citalopram or placebo in a 12-week controlled trial. The mean dosage of citalopram at endpoint was 16.5 mg/day. There was no significant difference in rates of response (CGI-I score  $\leq 2$ ) between citalopram-treated patients (39.2%) and placebo-treated

patients (34.2%). No difference was found in reduction in CY-BOCS scores between the citalopram group and the placebo group. Adverse events that were significantly more common in the citalopram group were increased energy level, impulsiveness, hyperactivity, stereotypy, decreased concentration, diarrhea, insomnia, and dry skin or pruritus.

## **Escitalopram**

In a 10-week open-label study, 28 children and adolescents (ages 6–17 years) with pervasive developmental disorder received escitalopram. There was significant improvement in irritability and clinical global functioning. Twenty-five percent of youths responded at escitalopram daily dosages less than 10 mg, and 36% of youths responded at dosages greater than or equal to 10 mg ([Owley et al. 2005](#)).

# **Other Antidepressants**

## **Clomipramine**

Controlled trials with clomipramine in the treatment of autism spectrum disorder have yielded mixed results. Clomipramine and haloperidol were compared in a placebo-controlled crossover study for 7 weeks with active treatment ([Remington et al. 2001](#)). Thirty-six patients (ages 10–36 years) with DSM-IV autistic disorder were randomly assigned to clomipramine (mean dosage=128.4 mg/day; range=100–150 mg/day), haloperidol (mean dosage=1.3 mg/day; range=1–1.5 mg/day), or placebo. A significant advantage for haloperidol was found on global measures of autism symptom severity and on specific measures of irritability and hyperactivity. Clomipramine was comparable

to haloperidol only among patients who were able to complete a full therapeutic trial. However, significantly fewer patients receiving clomipramine versus haloperidol were able to complete the trial (37.5% vs. 69.7%, respectively) for reasons related to inefficacy, side effects, or behavioral problems.

## **Mirtazapine**

In an open-label study of mirtazapine (dosage range=7.5–45 mg/day; mean=30.3 mg/day) in 26 patients (ages 3–23 years) with pervasive developmental disorders, 9 patients (34.6%) were judged much or very much improved in symptoms of aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia ([Posey et al. 2001](#)). Mirtazapine did not improve symptoms of social or communication impairment. Common side effects included increased appetite, irritability, and transient sedation.

## **Venlafaxine**

The effectiveness of venlafaxine was assessed in an open retrospective study of 10 patients (ages 3–21 years) with pervasive developmental disorders ([Hollander et al. 2000](#)). Six of 10 patients who received venlafaxine (mean dosage=24.4 mg/day; range=6.25–50 mg/day) over an average of 5 months were much or very much improved. Improvements were observed in repetitive behaviors, restricted interests, social deficits, communication and language function, inattention, and hyperactivity. Side effects of venlafaxine included behavioral activation, nausea, inattention, and polyuria.

## **Reboxetine**

Eleven adolescents with autism spectrum disorder with depressive and ADHD symptoms were treated with reboxetine (maximum dosage 4 mg/day) in a 12-week open-label trial ([Golubchik et al. 2013](#)). Significant, but modest, decreases in depressive and ADHD symptoms were found with reboxetine treatment. Irritability and insomnia were adverse events.

## Anticonvulsants

### Lamotrigine

Twenty-eight children (ages 3–11 years) with DSM-IV autistic disorder participated in a double-blind, placebo-controlled study of lamotrigine (mean main-maintenance dosage=5 mg/kg/day) for a 12-week study period ([Belsito et al. 2001](#)). There were no significant differences between the lamotrigine and placebo groups on severity of behavioral symptoms. Insomnia and hyperactivity were the most frequently reported side effects. No children in the study were withdrawn because of rash.

### Valproate

Three double-blind, placebo-controlled trials have been conducted to assess the efficacy of valproate in the treatment of autism spectrum disorder. In one 8-week trial with 13 children, divalproex was superior to placebo in improvement in repetitive behaviors ([Hollander et al. 2006](#)). In another 8-week trial that included 27 youths with autism spectrum disorder, divalproex significantly reduced symptoms of irritability compared with placebo ([Hollander et al. 2010](#)). However, valproate was not superior to



placebo in reduction of aggression and irritability for 30 youths with pervasive developmental disorders who participated in an 8-week trial ([Hellings et al. 2005](#)).

## **Oxcarbazepine**

In a retrospective case series of 30 youths (ages 5–21 years) with autism spectrum disorder, 14 patients (47%) who were treated with oxcarbazepine (mean final dosage=1,360 mg/day) had CGI-I scores of 2 or lower on ratings of irritability/agitation symptoms ([Douglas et al. 2013](#)).

## **Levetiracetam**

A 10-week double-blind, placebo-controlled trial was conducted to assess the efficacy of levetiracetam in the treatment of 20 children with autism ([Wasserman et al. 2006](#)). The mean maximum dosage of levetiracetam was 862.50 mg/day. There were no significant differences between levetiracetam and placebo on measures of global improvement of autism, aggression and affective instability, and impulsivity and hyperactivity.

# **Other Agents**

## **Lithium**

In a retrospective chart review of 30 children with autism spectrum disorder who were treated with lithium (mean blood level 0.70 mEq/L), 13 youths (43%) were rated as improved on the CGI-I ([Siegel et al. 2014](#)). Vomiting, tremor, fatigue, irritability, and enuresis were the most common adverse effects.

## Clonidine

A double-blind, placebo-controlled crossover study of transdermal clonidine (0.005 mg/kg/day or placebo by a weekly transdermal patch) in nine patients (ages 5–33 years) with autistic disorder was conducted for a total active period of 8 weeks ([Fankhauser et al. 1992](#)). Significant improvement with clonidine, compared with placebo, was found on measures of social relationship, affectual responses, and sensory responses. In a double-blind, placebo-controlled crossover trial of clonidine in eight children with autistic disorder, clonidine was found to be modestly effective in reducing irritability and hyperactivity ([Jaselskis et al. 1992](#)).

## Guanfacine Extended Release

The efficacy of GXR was assessed in an 8-week randomized, placebo-controlled trial that included 62 children with autism spectrum disorder ([Scahill et al. 2015](#)). The GXR modal dose at week 8 was 3 mg/day. The GXR group showed significantly greater decline (43.6%) in scores on the ABC Hyperactivity subscale compared with the placebo group (13.2%). The most common adverse events were drowsiness, fatigue, and decreased appetite.

## Methylphenidate

A meta-analysis of four methylphenidate trials for treatment of ADHD symptoms in children with pervasive developmental disorders showed an effect size of 0.67 ([Reichow et al. 2013](#)). The most likely adverse events were decreased appetite, insomnia, depressive symptoms, irritability, and social withdrawal. Use of an extended-release methylphenidate formulation has also been shown to

reduce hyperactive and impulsive behavior in children with autism spectrum disorder and ADHD symptoms ([Pearson et al. 2013](#)).

## **Atomoxetine**

Atomoxetine as a treatment for symptoms of ADHD in children and adolescents with autism spectrum disorder was examined in a double-blind, placebo-controlled 8-week trial that included 97 youths ([Harfterkamp et al. 2012](#)). The atomoxetine dosage was 1.2 mg/kg/day. There was a statistically significant difference between atomoxetine and placebo on change from baseline to endpoint ADHD-RS-IV scores. Adverse effects of nausea, decrease in appetite, fatigue, and early morning awakening were more common in the atomoxetine group than in the placebo group. In a subsequent analysis, atomoxetine did not improve social functioning, but there was some improvement on stereotyped behaviors, inappropriate speech, and fear of change ([Harfterkamp et al. 2014](#)).

In a placebo-controlled crossover trial that included 16 youths with autism spectrum disorder and ADHD symptoms, atomoxetine was superior to placebo in reduction of hyperactivity and impulsivity symptoms as measured on the ABC ([Arnold et al. 2006](#)).

Long-term efficacy and tolerability of atomoxetine were assessed in a 20-week follow-up of an 8-week controlled trial for 88 youths with autism spectrum disorder and autism ([Harfterkamp et al. 2013](#)). Continued treatment with atomoxetine resulted in further improvement of ADHD symptoms. Adverse events, particularly nausea and fatigue, diminished over time with continued treatment.

## **N-Acetylcysteine**

The efficacy of NAC in the treatment of behavioral disturbance was assessed in 33 children with autism in a 12-week double-blind, placebo-controlled trial ([Hardan et al. 2012](#)). The NAC dosage was titrated up to 900 mg three times daily. Compared with placebo, NAC resulted in significant improvement on scores on the ABC Irritability subscale. The most common adverse effects were constipation, nausea and vomiting, and diarrhea. One participant treated with NAC had worsening agitation and irritability and was removed from the study.

## **Bumetanide**

The efficacy of bumetanide for the treatment of 60 children with autism spectrum disorder was evaluated in a 3-month double-blind, placebo-controlled trial ([Lemonnier et al. 2012](#)). The bumetanide dosage was 1 mg/day. Bumetanide was significantly superior to placebo in reduction of symptoms on the primary outcome measure, the Childhood Autism Rating Scale (CARS). Occasional mild hypokalemia was an adverse event.

## **Intranasal Oxytocin**

Intranasal oxytocin has been examined as a treatment for autism spectrum disorder in controlled trials and a long-term open-label study. Oxytocin nasal spray (18 or 24 international units [IU]) or placebo was administered to 16 youths with autism spectrum disorder in a double-blind, placebo-controlled crossover design ([Guastella et al. 2010](#)). Compared with placebo, oxytocin significantly improved emotion recognition.

In a double-blind, placebo-controlled trial, 36 male youths with autism spectrum disorder received 24 or 12 IU of

oxytocin or placebo over a 4-day period ([Dadds et al. 2014](#)). There were no significant differences between intranasal oxytocin and placebo on measures of social interaction skills, repetitive behaviors, and emotion recognition.

In a 7-month open-label study, intranasal oxytocin was administered (8- to 24-IU dose every 2 months) to eight male youths with autism spectrum disorder ([Tachibana et al. 2013](#)). Six of eight youths showed improvement in communication and social interaction on the Autism Diagnostic Observation Schedule—Generic (ADOS-G).

## **Arbaclofen**

The efficacy of arbaclofen was assessed in a 12-week double-blind, placebo-controlled trial that included 150 children, adolescents, and young adults ([Delahunty et al. 2013](#)). Arbaclofen was titrated to a maximum of 10 mg three times daily for youths ages 5–11 years and 15 mg three times daily for youths ages 12–21 years. There was no significant difference between arbaclofen and placebo in improving lethargy or social withdrawal.

# **Adjunctive Treatments**

## **Memantine**

Memantine as adjunctive treatment to risperidone for autism spectrum disorder was assessed in a 10-week double-blind, placebo-controlled trial for 40 children ([Ghaleiha et al. 2013a](#)). The dosage of memantine was titrated to 20 mg/day, and the risperidone dosage was titrated to 3 mg/day. Compared with the placebo group, the group that received adjunctive memantine had a

significantly greater reduction in the Irritability score on the ABC—Community version. There was no significant difference in adverse effects between the groups.

## **Amantadine**

Amantadine as adjunctive treatment to risperidone for treatment of 40 children with autism spectrum disorder was evaluated in a 10-week double-blind, placebo-controlled trial ([Mohammadi et al. 2013](#)). Amantadine was titrated to 100–150 mg/day, and risperidone was titrated to 1–2 mg/day. Compared with the placebo group, the adjunctive amantadine group had a significantly greater reduction in Hyperactivity and Irritability scores on the ABC—Community version. There were no significant adverse effects among the groups.

## **Riluzole**

The efficacy of riluzole as adjunctive treatment to risperidone was assessed in a 10-week double-blind, placebo-controlled trial for 40 children with autism spectrum disorder ([Ghaleiha et al. 2013b](#)). Riluzole was titrated to 50–100 mg/day, and risperidone was titrated to 2–3 mg/day. Significantly greater improvement in irritability, as assessed by the ABC—Community version, was found for the adjunctive riluzole group than the placebo group. Increased appetite and weight gain were more common in the riluzole group than the placebo group.

## **Buspirone**

Buspirone as adjunctive treatment to risperidone was evaluated in an 8-week double-blind, placebo-controlled trial for 40 youths with autism ([Ghanizadeh and](#)

[Ayoozbadehshirazi 2015](#)). The mean dosage of buspirone was 6.7 mg/day. Compared with the placebo group, the adjunctive buspirone group showed a significantly greater reduction in the Irritability subscale score of the ABC—Community version. The most common adverse events in the buspirone group were increased appetite, drowsiness, and fatigue.

## **Celecoxib**

Adjunctive treatment with celecoxib to risperidone was evaluated in a 10-week double-blind, placebo-controlled trial that included 40 children with autism ([Asadabadi et al. 2013](#)). Celecoxib was titrated to 300 mg/day and risperidone to 3 mg/day. Adjunctive celecoxib was superior to placebo in reducing irritability, social withdrawal, and stereotypy as measured on the ABC—Community version.

## **Pentoxifylline**

The efficacy of adjunctive pentoxifylline to risperidone was assessed in a 10-week double-blind, placebo-controlled trial that included 40 children with a DSM-IV-TR ([American Psychiatric Association 2000](#)) diagnosis of autistic disorder ([Akhondzadeh et al. 2010](#)). Pentoxifylline was titrated to 600 mg/day, and risperidone was titrated to 3 mg/day. Adjunctive pentoxifylline was superior to placebo in reducing scores on the ABC—Community version subscales for irritability, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech. There was no significant difference between the groups in adverse events.

## **N-Acetylcysteine**

NAC as adjunctive treatment to risperidone for treatment of irritability in autism spectrum disorder has been evaluated in two double-blind, placebo-controlled studies. In a 10-week study that included 40 children with autism spectrum disorder, the NAC dosage was 600–900 mg/day ([Nikoo et al. 2015](#)). In an 8-week study that included 40 children with autism spectrum disorder, the NAC dosage was 1,200 mg/day ([Ghanizadeh and Moghimi-Sarani 2013](#)). Adjunctive NAC was superior to placebo in the reduction of irritability as assessed by the ABC in both studies.

## Clinical Recommendations for Autism Spectrum Disorder

Although there is no evidence that pharmacotherapy is effective in treating the core social and communication deficits in autism spectrum disorder, medications have been shown to be useful in treating associated symptoms, such as hyperactivity, inattention, stereotypies, self-injurious behavior, tantrums, aggression, mood lability, and anxiety. Antipsychotics may decrease withdrawal, stereotypies, and aggression and may facilitate learning. To date, most available data support the use of risperidone or aripiprazole for treating irritability, aggression, self-injurious behavior, temper tantrums, and mood lability associated with autism spectrum disorder in children and adolescents. Serotonin reuptake inhibitors and other antidepressants have been shown to reduce compulsions, anxiety, and depression in children with autism spectrum disorder. Other agents that may be beneficial to treat associated symptoms are  $\alpha_2$  agonists, stimulants, mood



stabilizers, and norepinephrine reuptake inhibitors ([Volkmar et al. 2014](#)).

Limited data are available on the long-term use of pharmacotherapy in children with autism spectrum disorder. After receiving an intermediate-length (4- to 6-month) course of treatment with risperidone, children withdrawn from the medication through placebo substitution had high relapse rates ([Research Units on Pediatric Psychopharmacology Autism Network 2005](#); [Troost et al. 2005](#)). Therefore, clinicians must weigh the risk-benefit ratio of maintenance medication treatment in this population and carefully monitor children for side effects.

---

## References

---

- Actavis: Saphris (asenapine) sublingual tablets, full prescribing information. Revised January 2017. Irvine, CA, Allergan USA, Inc., 2017. Available at: [http://www.allergan.com/assets/pdf/saphris\\_pi](http://www.allergan.com/assets/pdf/saphris_pi). Accessed January 2017.
- Akhondzadeh S, Fallah J, Mohammadi MR, et al: Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. *Prog Neuropsychopharmacol Biol Psychiatry* 34(1):32-36, 2010 19772883
- Allen AJ, Kurlan RM, Gilbert DL, et al: Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology* 65(12):1941-1949, 2005 16380617
- Aman MG, De Smedt G, Derivan A, et al; Risperidone Disruptive Behavior Study Group: Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry* 159(8):1337-1346, 2002 12153826
- Aman MG, Binder C, Turgay A: Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. *J Child Adolesc Psychopharmacol* 14(2):243-254, 2004 15319021
- Aman MG, Bukstein OG, Gadow KD, et al: What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? *J Am Acad Child Adolesc Psychiatry* 53(1):47-60, 2014 24342385
- Aman M, Rettiganti M, Nagaraja HN, et al: Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. *J Child Adolesc Psychopharmacol* 25(6):482-493, 2015 26262903
- American Academy of Child and Adolescent Psychiatry: Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 51(1):98-113, 2012 22176943
- American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity: Consensus

- development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 27(2):596-601, 2004 14747245
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1984
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Association, 2013
- Anderson JC, Williams S, McGee R, et al: DSM-III disorders in preadolescent children: prevalence in a large sample from the general population. *Arch Gen Psychiatry* 44(1):69-76, 1987 2432848
- Anderson LT, Campbell M, Grega DM, et al: Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. *Am J Psychiatry* 141(10): 1195-1202, 1984 6385731
- Anderson LT, Campbell M, Adams P, et al: The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *J Autism Dev Disord* 19(2):227-239, 1989 2663834
- Armenteros JL, Lewis JE, Davalos M: Risperidone augmentation for treatment-resistant aggression in attention-deficit/hyperactivity disorder: a placebo-controlled pilot study. *J Am Acad Child Adolesc Psychiatry* 46(5):558-565, 2007 17450046
- Arnold LE: Methylphenidate vs amphetamine: comparative review. *J Atten Disord* 3(4):200-211, 2000
- Arnold LE, Aman MG, Cook AM, et al: Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry* 45(10):1196-1205, 2006 17003665
- Arnold LE, Aman MG, Li X, et al: Research Units of Pediatric Psychopharmacology (RUPP) autism network randomized clinical trial of parent training and medication: one-year follow-up. *J Am Acad Child Adolesc Psychiatry* 51(11):1173-1184, 2012 23101743
- Asadabadi M, Mohammadi MR, Ghanizadeh A, et al: Celecoxib as adjunctive treatment to risperidone in children with autistic

- disorder: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology (Berl)* 225(1):51-59, 2013 22782459
- Atkinson SD, Prakash A, Zhang Q, et al: A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 24(4):180-189, 2014 24813026
- Barbey JT, Roose SP: SSRI safety in overdose. *J Clin Psychiatry* 59 (suppl 15):42-48, 1998 9786310
- Barkley RA: *Attention Deficit Hyperactivity Disorder: A Clinical Handbook*, 3rd Edition. New York, Guilford, 2005
- Barrickman LL, Perry PJ, Allen AJ, et al: Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 34(5):649-657, 1995 7775360
- Beidel DC, Turner SM, Sallee FR, et al: SET-C versus fluoxetine in the treatment of childhood social phobia. *J Am Acad Child Adolesc Psychiatry* 46(12):1622-1632, 2007 18030084
- Belsito KM, Law PA, Kirk KS, et al: Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord* 31(2): 175-181, 2001 11450816
- Berard R, Fong R, Carpenter DJ, et al: An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 16(1-2):59-75, 2006 16553529
- Bernstein GA, Borchardt CM, Perwien AR: Anxiety disorders in children and adolescents: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 35(9): 1110-1119, 1996 8824054
- Biederman J, Spencer TJ: Psychopharmacological interventions. *Child Adolesc Psychiatr Clin N Am* 17(2):439-458, xi, 2008 18295155
- Biederman J, Faraone SV, Marrs A, et al: Panic disorder and agoraphobia in consecutively referred children and adolescents. *J Am Acad Child Adolesc Psychiatry* 36(2):214-223, 1997 9031574
- Biederman J, Mick E, Hammerness P, et al: Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. *Biol Psychiatry* 58(7):589-594, 2005 16239162
- Biederman J, Mick E, Surman C, et al: A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 59(9):829-835, 2006a 16373066

- Biederman J, Wigal SB, Spencer TJ, et al: A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-age girls with attention-deficit/hyperactivity disorder. *Clin Ther* 28(2):280-293, 2006b 16678649
- Biederman J, Melmed RD, Patel A, et al; SPD503 Study Group: A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics* 121(1):e73-e84, 2008 18166547
- Biederman J, Joshi G, Mick E, et al: A prospective open-label trial of lamotrigine monotherapy in children and adolescents with bipolar disorder. *CNS Neurosci Ther* 16(2):91-102, 2010 20415838
- Birmaher B, Arbelaez C, Brent D: Course and outcome of child and adolescent major depressive disorder. *Child Adolesc Psychiatr Clin N Am* 11(3):619-637, x, 2002 12222086
- Birmaher B, Axelson DA, Monk K, et al: Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 42(4):415-423, 2003 12649628
- Blader JC, Schooler NR, Jensen PS, et al: Adjunctive divalproex versus placebo for children with ADHD and aggression refractory to stimulant monotherapy. *Am J Psychiatry* 166(12):1392-1401, 2009 19884222
- Brent D, Emslie G, Clarke G, et al: Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA* 299(8):901-913, 2008 18314433
- Bridge JA, Iyengar S, Salary CB, et al: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 297(15):1683-1696, 2007 17440145
- Bristol-Myers Squibb: BuSpar (buspirone hydrochloride tablets), full prescribing information. Revised November 2010. Princeton, NJ, Bristol-Myers Squibb Company, 2010. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/018731s051lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018731s051lbl.pdf). Accessed March 2, 2016.
- Bruggeman R, van der Linden C, Buitelaar JK, et al: Risperidone versus pimozide in Tourette's disorder: a comparative double-

- blind parallel-group study. *J Clin Psychiatry* 62(1):50-56, 2001 11235929
- Buitelaar JK, Willemsen-Swinkels SH: Medication treatment in subjects with autistic spectrum disorders. *Eur Child Adolesc Psychiatry* 9 (suppl 1):I85-I97, 2000 11140783
- Buitelaar JK, van der Gaag RJ, Cohen-Kettenis P, et al: A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities (comment). *J Clin Psychiatry* 62(4):239-248, 2001 11379837
- Bymaster FP, Katner JS, Nelson DL, et al: Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 27(5):699-711, 2002 12431845
- Campbell M, Anderson LT, Small AM, et al: The effects of haloperidol on learning and behavior in autistic children. *J Autism Dev Disord* 12(2):167-175, 1982 7174605
- Campbell M, Small AM, Green WH, et al: Behavioral efficacy of haloperidol and lithium carbonate. A comparison in hospitalized aggressive children with conduct disorder. *Arch Gen Psychiatry* 41(7):650-656, 1984 6428371
- Campbell M, Adams PB, Small AM, et al: Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 34(4): 445-453, 1995 7751258
- Cantwell DP, Swanson J, Connor DF: Case study: adverse response to clonidine. *J Am Acad Child Adolesc Psychiatry* 36(4):539-544, 1997 9100429
- Chappell PB, Riddle MA, Scahill L, et al: Guanfacine treatment of comorbid attention-deficit hyperactivity disorder and Tourette's syndrome: preliminary clinical experience. *J Am Acad Child Adolesc Psychiatry* 34(9):1140-1146, 1995 7559307
- Charach A, Figueroa M, Chen S, et al: Stimulant treatment over 5 years: effects on growth. *J Am Acad Child Adolesc Psychiatry* 45(4):415-421, 2006 16601646
- Chavira DA, Stein MB: Combined psychoeducation and treatment with selective serotonin reuptake inhibitors for youth with generalized social anxiety disorder. *J Child Adolesc Psychopharmacol* 12(1): 47-54, 2002 12014595
- Clark DB, Birmaher B, Axelson D, et al: Fluoxetine for the treatment of childhood anxiety disorders: open-label, long-term extension to

- a controlled trial. *J Am Acad Child Adolesc Psychiatry* 44(12):1263-1270, 2005 16292118
- Clarke GN, Sack WH, Ben R, et al: English language skills in a group of previously traumatized Khmer adolescent refugees. *J Nerv Ment Dis* 181(7):454-456, 1993 8320549
- Cohen IL, Campbell M, Posner D, et al: Behavioral effects of haloperidol in young autistic children. An objective analysis using a within-subjects reversal design. *J Am Acad Child Psychiatry* 19(4):665-677, 1980 7204797
- Cohen JA, Mannarino AP, Perel JM, et al: A pilot randomized controlled trial of combined trauma-focused CBT and sertraline for childhood PTSD symptoms. *J Am Acad Child Adolesc Psychiatry* 46(7):811-819, 2007 17581445
- Cohen JA, Bukstein O, Walter H, et al; AACAP Work Group On Quality Issues: Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. *J Am Acad Child Adolesc Psychiatry* 49(4):414-430, 2010 20410735
- Comings DE, Himes JA, Comings BG: An epidemiologic study of Tourette's syndrome in a single school district. *J Clin Psychiatry* 51(11):463-469, 1990 2228981
- Compton SN, Grant PJ, Chrisman AK, et al: Sertraline in children and adolescents with social anxiety disorder: an open trial. *J Am Acad Child Adolesc Psychiatry* 40(5):564-571, 2001 11349701
- Conners CK, Casat CD, Gualtieri CT, et al: Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 35(10):1314-1321, 1996 8885585
- Connor DF, Fletcher KE, Swanson JM: A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 38(12):1551-1559, 1999 10596256
- Connor DF, Barkley RA, Davis HT: A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. *Clin Pediatr (Phila)* 39(1):15-25, 2000 10660814
- Connor DF, Glatt SJ, Lopez ID, et al: Psychopharmacology and aggression, I: a meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD. *J Am Acad Child Adolesc Psychiatry* 41(3):253-261, 2002 11886019
- Connor DF, Grasso DJ, Slivinsky MD, et al: An open-label study of guanfacine extended release for traumatic stress related symptoms in children and adolescents. *J Child Adolesc Psychopharmacol* 23(4):244-251, 2013 23683139

- Cook EH Jr, Rowlett R, Jaselskis C, et al: Fluoxetine treatment of children and adults with autistic disorder and mental retardation. *J Am Acad Child Adolesc Psychiatry* 31(4):739-745, 1992 1644739
- Cook EH, Wagner KD, March JS, et al: Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 40(10):1175-1181, 2001 11589530
- Correll CU, Carlson HE: Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 45(7):771-791, 2006 16832314
- Correll CU, Penzner JB, Parikh UH, et al: Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. *Child Adolesc Psychiatr Clin N Am* 15(1):177-206, 2006 16321730
- Correll CU, Sheridan EM, DelBello MP: Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord* 12(2):116-141, 2010 20402706
- Correll CU, Zhao J, Carson W, et al: Early antipsychotic response to aripiprazole in adolescents with schizophrenia: predictive value for clinical outcomes. *J Am Acad Child Adolesc Psychiatry* 52(7):689.e3-698.e3, 2013 23800482
- Cummings DD, Singer HS, Krieger M, et al: Neuropsychiatric effects of guanfacine in children with mild Tourette syndrome: a pilot study. *Clin Neuropharmacol* 25(6): 325-332, 2002 12469007
- da Costa CZ, de Morais RM, Zanetta DM, et al: Comparison among clomipramine, fluoxetine, and placebo for the treatment of anxiety disorders in children and adolescents. *J Child Adolesc Psychopharmacol* 23(10):687-692, 2013 24350814
- Dadds MR, MacDonald E, Cauchi A, et al: Nasal oxytocin for social deficits in childhood autism: a randomized controlled trial. *J Autism Dev Disord* 44(3):521-531, 2014 23888359
- Davanzo PA, McCracken JT: Mood stabilizers in the treatment of juvenile bipolar disorder. *Advances and controversies. Child Adolesc Psychiatr Clin N Am* 9(1):159-182, 2000 10674195
- Davies L, Stern JS, Agrawal N, Robertson MM: A case series of patients with Tourette's syndrome in the United Kingdom treated with aripiprazole. *Hum Psychopharmacol* 21(7):447-453, 2006 17029306



- Daviss WB, Bentivoglio P, Racusin R, et al: Bupropion sustained release in adolescents with comorbid attention-deficit/hyperactivity disorder and depression. *J Am Acad Child Adolesc Psychiatry* 40(3): 307-314, 2001 11288772
- Delahunty C, Walton-Bowen K, Kuriyama N, et al: Randomized, controlled, phase 2 trial of STX209 (Arbaclofen) for social function in ASD. Paper presented at the American Academy of Pediatrics (AAP) 2013 National Conference and Exhibition, Orlando, FL, October 26-29, 2013
- DelBello MP, Kowatch RA: Pharmacological interventions for bipolar youth: developmental considerations. *Dev Psychopathol* 18(4):1231-1246, 2006 17064436
- DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SML: A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 41(10):1216-1223, 2002 12364843
- DelBello MP, Findling RL, Kushner S, et al: A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44(6):539-547, 2005 15908836
- DelBello MP, Kowatch RA, Adler CM, et al: A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 45(3):305-313, 2006 16540815
- DelBello MP, Findling RL, Earley WR, et al: Efficacy of quetiapine in children and adolescents with bipolar mania: a 3-week, double-blind, randomized, placebo-controlled trial. Presented at the 46th Annual Meeting of the American College of Neuropsychopharmacology, Boca Raton, FL, December 9-13, 2007
- DelBello MP, Findling R, Wang RP, et al: Safety and efficacy of ziprasidone in pediatric bipolar disorder. Presented at the 63rd Annual Meeting of the Society of Biological Psychiatry, Washington, DC, May 1-3, 2008
- DelBello MP, Hochadel TJ, Portland KB, et al: A double-blind, placebo-controlled study of selegiline transdermal system in depressed adolescents. *J Child Adolesc Psychopharmacol* 24(6):311-317, 2014 24955812
- DeVaugh-Geiss J, Moroz G, Biederman J, et al: Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive

- disorder—a multicenter trial. *J Am Acad Child Adolesc Psychiatry* 31(1):45-49, 1992 1537780
- Dickstein DP, Towbin KE, Van Der Veen JW, et al: Randomized double-blind placebo-controlled trial of lithium in youths with severe mood dysregulation. *J Child Adolesc Psychopharmacol* 19(1):61-73, 2009 19232024
- Dion Y, Annable L, Sandor P, et al: Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 22(1):31-39, 2002 11799340
- Donovan SJ, Stewart JW, Nunes EV, et al: Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. *Am J Psychiatry* 157(5):818-820, 2000 10784478
- Douglas JF, Sanders KB, Benneyworth MH, et al: Brief report: retrospective case series of oxcarbazepine for irritability/agitation symptoms in autism spectrum disorder. *J Autism Dev Disord* 43(5):1243-1247, 2013 22976374
- Douglass HM, Moffitt TE, Dar R, et al: Obsessive-compulsive disorder in a birth cohort of 18-year-olds: prevalence and predictors. *J Am Acad Child Adolesc Psychiatry* 34(11):1424-1431, 1995 8543509
- Du YS, Li HF, Vance A, et al: Randomized double-blind multicentre placebo-controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders. *Aust N Z J Psychiatry* 42(9):807-813, 2008 18696285
- Eggers C, Bunk D: The long-term course of childhood-onset schizophrenia: a 42-year followup. *Schizophr Bull* 23(1):105-117, 1997 9050117
- Emslie GJ, Rush AJ, Weinberg WA, et al: A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 54(11):1031-1037, 1997 9366660
- Emslie GJ, Wagner KD, Riddle M, et al: Efficacy and safety of paroxetine in juvenile OCD. Poster presented at the 153rd annual meeting of the American Psychiatric Association, Chicago, IL, May 13-18, 2000
- Emslie GJ, Heiligenstein JH, Wagner KD, et al: Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 41(10):1205-1215, 2002 12364842
- Emslie GJ, Wagner KD, Kutcher S, et al: Paroxetine treatment in children and adolescents with major depressive disorder: a

- randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 45(6):709-719, 2006 16721321
- Emslie GJ, Findling RL, Yeung PP, et al: Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry* 46(4):479-488, 2007 17420682
- Emslie GJ, Ventura D, Korotzer A, et al: Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry* 48(7):721-729, 2009 19465881
- Emslie GJ, Prakash A, Zhang Q, et al: A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 24(4):170-179, 2014 24815533
- Famularo R, Kinscherff R, Fenton T: Propranolol treatment for childhood posttraumatic stress disorder, acute type. A pilot study. *Am J Dis Child* 142(11):1244-1247, 1988 3177336
- Fankhauser MP, Karumanchi VC, German ML, et al: A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. *J Clin Psychiatry* 53(3):77-82, 1992 1548248
- Farrell LJ, Waters AM, Boschen MJ, et al: Difficult-to-treat pediatric obsessive-compulsive disorder: feasibility and preliminary results of a randomized pilot trial of D-cycloserine-augmented behavior therapy. *Depress Anxiety* 30(8):723-731, 2013 23722990
- Fenichel R: Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 5(3):155-156, 1995
- Findling RL, Ginsberg LD: The safety and effectiveness of open-label extended-release carbamazepine in the treatment of children and adolescents with bipolar I disorder suffering from a manic or mixed episode. *Neuropsychiatr Dis Treat* 10: 1589-1597, 2014 25210452
- Findling RL, McNamara NK, Gracious BL, et al: Combination lithium and divalproex sodium in pediatric bipolarity. *J Am Acad Child Adolesc Psychiatry* 42(8):895-901, 2003 12874490
- Findling RL, McNamara NK, Gracious BL, et al: Quetiapine in nine youths with autistic disorder. *J Child Adolesc Psychopharmacol* 14(2):287-294, 2004 15319025
- Findling RL, McNamara NK, Youngstrom EA, et al: Double-blind 18-month trial of lithium versus divalproex maintenance treatment in

- pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44(5):409-417, 2005 15843762
- Findling RL, Reed MD, O'Riordan MA, et al: Effectiveness, safety, and pharmacokinetics of quetiapine in aggressive children with conduct disorder. *J Am Acad Child Adolesc Psychiatry* 45(7):792-800, 2006 16832315
- Findling RL, Robb A, Nyilas M, et al: A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *Am J Psychiatry* 165(11): 1432-1441, 2008 18765484
- Findling RL, Nyilas M, Forbes RA, et al: Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 70(10):1441-1451, 2009 19906348
- Findling RL, Johnson JL, McClellan J, et al: Double-blind maintenance safety and effectiveness findings from the Treatment of Early Onset Schizophrenia Spectrum (TEOSS) study. *J Am Acad Child Adolesc Psychiatry* 49(6):583-594, quiz 632, 2010 20494268
- Findling RL, McKenna K, Earley WR, et al: Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol* 22(5):327-342, 2012 23083020
- Findling RL, Cavuş I, Pappadopulos E, et al: Ziprasidone in adolescents with schizophrenia: results from a placebo-controlled efficacy and long-term open-extension study. *J Child Adolesc Psychopharmacol* 23(8):531-544, 2013 24111983
- Findling RL, Mankoski R, Timko K, et al: A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry* 75(1):22-30, 2014 24502859
- Findling RL, Landbloom RP, Mackle M, et al: Safety and efficacy from an 8-week double-blind trial and a 26-week open-label extension of asenapine in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol* 25(5):384-396, 2015a 26091193
- Findling RL, Robb A, McNamara NK, et al: Lithium in the acute treatment of bipolar I disorder: a double-blind, placebo-controlled study. *Pediatrics* 136(5):885-894, 2015b 26459650
- Flament MF, Rapoport JL, Berg CJ, et al: Clomipramine treatment of childhood obsessive-compulsive disorder. A double-blind

- controlled study. Arch Gen Psychiatry 42(10):977-983, 1985 3899048
- Fristad MA, Goldberg-Arnold JS, Gavazzi SM: Multi-family psychoeducation groups in the treatment of children with mood disorders. J Marital Fam Ther 29(4):491-504, 2003 14593691
- Gaffney GR, Perry PJ, Lund BC, et al: Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 41(3):330-336, 2002 11886028
- Geller B, Cooper TB, Sun K, et al: Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 37(2):171-178, 1998 9473913
- Geller B, Zimerman B, Williams M, et al: Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 10(3):157-164, 2000 11052405
- Geller B, Tillman R, Craney JL, et al: Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 61(5):459-467, 2004 15123490
- Geller B, Luby JL, Joshi P, et al: A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. Arch Gen Psychiatry 69(5):515-528, 2012 22213771
- Geller DA, Hoog SL, Heiligenstein JH, et al; Fluoxetine Pediatric OCD Study Team: Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. J Am Acad Child Adolesc Psychiatry 40(7):773-779, 2001 11437015
- Geller DA, Wagner KD, Emslie G, et al: Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry 43(11):1387-1396, 2004 15502598
- Gelperin K: Psychiatric adverse events associated with drug treatment of ADHD: review of postmarketing safety data. U.S. Food and Drug Administration Pediatric Advisory Committee, March 22, 2006. Available at:

[http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b\\_11\\_01\\_AdverseEvents.pdf](http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_11_01_AdverseEvents.pdf). Accessed March 3, 2016.

- Gencer O, Emiroglu FN, Miral S, et al: Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder. An open label maintenance study. *Eur Child Adolesc Psychiatry* 17(4):217-225, 2008 18026891
- Ghaleiha A, Asadabadi M, Mohammadi MR, et al: Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. *Int J Neuropsychopharmacol* 16(4):783-789, 2013a 22999292
- Ghaleiha A, Mohammadi E, Mohammadi MR, et al: Riluzole as an adjunctive therapy to risperidone for the treatment of irritability in children with autistic disorder: a double-blind, placebo-controlled, randomized trial. *Paediatr Drugs* 15(6): 505-514, 2013b 23821414
- Ghanizadeh A, Ayoobzadehshirazi A: A randomized double-blind placebo-controlled clinical trial of adjuvant buspirone for irritability in autism. *Pediatr Neurol* 52(1):77-81, 2015 25451017
- Ghanizadeh A, Moghimi-Sarani E: A randomized double blind placebo controlled clinical trial of N-acetylcysteine added to risperidone for treating autistic disorders. *BMC Psychiatry* 13:196, 2013 23886027
- Ghanizadeh A, Sahraeizadeh A, Berk M: A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev* 45(2):185-192, 2014 23801256
- Gibbons RD, Hur K, Bhaumik DK, et al: The relationship between antidepressant prescription rates and rate of early adolescent suicide. *Am J Psychiatry* 163(11):1898-1904, 2006 17074941
- Gilbert DL, Batterson JR, Sethuraman G, et al: Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. *J Am Acad Child Adolesc Psychiatry* 43(2):206-214, 2004 14726728
- Glod CA, Lynch A, Flynn E, et al: Bupropion SR in the treatment of adolescent depression. Poster presented at the 40th Annual Meeting of the New Clinical Drug Evaluation Unit, Boca Raton, FL, 2000
- Golubchik P, Sever J, Weizman A: Reboxetine treatment for autistic spectrum disorder of pediatric patients with depressive and

- inattentive/hyperactive symptoms: an open-label trial. *Clin Neuropharmacol* 36(2):37-41, 2013 23503544
- Goodyer IM, Dubicka B, Wilkinson P, et al: A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. *Health Technol Assess* 12(14):iii-iv, ix-60, 2008 18462573
- Grant PJ, Joseph LA, Farmer CA, et al: 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. *Neuropsychopharmacology* 39(6):1453-1459, 2014 24356715
- Green WH: *Child and Adolescent Clinical Psychopharmacology*, 3rd Edition. Philadelphia, PA, Lippincott Williams & Wilkins, 2001
- Greenhill L, Halperin JM, Abikoff H: Stimulant medications. *J Am Acad Child Adolesc Psychiatry* 38(5):503-512, 1999 10230181
- Greenhill L, Kollins S, Abikoff H, et al: Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry* 45(11):1284-1293, 2006 17023867
- Guastella AJ, Einfeld SL, Gray KM, et al: Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry* 67(7):692-694, 2010 19897177
- Günther T, Herpertz-Dahlmann B, Jolles J, et al: The influence of risperidone on attentional functions in children and adolescents with attention-deficit/hyperactivity disorder and co-morbid disruptive behavior disorder. *J Child Adolesc Psychopharmacol* 16(6):725-735, 2006 17201616
- Haas M, Unis AS, Copenhaver M, et al: Efficacy and safety of risperidone in adolescents with schizophrenia. Presented at the 160th Annual Meeting of the American Psychiatric Association, San Diego, CA, May 19-24, 2007
- Haas M, Delbello MP, Pandina G, et al: Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. *Bipolar Disord* 11(7):687-700, 2009 19839994
- Hamilton BE, Miniño AM, Martin JA, et al: Annual summary of vital statistics: 2005. *Pediatrics* 119(2):345-360, 2007 17272625
- Hammerness PG, Vivas FM, Geller DA: Selective serotonin reuptake inhibitors in pediatric psychopharmacology: a review of the evidence. *J Pediatr* 148(2):158-165, 2006 16492422

- Hardan AY, Fung LK, Libove RA, et al: A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. *Biol Psychiatry* 71(11):956-961, 2012 22342106
- Harfterkamp M, van de Loo-Neus G, Minderaa RB, et al: A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 51(7):733-741, 2012 22721596
- Harfterkamp M, Buitelaar JK, Minderaa RB, et al: Long-term treatment with atomoxetine for attention-deficit/hyperactivity disorder symptoms in children and adolescents with autism spectrum disorder: an open-label extension study. *J Child Adolesc Psychopharmacol* 23(3):194-199, 2013 23578015
- Harfterkamp M, Buitelaar JK, Minderaa RB, et al: Atomoxetine in autism spectrum disorder: no effects on social functioning; some beneficial effects on stereotyped behaviors, inappropriate speech, and fear of change. *J Child Adolesc Psychopharmacol* 24(9):481-485, 2014 25369243
- Harmon RJ, Riggs PD: Clonidine for posttraumatic stress disorder in preschool children. *J Am Acad Child Adolesc Psychiatry* 35(9):1247-1249, 1996 8824068
- Hazaray E, Ehret J, Posey DJ, et al: Intramuscular ziprasidone for acute agitation in adolescents. *J Child Adolesc Psychopharmacol* 14(3):464-470, 2004 15650504
- Hazell PL, Stuart JE: A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. *J Am Acad Child Adolesc Psychiatry* 42(8):886-894, 2003 12874489
- Hellings JA, Nickel EJ, Weckbaugh M, et al: The Overt Aggression Scale for rating aggression in outpatient youth with autistic disorder: preliminary findings. *J Neuropsychiatry Clin Neurosci* 17(1):29-35, 2005 15746480
- Hollander E, Kaplan A, Cartwright C, et al: Venlafaxine in children, adolescents, and young adults with autism spectrum disorders: an open retrospective clinical report. *J Child Neurol* 15(2):132-135, 2000 10695900
- Hollander E, Phillips A, Chaplin W, et al: A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology* 30(3):582-589, 2005 15602505



- Hollander E, Wasserman S, Swanson EN, et al: A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *J Child Adolesc Psychopharmacol* 16(5):541-548, 2006 17069543
- Hollander E, Chaplin W, Soorya L, et al: Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology* 35(4):990-998, 2010 20010551
- Horrigan JP, Barnhill LJ: Risperidone and explosive aggressive autism. *J Autism Dev Disord* 27(3):313-323, 1997 9229261
- Howlin P: Autism and intellectual disability: diagnostic and treatment issues. *J R Soc Med* 93(7):351-355, 2000 10928021
- Hughes CW, Emslie GJ, Crismon MJ, et al: The Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. *J Am Acad Child Adolesc Psychiatry* 46(6):667-686, 2007 17513980
- Hunt RD, Capper L, O'Connell P: Clonidine in child and adolescent psychiatry. *J Child Adolesc Psychopharmacol* 1(1):87-102, 1990 19630604
- Hunt RD, Arnsten AF, Asbell MD: An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 34(1):50-54, 1995 7860456
- Isolan L, Pheula G, Salum GA Jr, et al: An open-label trial of escitalopram in children and adolescents with social anxiety disorder. *J Child Adolesc Psychopharmacol* 17(6):751-760, 2007 18315447
- Jain R, Segal S, Kollins SH, et al: Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 50(2):171-179, 2011 21241954
- Jaselskis CA, Cook EH Jr, Fletcher KE, et al: Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol* 12(5):322-327, 1992 1479049
- Kang H, Zhang YF, Jiao FY, et al: [Efficacy of clonidine transdermal patch for treatment of Tourette's syndrome in children]. *Zhongguo Dang Dai Er Ke Za Zhi* 11(7):537-539, 2009 19650984
- Kappagoda C, Schell DN, Hanson RM, et al: Clonidine overdose in childhood: implications of increased prescribing. *J Paediatr Child Health* 34(6):508-512, 1998 9928640

- Kashani JH, Orvaschel H: Anxiety disorders in mid-adolescence: a community sample. *Am J Psychiatry* 145(8):960-964, 1988 3394880
- Keeshin BR, Strawn JR: Risperidone treatment of an adolescent with severe posttraumatic stress disorder. *Ann Pharmacother* 43(7):1374, 2009 19584378
- Keller MB, Lavori PW, Wunder J, et al: Chronic course of anxiety disorders in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 31(4):595-599, 1992 1644719
- Keller MB, Ryan ND, Strober M, et al: Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 40(7):762-772, 2001 11437014
- Kemner C, Willemsen-Swinkels SH, de Jonge M, et al: Open-label study of olanzapine in children with pervasive developmental disorder. *J Clin Psychopharmacol* 22(5):455-460, 2002 12352267
- Kent JM, Hough D, Singh J, et al: An open-label extension study of the safety and efficacy of risperidone in children and adolescents with autistic disorder. *J Child Adolesc Psychopharmacol* 23(10):676-686, 2013a 24350813
- Kent JM, Kushner S, Ning X, et al: Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev Disord* 43(8):1773-1783, 2013b 23212807
- Kessler RC, Adler L, Barkley R, et al: The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry* 163(4):716-723, 2006 16585449
- Khan SS, Mican LM: A naturalistic evaluation of intramuscular ziprasidone versus intramuscular olanzapine for the management of acute agitation and aggression in children and adolescents. *J Child Adolesc Psychopharmacol* 16(6):671-677, 2006 17201611
- King BH, Hollander E, Sikich L, et al; STAART Psychopharmacology Network: Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry* 66(6):583-590, 2009 19487623
- Kisicki J, Fiske K, Scheckner B, et al: Abrupt cessation of guanfacine extended release in healthy young adults. Presented at the 53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry, San Diego, CA, October 24-29, 2006

- Klein RG, Mannuzza S: Hyperactive boys almost grown up, III: methylphenidate effects on ultimate height. *Arch Gen Psychiatry* 45(12):1131-1134, 1988 3058089
- Klein RG, Abikoff H, Klass E, et al: Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Arch Gen Psychiatry* 54(12):1073-1080, 1997 9400342
- Kofoed L, Tadepalli G, Oesterheld JR, et al: Case series: clonidine has no systematic effects on PR or QTc intervals in children. *J Am Acad Child Adolesc Psychiatry* 38(9):1193-1196, 1999 10504820
- Kollins SH, Jain R, Brams M, et al: Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. *Pediatrics* 127(6):e1406-e1413, 2011 21555501
- Kowatch RA, Carmody TJ, Suppes T, et al: Acute and continuation pharmacological treatment of children and adolescents with bipolar disorders: a summary of two previous studies. *Acta Neuropsychiatr* 12(3):145-149, 2000a 26975276
- Kowatch RA, Suppes T, Carmody TJ, et al: Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 39(6): 713-720, 2000b 10846305
- Kowatch RA, Fristad M, Birmaher B, et al: Treatment guidelines for children and adolescents with bipolar disorders. *J Am Acad Child Adolesc Psychiatry* 44(3):213-235, 2005 15725966
- Kowatch RA, Findling RL, Scheffer RE, et al: Pediatric bipolar collaborative mood stabilizer trial. Presented at the 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Boston, MA, October 23-28, 2007
- Kowatch RA, Scheffer RE, Monroe E, et al: Placebo-controlled trial of valproic acid versus risperidone in children 3-7 years of age with bipolar I disorder. *J Child Adolesc Psychopharmacol* 25(4):306-313, 2015 25978742
- Kramer JR, Loney J, Ponto LB, et al: Predictors of adult height and weight in boys treated with methylphenidate for childhood behavior problems. *J Am Acad Child Adolesc Psychiatry* 39(4):517-524, 2000 10761355
- Krasny L, Williams BJ, Provencal S, et al: Social skills interventions for the autism spectrum: essential ingredients and a model curriculum. *Child Adolesc Psychiatr Clin N Am* 12(1):107-122, 2003 12512401

- Kratochvil CJ, Heiligenstein JH, Dittmann R, et al: Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. *J Am Acad Child Adolesc Psychiatry* 41(7):776-784, 2002 12108801
- Kratochvil CJ, Vaughan BS, Harrington MJ, et al: Atomoxetine: a selective noradrenaline reuptake inhibitor for the treatment of attention-deficit/hyperactivity disorder. *Expert Opin Pharmacother* 4(7):1165-1174, 2003 12831341
- Kryzhanovskaya L, Schulz SC, McDougale C, et al: Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 48(1):60-70, 2009 19057413
- Kumra S: The diagnosis and treatment of children and adolescents with schizophrenia. "My mind is playing tricks on me." *Child Adolesc Psychiatr Clin N Am* 9(1):183-199, x, 2000 10674196
- Kumra S, Frazier JA, Jacobsen LK, et al: Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry* 53(12):1090-1097, 1996 8956674
- Kutcher SP, MacKenzie S: Successful clonazepam treatment of adolescents with panic disorder. *J Clin Psychopharmacol* 8(4):299-301, 1988 3209726
- Law SF, Schachar RJ: Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder? *J Am Acad Child Adolesc Psychiatry* 38(8):944-951, 1999 10434485
- LeBlanc JC, Binder CE, Armenteros JL, et al: Risperidone reduces aggression in boys with a disruptive behaviour disorder and below average intelligence quotient: analysis of two placebo-controlled randomized trials. *Int Clin Psychopharmacol* 20(5):275-283, 2005 16096518
- Leckman JF: Tourette's syndrome. *Lancet* 360(9345):1577-1586, 2002 12443611
- Leckman JF, Hardin MT, Riddle MA, et al: Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 48(4):324-328, 1991 2009034
- Lemonnier E, Degrez C, Phelep M, et al: A randomised controlled trial of bumetanide in the treatment of autism in children. *Transl Psychiatry* 2:e202, 2012 23233021
- Lepola U, Leinonen E, Koponen H: Citalopram in the treatment of early onset panic disorder and school phobia. *Pharmacopsychiatry* 29(1):30-32, 1996 8852532

- Libby AM, Brent DA, Morrato EH, et al: Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *Am J Psychiatry* 164(6):884-891, 2007 17541047
- Liberthson RR: Sudden death from cardiac causes in children and young adults. *N Engl J Med* 334(16):1039-1044, 1996 8598843
- Liebowitz MR, Turner SM, Piacentini J, et al: Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 41(12):1431-1438, 2002 12447029
- Looft D, Grimley P, Kuller F, et al: Carbamazepine for PTSD. *J Am Acad Child Adolesc Psychiatry* 34(6):703-704, 1995 7608041
- Malone RP, Delaney MA, Luebbert JF, et al: A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. *Arch Gen Psychiatry* 57(7):649-654, 2000 10891035
- Malone RP, Cater J, Sheikh RM, et al: Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry* 40(8):887-894, 2001 11501687
- Malone RP, Delaney MA, Hyman SB, et al: Ziprasidone in adolescents with autism: an open-label pilot study. *J Child Adolesc Psychopharmacol* 17(6):779-790, 2007 18315450
- March JS, Biederman J, Wolkow R, et al: Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA* 280(20):1752-1756, 1998 9842950
- March J, Silva S, Petrycki S, et al; Treatment for Adolescents With Depression Study (TADS) Team: Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 292(7):807-820, 2004 15315995
- March JS, Entusah AR, Rynn M, et al: A Randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biol Psychiatry* 62(10):1149-1154, 2007 17553467
- Marcus RN, Owen R, Kamen L, et al: A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry* 48(11):1110-1119, 2009 19797985
- Markowitz S, Cuellar A: Antidepressants and youth: healing or harmful? *Soc Sci Med* 64(10):2138-2151, 2007 17374550
- Martin A, Koenig K, Scahill L, et al: Open-label quetiapine in the treatment of children and adolescents with autistic disorder. *J*

- Child Adolesc Psychopharmacol 9(2):99-107, 1999 10461820
- Masi G, Toni C, Mucci M, et al: Paroxetine in child and adolescent outpatients with panic disorder. J Child Adolesc Psychopharmacol 11(2):151-157, 2001 11436954
- Masi G, Millepiedi S, Perugi G, et al: Pharmacotherapy in paediatric obsessive-compulsive disorder: a naturalistic, retrospective study. CNS Drugs 23(3):241-252, 2009 19320532
- Masi G, Pfanner C, Millepiedi S, et al: Aripiprazole augmentation in 39 adolescents with medication-resistant obsessive-compulsive disorder. J Clin Psychopharmacol 30(6):688-693, 2010 21105283
- McClellan J, Werry J; American Academy of Child and Adolescent Psychiatry: Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry 40 (7 suppl):4S-23S, 2001 11434484
- McClellan J, Kowatch R, Findling RL; Work Group on Quality Issues: Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 46(1):107-125, 2007 17195735
- McClellan J, Stock S; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI): Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry 52(9):976-990, 2013 23972700
- McCracken JT, McGough J, Shah B, et al; Research Units on Pediatric Psychopharmacology Autism Network: Risperidone in children with autism and serious behavioral problems. N Engl J Med 347(5):314-321, 2002 12151468
- McDougle CJ, Kresch LE, Posey DJ: Repetitive thoughts and behavior in pervasive developmental disorders: treatment with serotonin reuptake inhibitors. J Autism Dev Disord 30(5):427-435, 2000 11098879
- McDougle CJ, Kem DL, Posey DJ: Case series: use of ziprasidone for maladaptive symptoms in youths with autism. J Am Acad Child Adolesc Psychiatry 41(8):921-927, 2002 12164181
- McDougle CJ, Scahill L, Aman MG, et al: Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. Am J Psychiatry 162(6):1142-1148, 2005 15930063
- Mei Z, Grummer-Strawn LM, Thompson D, et al: Shifts in percentiles of growth during early childhood: analysis of longitudinal data

- from the California Child Health and Development Study. *Pediatrics* 113(6):e617-e627, 2004 15173545
- Meighen KG, Hines LA, Lagges AM: Risperidone treatment of preschool children with thermal burns and acute stress disorder. *J Child Adolesc Psychopharmacol* 17(2):223-232, 2007 17489717
- Melmed RD, Patel A, Konow J, et al: Efficacy and safety of guanfacine extended release for ADHD treatment. Presented at the 53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry, San Diego, CA, October 24-29, 2006
- Melvin GA, Tonge BJ, King NJ, et al: A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J Am Acad Child Adolesc Psychiatry* 45(10):1151-1161, 2006 17003660
- Melvin GA, Dudley AL, Gordon MS, et al: What happens to depressed adolescents? A follow-up study into early adulthood. *J Affect Disord* 151(1):298-305, 2013 23829999
- Merikangas KR, He JP, Burstein M, et al: Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry* 49(10): 980-989, 2010 20855043
- Messenheimer JA: Rash in adult and pediatric patients treated with lamotrigine. *Can J Neurol Sci* 25(4):S14-S18, 1998 9827240
- Michelson D, Faries D, Wernicke J, et al; Atomoxetine ADHD Study Group: Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics* 108(5):E83, 2001 11694667
- Michelson D, Allen AJ, Busner J, et al: Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry* 159(11):1896-1901, 2002 12411225
- Michelson D, Adler L, Spencer T, et al: Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biol Psychiatry* 53(2):112-120, 2003 12547466
- Miller M, Swanson SA, Azrael D, et al: Antidepressant dose, age, and the risk of deliberate self-harm. *JAMA Intern Med* 174(6):899-909, 2014 24782035
- Miral S, Gencer O, Inal-Emiroglu FN, et al: Risperidone versus haloperidol in children and adolescents with AD: a randomized,

- controlled, double-blind trial. *Eur Child Adolesc Psychiatry* 17(1):1-8, 2008 18080171
- Mohammadi MR, Yadegari N, Hassanzadeh E, et al: Double-blind, placebo-controlled trial of risperidone plus amantadine in children with autism: a 10-week randomized study. *Clin Neuropharmacol* 36(6):179-184, 2013 24201232
- Molina BS, Hinshaw SP, Swanson JM, et al; MTA Cooperative Group: The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry* 48(5):484-500, 2009 19318991
- Mosholder A: Psychiatric adverse events in clinical trials of drugs for attention deficit hyperactivity disorder (ADHD). FDA Report PID D060163. U.S. Food and Drug Administration, March 3, 2006. Available at: [http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b\\_10\\_01\\_Mosholder.pdf](http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_10_01_Mosholder.pdf). Accessed March 4, 2016.
- Mozes T, Ebert T, Michal SE, et al: An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. *J Child Adolesc Psychopharmacol* 16(4): 393-403, 2006 16958565
- MTA Cooperative Group: National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics* 113(4):762-769, 2004 15060225
- Mukaddes NM, Abali O: Quetiapine treatment of children and adolescents with Tourette's disorder. *J Child Adolesc Psychopharmacol* 13(3):295-299, 2003 14642017
- Murphy TK, Bengtson MA, Soto O, et al: Case series on the use of aripiprazole for Tourette syndrome. *Int J Neuropsychopharmacol* 8(3):489-490, 2005 15857570
- Nagaraj R, Singhi P, Malhi P: Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol* 21(6):450-455, 2006 16948927
- Newcorn JH, Spencer TJ, Biederman J, et al: Atomoxetine treatment in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry* 44(3):240-248, 2005 15725968
- Newcorn JH, Kratochvil CJ, Allen AJ, et al; Atomoxetine/Methylphenidate Comparative Study Group: Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute



- comparison and differential response. *Am J Psychiatry* 165(6):721-730, 2008 18281409
- Nikoo M, Radnia H, Farokhnia M, et al: N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. *Clin Neuropharmacol* 38(1):11-17, 2015 25580916
- Nugent NR, Christopher NC, Crow JP, et al: The efficacy of early propranolol administration at reducing PTSD symptoms in pediatric injury patients: a pilot study. *J Trauma Stress* 23(2):282-287, 2010 20419738
- Oluwabusi OO, Sedky K, Bennett DS: Prazosin treatment of nightmares and sleep disturbances associated with posttraumatic stress disorder: two adolescent cases. *J Child Adolesc Psychopharmacol* 22(5):399-402, 2012 23083029
- Owen R, Sikich L, Marcus RN, et al: Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics* 124(6):1533-1540, 2009 19948625
- Owley T, Walton L, Salt J, et al: An open-label trial of escitalopram in pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry* 44(4):343-348, 2005 15782081
- Pandina GJ, Aman MG, Findling RL: Risperidone in the management of disruptive behavior disorders. *J Child Adolesc Psychopharmacol* 16(4):379-392, 2006 16958564
- Pappadopulos E, Macintyre Ii JC, Crismon ML, et al: Treatment recommendations for the use of antipsychotics for aggressive youth (TRAAY), Part II. *J Am Acad Child Adolesc Psychiatry* 42(2):145-161, 2003 12544174
- Pappadopulos E, Woolston S, Chait A, et al: Pharmacotherapy of aggression in children and adolescents: efficacy and effect size. *J Can Acad Child Adolesc Psychiatry* 15(1):27-39, 2006 18392193
- Pavuluri MN, Henry DB, Carbray JA, et al: Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. *J Affect Disord* 82 (suppl 1):S103-S111, 2004 15571784
- Pavuluri MN, Henry DB, Carbray JA, et al: A one-year open-label trial of risperidone augmentation in lithium nonresponder youth with preschool-onset bipolar disorder. *J Child Adolesc Psychopharmacol* 16(3):336-350, 2006 16768641
- Pavuluri MN, Henry DB, Findling RL, et al: Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder.

- Bipolar Disord 12(6):593-605, 2010 20868458
- Pearson DA, Santos CW, Aman MG, et al: Effects of extended release methylphenidate treatment on ratings of attention-deficit/hyperactivity disorder (ADHD) and associated behavior in children with autism spectrum disorders and ADHD symptoms. J Child Adolesc Psychopharmacol 23(5):337-351, 2013 23782128
- Pediatric OCD Treatment Study (POTS) Team: Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA 292(16):1969-1976, 2004 15507582
- Pelham WE Jr, Wheeler T, Chronis A: Empirically supported psychosocial treatments for attention deficit hyperactivity disorder. J Clin Child Psychol 27(2):190-205, 1998 9648036
- Perry R, Campbell M, Adams P, et al: Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. J Am Acad Child Adolesc Psychiatry 28(1):87-92, 1989 2914841
- Pfizer: Pfizer reports top line results from a phase 3 study evaluating desvenlafaxine succinate sustained-release formulation in pediatric patients with major depressive disorder. June 11, 2015. Available at: [http://www.pfizer.com/news/press-release/press-release-detail/pfizer\\_reports\\_top\\_line\\_results\\_from\\_a\\_phase\\_3\\_study\\_evaluating\\_desvenlafaxine\\_succinate\\_sustained\\_release\\_formulation\\_in\\_pediatric\\_patients\\_with\\_major\\_depressive\\_disorder](http://www.pfizer.com/news/press-release/press-release-detail/pfizer_reports_top_line_results_from_a_phase_3_study_evaluating_desvenlafaxine_succinate_sustained_release_formulation_in_pediatric_patients_with_major_depressive_disorder). Accessed March 4, 2016.
- Piacentini JC, Chang SW: Behavioral treatments for tic suppression: habit reversal training. Adv Neurol 99:227-233, 2006 16536370
- Piacentini J, Bennett S, Compton SN, et al: 24- and 36-week outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS). J Am Acad Child Adolesc Psychiatry 53(3):297-310, 2014 24565357
- Pliszka S; AACAP Work Group on Quality Issues: Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 46(7):894-921, 2007 17581453
- Pliszka SR, Carlson CL, Swanson JM: ADHD With Comorbid Disorders: Clinical Assessment and Management. New York, Guilford, 1999

- Pliszka SR, Crismon ML, Hughes CW, et al: Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder: The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 45(6):642-657, 2006a 16721314
- Pliszka SR, Matthews TL, Braslow KJ, et al: Comparative effects of methylphenidate and mixed salts amphetamine on height and weight in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 45(5):520-526, 2006b 16670648
- Pool D, Bloom W, Mielke DH, et al: A controlled evaluation of loxitane in seventy-five adolescent schizophrenic patients. *Curr Ther Res Clin Exp* 19(1):99-104, 1976 812671
- Popper CW: Medical unknowns and ethical consent: prescribing psychotropic medications for children in the face of uncertainty, in *Psychiatric Pharmacosciences of Children and Adolescents*. Edited by Popper CW. Washington, DC, American Psychiatric Press, 1987, pp 127-161
- Popper CW: Pharmacologic alternatives to psychostimulants for the treatment of attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 9(3):605-646, viii, 2000 10944659
- Posey DJ, Guenin KD, Kohn AE, et al: A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 11(3):267-277, 2001 11642476
- Potenza MN, Holmes JP, Kanes SJ, et al: Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. *J Clin Psychopharmacol* 19(1):37-44, 1999 9934941
- Poulton A: Growth on stimulant medication; clarifying the confusion: a review. *Arch Dis Child* 90(8):801-806, 2005 16040876
- Rasgon N: The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *J Clin Psychopharmacol* 24(3):322-334, 2004 15118487
- Realmuto GM, Erickson WD, Yellin AM, et al: Clinical comparison of thiothixene and thioridazine in schizophrenic adolescents. *Am J Psychiatry* 141(3):440-442, 1984 6367494
- Reichow B, Volkmar FR, Bloch MH: Systematic review and meta-analysis of pharmacological treatment of the symptoms of attention-deficit/hyperactivity disorder in children with pervasive

- developmental disorders. *J Autism Dev Disord* 43(10):2435–2441, 2013 23468071
- Reinblatt SP, Walkup JT: Psychopharmacologic treatment of pediatric anxiety disorders. *Child Adolesc Psychiatr Clin N Am* 14(4):877–908, x, 2005 16171707
- Remington G, Sloman L, Konstantareas M, et al: Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol* 21(4):440–444, 2001 11476129
- Renaud J, Birmaher B, Wassick SC, et al: Use of selective serotonin reuptake inhibitors for the treatment of childhood panic disorder: a pilot study. *J Child Adolesc Psychopharmacol* 9(2):73–83, 1999 10461817
- Research Unit on Pediatric Psychopharmacology Anxiety Study Group: Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 344(17):1279–1285, 2001 11323729
- Research Units on Pediatric Psychopharmacology Autism Network: Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry* 162(7):1361–1369, 2005 15994720
- Riddle MA, Bernstein GA, Cook EH, et al: Anxiolytics, adrenergic agents, and naltrexone. *J Am Acad Child Adolesc Psychiatry* 38(5):546–556, 1999 10230186
- Riddle MA, Reeve EA, Yaryura-Tobias JA, et al: Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry* 40(2):222–229, 2001 11211371
- Rifkin A, Karajgi B, Dicker R, et al: Lithium treatment of conduct disorders in adolescents. *Am J Psychiatry* 154(4):554–555, 1997 9090346
- Robb AS, Cueva JE, Sporn J, et al: Sertraline treatment of children and adolescents with posttraumatic stress disorder: a double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol* 20(6):463–471, 2010 21186964
- Roblek T, Piacentini J: Cognitive-behavior therapy for childhood anxiety disorders. *Child Adolesc Psychiatr Clin N Am* 14(4): 863–876, x, 2005 16171706
- Rugino TA, Janvier YM: Aripiprazole in children and adolescents: clinical experience. *J Child Neurol* 20(7):603–610, 2005 16159529

- Rynn MA, Siqueland L, Rickels K: Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry* 158(12):2008-2014, 2001 11729017
- Rynn MA, Findling RL, Emslie GJ, et al: Efficacy and safety of nefazodone in adolescents with MDD. Poster presented at the 155th Annual Meeting of the American Psychiatric Association, Philadelphia, PA, May 18-23, 2002
- Rynn MA, Riddle MA, Yeung PP, et al: Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *Am J Psychiatry* 164(2):290-300, 2007 17267793
- Sallee FR, Nesbitt L, Jackson C, et al: Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 154(8):1057-1062, 1997 9247389
- Sallee FR, Kurlan R, Goetz CG, et al: Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 39(3):292-299, 2000 10714048
- Sallee FR, Lyne A, Wigal T, et al: Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 19(3):215-226, 2009 19519256
- Savitz A, Lane R, Nuamah I, et al: Long-term safety of paliperidone extended release in adolescents with schizophrenia: an open-label, flexible dose study. *J Child Adolesc Psychopharmacol* 25(7):548-557, 2015 26218669
- Saxena K, Silverman MA, Chang K, et al: Baseline predictors of response to divalproex in conduct disorder. *J Clin Psychiatry* 66(12):1541-1548, 2005 16401155
- Scahill L, Chappell PB, Kim YS, et al: A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry* 158(7):1067-1074, 2001 11431228
- Scahill L, Leckman JF, Schultz RT, et al: A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology* 60(7): 1130-1135, 2003 12682319
- Scahill L, McDougle CJ, Aman MG, et al; Research Units on Pediatric Psychopharmacology Autism Network: Effects of risperidone and parent training on adaptive functioning in children with pervasive developmental disorders and serious behavioral problems. *J Am Acad Child Adolesc Psychiatry* 51(2):136-146, 2012 22265360

- Scahill L, McCracken JT, King BH, et al: Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *Am J Psychiatry* 172(12):1197-1206, 2015 26315981
- Scheeringa MS, Weems CF: Randomized placebo-controlled D-cycloserine with cognitive behavior therapy for pediatric posttraumatic stress. *J Child Adolesc Psychopharmacol* 24(2):69-77, 2014 24506079
- Schur SB, Sikich L, Findling RL, et al: Treatment recommendations for the use of antipsychotics for aggressive youth (TRAAY). Part I: a review. *J Am Acad Child Adolesc Psychiatry* 42(2):132-144, 2003 12544173
- Seedat S, Lockhat R, Kaminer D, et al: An open trial of citalopram in adolescents with post-traumatic stress disorder. *Int Clin Psychopharmacol* 16(1):21-25, 2001 11195256
- Seedat S, Stein DJ, Ziervogel C, et al: Comparison of response to a selective serotonin reuptake inhibitor in children, adolescents, and adults with posttraumatic stress disorder. *J Child Adolesc Psychopharmacol* 12(1):37-46, 2002 12014594
- Shapiro E, Shapiro AK, Fulop G, et al: Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 46(8):722-730, 1989 2665687
- Shaw P, Sporn A, Gogtay N, et al: Childhood-onset schizophrenia: a double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry* 63(7):721-730, 2006 16818861
- Shea S, Turgay A, Carroll A, et al: Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics* 114(5):e634-e641, 2004 15492353
- Siegel M, Beresford CA, Bunker M, et al: Preliminary investigation of lithium for mood disorder symptoms in children and adolescents with autism spectrum disorder. *J Child Adolesc Psychopharmacol* 24(7):399-402, 2014 25093602
- Sikich L, Hamer RM, Bashford RA, et al: A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology* 29(1):133-145, 2004 14583740
- Sikich L, Frazier JA, McClellan J, et al: Double-blind comparison of first- and second-generation antipsychotics in early onset schizophrenia and schizoaffective disorder: findings from the treatment of early onset schizophrenia spectrum disorders

- (TEOSS) study. *Am J Psychiatry* 165(11):1420-1431, 2008 18794207
- Silva RR, Malone RP, Anderson LT, et al: Haloperidol withdrawal and weight changes in autistic children. *Psychopharmacol Bull* 29(2):287-291, 1993 8290679
- Simon GE, Savarino J, Operskalski B, et al: Suicide risk during antidepressant treatment. *Am J Psychiatry* 163(1):41-47, 2006 16390887
- Singer HS, Brown J, Quaskey S, et al: The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 95(1):74-81, 1995 7770313
- Singh J, Robb A, Vijapurkar U, et al: A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. *Biol Psychiatry* 70(12):1179-1187, 2011 21831359
- Snyder R, Turgay A, Aman M, et al; Risperidone Conduct Study Group: Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *J Am Acad Child Adolesc Psychiatry* 41(9):1026-1036, 2002 12218423
- Søndergård L, Kvist K, Andersen PK, et al: Do antidepressants precipitate youth suicide? A nationwide pharmacoepidemiological study. *Eur Child Adolesc Psychiatry* 15(4):232-240, 2006 16502208
- Spencer EK, Kafantaris V, Padron-Gayol MV, et al: Haloperidol in schizophrenic children: early findings from a study in progress. *Psychopharmacol Bull* 28(2):183-186, 1992 1513922
- Spencer TJ, Abikoff HB, Connor DF, et al: Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of oppositional defiant disorder with or without comorbid attention-deficit/hyperactivity disorder in school-aged children and adolescents: a 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study. *Clin Ther* 28(3):402-418, 2006a 16750455
- Spencer TJ, Wilens TE, Biederman J, et al: Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of attention-deficit/hyperactivity disorder in adolescent patients: a 4-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 28(2):266-279, 2006b 16678648

- Staller JA: Intramuscular ziprasidone in youth: a retrospective chart review. *J Child Adolesc Psychopharmacol* 14(4):590-592, 2004 15662151
- Stathis S, Martin G, McKenna JG: A preliminary case series on the use of quetiapine for posttraumatic stress disorder in juveniles within a youth detention center. *J Clin Psychopharmacol* 25(6):539-544, 2005 16282834
- Stein MB, Fuetsch M, Müller N, et al: Social anxiety disorder and the risk of depression: a prospective community study of adolescents and young adults. *Arch Gen Psychiatry* 58(3):251-256, 2001 11231832
- Steiner H, Petersen ML, Saxena K, et al: Divalproex sodium for the treatment of conduct disorder: a randomized controlled clinical trial. *J Clin Psychiatry* 64(10):1183-1191, 2003 14658966
- Steingard RJ, Zimnitzky B, DeMaso DR, et al: Sertraline treatment of transition-associated anxiety and agitation in children with autistic disorder. *J Child Adolesc Psychopharmacol* 7(1):9-15, 1997 9192538
- Stentebjerg-Olesen M, Ganocy SJ, Findling RL, et al: Early response or nonresponse at week 2 and week 3 predict ultimate response or nonresponse in adolescents with schizophrenia treated with olanzapine: results from a 6-week randomized, placebo-controlled trial. *Eur Child Adolesc Psychiatry* 24(12):1485-1496, 2015 26032132
- Stephens RJ, Bassel C, Sandor P: Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome—a pilot study. *J Child Adolesc Psychopharmacol* 14(2):255-266, 2004 15319022
- Storch EA, Lehmkuhl H, Geffken GR, et al: Aripiprazole augmentation of incomplete treatment response in an adolescent male with obsessive-compulsive disorder. *Depress Anxiety* 25(2):172-174, 2008 17340610
- Storch EA, Murphy TK, Goodman WK, et al: A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *Biol Psychiatry* 68(11):1073-1076, 2010 20817153
- Storch EA, Bussing R, Small BJ, et al: Randomized, placebo-controlled trial of cognitive-behavioral therapy alone or combined with sertraline in the treatment of pediatric obsessive-compulsive disorder. *Behav Res Ther* 51(12):823-829, 2013 24184429



- Strawn JR, Keeshin BR: Successful treatment of posttraumatic stress disorder with prazosin in a young child. *Ann Pharmacother* 45(12):1590-1591, 2011 22116993
- Strawn JR, Delbello MP, Geraciotti TD: Prazosin treatment of an adolescent with posttraumatic stress disorder. *J Child Adolesc Psychopharmacol* 19(5):599-600, 2009 19877989
- Strawn JR, Prakash A, Zhang Q, et al: A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. *J Am Acad Child Adolesc Psychiatry* 54(4):283-293, 2015a 25791145
- Sumner CS, Donnelly C, Lopez FA, et al: Atomoxetine treatment for pediatric patients with ADHD and comorbid anxiety. Presented at the annual meeting of the American Psychiatric Association, Atlanta, GA, May 2005
- Swanson JM, Flockhart D, Udreá D, et al: Clonidine in the treatment of ADHD: questions about safety and efficacy (letter). *J Child Adolesc Psychopharmacol* 5(4):301-304, 1995a
- Swanson JM, McBurnett L, Christian DL, Wigal T: Stimulant medications and the treatment of children with ADHD, in *Advances in Clinical Child Psychology*, Volume 17. Edited by Ollendick TH, Prinz RJ. New York, Plenum, 1995b, pp 265-322
- Swanson J, Greenhill L, Wigal T, et al: Stimulant-related reductions of growth rates in the PATS. *J Am Acad Child Adolesc Psychiatry* 45(11):1304-1313, 2006 17023868
- Swanson JM, Elliott GR, Greenhill LL, et al; MTA Cooperative Group: Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. *J Am Acad Child Adolesc Psychiatry* 46(8):1015-1027, 2007 17667480
- Tachibana M, Kagitani-Shimono K, Mohri I, et al: Long-term administration of intranasal oxytocin is a safe and promising therapy for early adolescent boys with autism spectrum disorders. *J Child Adolesc Psychopharmacol* 23(2):123-127, 2013 23480321
- Thomsen PH: Child and adolescent obsessive-compulsive disorder treated with citalopram: findings from an open trial of 23 cases. *J Child Adolesc Psychopharmacol* 7(3):157-166, 1997 9466233
- Thomsen PH: Risperidone augmentation in the treatment of severe adolescent OCD in SSRI-refractory cases: a case-series. *Ann Clin Psychiatry* 16(4):201-207, 2004 15702568
- Thomsen PH, Ebbesen C, Persson C: Long-term experience with citalopram in the treatment of adolescent OCD. *J Am Acad Child Adolesc Psychiatry* 40(8):895-902, 2001 11501688

- Tohen M, Kryzhanovskaya L, Carlson G, et al: Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry* 164(10):1547-1556, 2007 17898346
- Tourette's Syndrome Study Group: Long-term experience with citalopram in the treatment of adolescent OCD. *Neurology* 58(4):527-536, 2002 11865128
- Troost PW, Lahuis BE, Steenhuis MP, et al: Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J Am Acad Child Adolesc Psychiatry* 44(11): 1137-1144, 2005 16239862
- U.S. Food and Drug Administration: FDA News: FDA launches a multi-pronged strategy to strengthen safeguards for children treated with antidepressant medication. October 15, 2004a. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108363.htm>. Accessed March 4, 2016.
- U.S. Food and Drug Administration: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Pediatric Advisory Committee: September 13-14, 2004b. Available at: <http://www.fda.gov/oc/advisory/accalendar/2004/cder12544dd09131404.html>. Accessed March 4, 2016.
- U.S. Food and Drug Administration: New warning for Strattera. *ScienceDaily*. December 22, 2004c. Available at: <https://www.sciencedaily.com/releases/2004/12/041219133156.htm>. Accessed March 4, 2016.
- U.S. Food and Drug Administration: FDA Alert [09/05]: Suicidal thinking in children and adolescents. September 2005. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124391.htm>. Accessed March 4, 2016.
- U.S. Food and Drug Administration: Pediatric Advisory Committee briefing information. March 22, 2006. Available at: [http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4210m\\_Minutes%20PAC%20March%2022%202006.pdf](http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4210m_Minutes%20PAC%20March%2022%202006.pdf). Accessed March 4, 2016.
- U.S. Food and Drug Administration: FDA News: FDA proposes new warnings about suicidal thinking, behavior in young adults who take antidepressant medications. May 2, 2007. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108905.htm>. Accessed March 4, 2016.

- Valicenti-McDermott MR, Demb H: Clinical effects and adverse reactions of off-label use of aripiprazole in children and adolescents with developmental disabilities. *J Child Adolesc Psychopharmacol* 16(5):549-560, 2006 17069544
- Villalaba L: Follow-up review of AERS search identifying cases of sudden death occurring with drugs used for the treatment of attention deficit hyper-activity disorder (ADHD). February 28, 2006. Available at: [http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b\\_07\\_01\\_safetyreview.pdf](http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_07_01_safetyreview.pdf). Accessed March 4, 2016.
- Volkmar F, Siegel M, Woodbury-Smith M, et al; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI): Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 53(2):237-257, 2014 24472258
- von Knorring AL, Olsson GI, Thomsen PH, et al: A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol* 26(3):311-315, 2006 16702897
- Wagner KD, Ambrosini P, Rynn M, et al; Sertraline Pediatric Depression Study Group: Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA* 290(8):1033-1041, 2003a 12941675
- Wagner KD, Cook EH, Chung H, et al: Remission status after long-term sertraline treatment of pediatric obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol* 13 (suppl 1):S53-S60, 2003b 12880500
- Wagner KD, Berard R, Stein MB, et al: A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry* 61(11):1153-1162, 2004a 15520363
- Wagner KD, Robb AS, Findling RL, et al: A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry* 161(6):1079-1083, 2004b 15169696
- Wagner KD, Jonas J, Findling RL, et al: A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry* 45(3):280-288, 2006a 16540812

- Wagner KD, Kowatch RA, Emslie GJ, et al: A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry* 163(7):1179-1186, 2006b 16816222
- Wagner KD, Redden L, Kowatch RA, et al: A double-blind, randomized, placebo-controlled trial of divalproex extended-release in the treatment of bipolar disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 48(5):519-532, 2009 19325497
- Walkup JT, Reeve E, Yaryura-Tobias J, et al: Fluvoxamine for childhood OCD: long-term treatment. Poster presented at the 45th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Anaheim, CA, October 27-November 1, 1998
- Walkup J, Labellarte M, Riddle MA, et al; Research Units on Pediatric Psychopharmacology Anxiety Study Group: Treatment of pediatric anxiety disorders: an open-label extension of the research units on pediatric psychopharmacology anxiety study. *J Child Adolesc Psychopharmacol* 12(3):175-188, 2002 12427292
- Walkup JT, Albano AM, Piacentini J, et al: Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med* 359(26):2753-2766, 2008 18974308
- Wasserman S, Iyengar R, Chaplin WF, et al: Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. *Int Clin Psychopharmacol* 21(6):363-367, 2006 17012983
- Weisler RH, Biederman J, Spencer TJ, et al: Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectr* 11(8):625-639, 2006 16871129
- Weisman H, Qureshi IA, Leckman JF, et al: Systematic review: pharmacological treatment of tic disorders—efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neurosci Biobehav Rev* 37(6):1162-1171, 2013 23099282
- Weiss G, Hechtman L: *Hyperactive Children Grown Up*, 2nd Edition. New York, Guilford, 2003
- Wigal SB, McGough JJ, McCracken JT, et al: A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *J Atten Disord* 9(1):275-289, 2005 16371674

- Wigal T, Greenhill L, Chuang S, et al: Safety and tolerability of methylphenidate in preschool children with ADHD. *J Am Acad Child Adolesc Psychiatry* 45(11): 1294-1303, 2006 17028508
- Wilens TE, McBurnett K, Bukstein O, et al: Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med* 160(1):82-90, 2006a 16389216
- Wilens TE, Newcorn JH, Kratochvil CJ, et al: Long-term atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. *J Pediatr* 149(1):112-119, 2006b 16860138
- Wilens TE, Hammerness P, Utzinger L, et al: An open study of adjunct OROS-methylphenidate in children and adolescents who are atomoxetine partial responders: I. Effectiveness. *J Child Adolesc Psychopharmacol* 19(5):485-492, 2009 19877972
- Wilens TE, Bukstein O, Brams M, et al: A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 51(1):74-85.e2, 2012 22176941
- Wolpert A, Hagamen MB, Merlis S: A comparative study of thiothixene and trifluoperazine in childhood schizophrenia. *Curr Ther Res Clin Exp* 9(9):482-485, 1967 4963982
- Yazici KU, Percinel I: The role of glutamatergic dysfunction in treatment-resistant obsessive-compulsive disorder: treatment of an adolescent case with N-acetylcysteine augmentation. *J Child Adolesc Psychopharmacol* 24(9):525-527, 2014 25264963
- Yazici KU, Percinel I: N-acetylcysteine augmentation in children and adolescents diagnosed with treatment-resistant obsessive-compulsive disorder: case series. *J Clin Psychopharmacol* 35(4):486-489, 2015 26066338
- Yoo HK, Kim JY, Kim CY: A pilot study of aripiprazole in children and adolescents with Tourette's disorder. *J Child Adolesc Psychopharmacol* 16(4):505-506, 2006 16958578
- Zheng W, Li XB, Xiang YQ, et al: Aripiprazole for Tourette's syndrome: a systematic review and meta-analysis. *Hum Psychopharmacol* 31(1):11-18, 2016 26310194
- Zhou X, Hetrick SE, Cuijpers P, et al: Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry* 14(2):207-222, 2015 26043339
- Zohar AH: The epidemiology of obsessive-compulsive disorder in children and adolescents. *Child Adolesc Psychiatr Clin N Am*

## Appendix

# Psychotropic Medications Commonly Prescribed for Children and Adolescents

This appendix describes common classes of psychotropic medications used to treat children and adolescents. Dosing information, monitoring schedules, and common side effects are presented for each medication class.

## Antidepressants

### Dosage and Monitoring

The starting dosages and target dosages of antidepressants for children and adolescents are listed in [Table 55-1](#).

**TABLE 55-1. Clinical use of antidepressants in children and adolescents**

Medication	Typical starting dose (mg)		Target dosage (mg/day)
	Child	Adolescent	

*Note.* bid=twice daily.

Medication	Typical starting dose (mg)		Target dosage (mg/day)
	Child	Adolescent	
Selective serotonin reuptake inhibitors			
Citalopram	5-10	10	20-40
Escitalopram	5	10	10-20
Fluoxetine	5-10	10	20-40
Paroxetine	5-10	10	20-40
Sertraline	25	50	100-200
Mirtazapine	15	15	30-45
Venlafaxine	37.5	37.5	150-225
Bupropion	50 bid	50 bid	100-200
Duloxetine	30	30	60-120

*Note.* bid=twice daily.

Premedication laboratory testing should include complete blood count, blood chemistries, and liver function tests. Blood pressure should be monitored during dosage titration with venlafaxine.

The [U.S. Food and Drug Administration \(2007\)](#) issued the following black box warning, which applies to all antidepressants:

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Name of Antidepressant] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24 years; there was a reduction in risk with antidepressants compared with placebo in adults ages 65 years and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored

appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

## Side Effects

Common side effects of selective serotonin reuptake inhibitors (SSRIs) are headache, nausea, abdominal pain, dry mouth, insomnia, and somnolence ([Emslie et al. 2002](#); [Keller et al. 2001](#); [Wagner et al. 2003a, 2004b, 2006a](#)). Potential serious adverse events include serotonin syndrome, extrapyramidal side effects (EPS) (tics, myoclonus), amotivational syndrome, and increased bleeding ([Hammerness et al. 2006](#)). A major advantage of SSRIs is their safety in overdose ([Barbey and Roose 1998](#)).

Common side effects of mirtazapine are somnolence, increased appetite, weight gain, dizziness, dry mouth, and constipation ([Green 2001](#)).

Common side effects of venlafaxine include anorexia, abdominal pain, insomnia, somnolence, dizziness, dry mouth, increased sweating and nervousness, and elevated blood pressure with dosage increase ([Emslie et al. 2007](#); [Green 2001](#)).

Common side effects of bupropion are headache, nausea, rash, irritability, drowsiness, fatigue, and anorexia ([Barrickman et al. 1995](#); [Connors et al. 1996](#); [Daviss et al. 2001](#)). Bupropion is contraindicated in children with seizure disorders, because it may lower the seizure threshold.

Common side effects of duloxetine are nausea, vomiting, nasopharyngitis, abdominal pain, headache, and somnolence ([Atkinson et al. 2014](#); [Emslie et al. 2014](#)).

---

## Atomoxetine

---

## Dosage and Monitoring



Atomoxetine can be taken in the late afternoon or evening, whereas stimulants generally cannot; atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although it may produce relatively more nausea or sedation. Gastrointestinal distress can be minimized by taking the medication after a meal. In children and young adolescents, atomoxetine is initiated at a dosage of 0.3 mg/kg/day and titrated over 1–3 weeks to a maximum dosage of 1.2–1.8 mg/kg/day ([Kratovich et al. 2003](#)). In adults or adult-sized adolescents, atomoxetine should be started at 40 mg/day and titrated to 80–100 mg/day over 1–3 weeks, if needed ([Kratovich et al. 2003](#)). Atomoxetine's labeling recommends both once-daily and twice-daily dosing, although its elimination half-life of 5 hours (as well as clinical experience) suggests that twice-daily dosing (early morning and early evening) is more effective and less prone to cause side effects. [Michelson et al. \(2002\)](#) showed that although atomoxetine was superior to placebo at week 1 of the trial, its greatest effects were observed at week 6, suggesting that patients should be maintained at the full therapeutic dosage for at least several weeks for the drug to reach its full effects.

## Side Effects

Side effects that occurred at higher rates with atomoxetine than with placebo in clinical trials included gastrointestinal distress, sedation, and decreased appetite. These can generally be managed by dosage adjustment and often attenuate with time. In December 2004, the FDA announced a new warning for atomoxetine due to reports of two patients (an adult and a child) who developed severe liver disease ([U.S. Food and Drug Administration 2004c](#)). Both patients recovered. The FDA has also issued an alert regarding suicidal thinking with atomoxetine in children and adolescents ([U.S. Food and Drug Administration 2005](#)). A black box warning is included in the package insert. In 12 controlled trials involving 1,357 patients receiving atomoxetine and 851 receiving placebo, the average risk of suicidal thinking was 4 per 1,000 patients in the atomoxetine-treated group versus none in the placebo group.

---

# Atypical Antipsychotics

---

## Dosage and Monitoring

Usual starting dosages and target dosages of atypical antipsychotics are listed in [Table 55-2](#).

---

**TABLE 55-2. Clinical use of atypical antipsychotics in children and adolescents**

---

Medication	Typical starting dose (mg)	Target dosage (mg/day)
Clozapine	25 bid	200-400
Olanzapine	2.5 bid	10-20
Quetiapine	50 bid	400-600
Risperidone	0.25 bid	1-2
Ziprasidone	20 bid	80-120
Aripiprazole	2.5-5.0 hs	10-25
Asenapine	2.5 sublingually bid	2.5-10 sublingually bid
Paliperidone ER		
Weight <51 kg	3	3-6
Weight ≥51 kg	3	3-12

---

*Note.* bid=twice daily; ER=extended release; hs=at bedtime.

*Source.* [DelBello et al. 2006](#).

Premedication laboratory testing should include complete blood count, blood chemistries, and liver function tests. In addition, the recommendations of the [American Diabetes Association et al. \(2004\)](#) should be followed. These include baseline BMI, waist circumference, blood pressure, and fasting glucose and lipid panels. BMI should be followed monthly for 3 months and then measured quarterly. Blood

pressure, fasting glucose, and lipid panels should be followed up at 3 months and then yearly. Monitoring should also be done for EPS.

## Side Effects

Side effects of atypical antipsychotics include weight gain, dyslipidemia, insulin resistance and diabetes, hyperprolactinemia, EPS and akathisia, QTc prolongation, sedation, liver toxicity, neutropenia, and neuroleptic malignant syndrome. Clozapine has also been associated with seizures, agranulocytosis, and myocarditis ([Correll et al. 2006](#)).

---

## Clonidine

---

### Dosage and Monitoring

Clonidine is initiated at 0.05 mg/day, with dosage increases of 0.05 mg every 3 days. Typical dosages for attention-deficit/hyperactivity disorder (ADHD) are in the range of 0.15–0.3 mg/day (on a three-times-per-day schedule). Transdermal clonidine delivers dosages of 0.1, 0.2, or 0.3 mg/day. During initial treatment, a temporary worsening of motor and phonic tics in Tourette syndrome may occur, which usually resolves within 2–4 weeks. Clonidine should be tapered by 0.05 mg/day during discontinuation ([Hunt et al. 1990](#)).

Due to reports of adverse cardiovascular side effects in children taking clonidine, recommendations have been made regarding cardiovascular monitoring ([Cantwell et al. 1997](#)). Pulse and blood pressure should be measured at baseline, weekly during dosage titration, and every 4–6 weeks during maintenance treatment. Electrocardiograms (ECGs) should be obtained at baseline and after the maximum dosage of clonidine is achieved. Abrupt discontinuation of clonidine is not recommended, because it increases the risk of adverse cardiovascular side effects, particularly hypertension.

## Side Effects

Common side effects of clonidine in children are sedation, depression, irritability, hypotension, sleep disturbance, dry mouth, and dizziness. Skin irritation and erythema are common with the clonidine patch ([Connor et al. 1999](#); [Hunt et al. 1990](#)). Rebound tachycardia and hypertension may occur if clonidine is abruptly discontinued, particularly after chronic use ([Popper 2000](#)).

Safety concerns have been raised about the combination of clonidine and methylphenidate, following the report of four cases of sudden death in children taking this medication combination ([Cantwell et al. 1997](#); [Fenichel 1995](#)). [Swanson et al. \(1995a\)](#) described two types of clonidine-related cardiovascular side effects. In one type, fatigue and sedation were associated with a decrease in pulse and blood pressure as well as changes in ECG. In the other type, tachycardia and tachypnea occurred, which led to anxiety, fever, and changes in mental status. Adverse cardiovascular side effects, including bradycardia and depressed level of consciousness, have been reported with clonidine overdose in children ([Kappagoda et al. 1998](#)). However, in a retrospective study of 42 children treated with clonidine alone or clonidine plus stimulants, no systematic effects were found on ECG parameters of pulse rate or QTc intervals ([Kofoed et al. 1999](#)).

---

## Guanfacine

---

### Dosage and Monitoring

Guanfacine is initiated at a daily dosage of 0.5 mg, with an upward titration of 0.5 mg every 3 days, based on clinical response and tolerability, to a maximum daily dosage of 4 mg ([Hunt et al. 1995](#)).

Pulse and blood pressure should be monitored during guanfacine treatment. Guanfacine should be tapered over a 4-day period upon discontinuation.

## Side Effects

Common side effects of guanfacine in children are sedation, fatigue, headache, dizziness, stomachache, and decreased appetite ([Chappell et al. 1995](#); [Hunt et al. 1995](#); [Melmed et al. 2006](#); [Scahill et al. 2001](#)). Rebound hypertension, nervousness, and anxiety may occur if guanfacine is abruptly discontinued ([Green 2001](#)).

---

## Mood Stabilizers

---

### Dosage and Monitoring

The starting dosages, target dosages, and therapeutic serum levels of mood stabilizers are listed in [Table 55-3](#).

---

**TABLE 55-3. Clinical use of mood stabilizers in children and adolescents**

---

Medication	Typical starting dose (mg)	Target dosage	Therapeutic serum level
Carbamazepine	7 mg/kg/day	Based on response and serum level	8–11 µg/L
Lamotrigine	12.5 mg/day	Based on response	N/A
Lithium	25 mg/kg/day (2–3 daily doses)	30 mg/kg/day (2–3 daily doses)	0.8–1.2 mEq/L

---

*Note.* bid=twice daily; N/A=not applicable.

*Source.* [DelBello and Kowatch 2006](#).

---

<b>Medication</b>	<b>Typical starting dose (mg)</b>	<b>Target dosage</b>	<b>Therapeutic serum level</b>
Oxcarbazepine	150 mg bid	20–29 kg: 900 mg/day 30–39 kg: 1,200 mg/day >39 kg: 1,800 mg/day	N/A
Topiramate	25 mg/day	100–400 mg/day	N/A
Valproic acid, divalproex	20 mg/kg/day (2 daily doses)	20 mg/kg/day (2–3 daily doses)	90–120 µg/mL

*Note.* bid=twice daily; N/A=not applicable.

*Source.* [DelBello and Kowatch 2006](#).

Premedication laboratory testing in general should include complete blood count, liver function tests, and a pregnancy test (for females).

For lithium, baseline thyroid function tests, electrolytes, urinalysis, blood urea nitrogen, creatinine, and serum calcium should also be obtained. Lithium levels, renal function, thyroid function, and urinalysis should be monitored every 3–6 months.

For individuals taking divalproex, drug serum levels, complete blood count, and liver function tests should be monitored every 3–6 months. Because of concerns about a possible relationship between divalproex and polycystic ovarian syndrome (PCOS; [Rasgon 2004](#)), female adolescents taking divalproex should be monitored for signs of PCOS, including menstrual abnormalities, weight gain, acne, and hirsutism ([DelBello and Kowatch 2006](#); [McClellan et al. 2007](#)). Parents and their female adolescents should be apprised about this possible association prior to initiating medication.

For oxcarbazepine, children should be monitored for hyponatremia.

## Side Effects

Common side effects of lithium in children and adolescents include hypothyroidism, nausea, polyuria, polydipsia, acne, tremor, and weight gain ([DelBello and Kowatch 2006](#)).

Common side effects of divalproex in children and adolescents include weight gain, nausea, sedation, and tremor ([DelBello and Kowatch 2006](#)). Concerns have been raised about a possible association between divalproex and PCOS ([Rasgon 2004](#)). Other potential adverse effects of concern are hepatic failure, pancreatitis, thrombocytopenia, behavioral deterioration, and hair loss ([Davanzo and McCracken 2000](#); [Green 2001](#)).

Side effects of topiramate include decreased appetite, weight loss, nausea, diarrhea, paresthesias, somnolence, and word-finding difficulties ([DelBello and Kowatch 2006](#); [DelBello et al. 2005](#)).

Side effects of oxcarbazepine in children include dizziness, nausea, somnolence, diplopia, fatigue, and rash ([Wagner et al. 2006b](#)). Hyponatremia is also a side effect of oxcarbazepine.

Common side effects of lamotrigine in children include ataxia, nausea, vomiting, and constipation. Of particular concern, the incidence of serious rash, including Stevens-Johnson syndrome, in pediatric populations is reported to be 1%. This high incidence of serious rash may be attributable to the prior use of high dosages of lamotrigine with concomitant divalproex ([Messenheimer 1998](#)). The current dosing guidelines may reduce this rash incidence in pediatric patients.

---

## Psychostimulants

---

### Dosage and Monitoring

The American Academy of Child and Adolescent Psychiatry has developed practice parameters for the diagnosis and treatment of ADHD ([Pliszka and AACAP Work Group on Quality Issues 2007](#)). A wide variety of stimulant preparations are available; [Table 55-4](#)

describes their use in clinical practice. Each stimulant has a maximum dosage suggested by the FDA-approved package insert, but higher off-label dosages are commonly used with careful monitoring. For safety monitoring, a patient's pulse, blood pressure, weight, and height should be obtained at baseline and at least annually. No laboratory measures or ECG monitoring is required.

**TABLE 55-4. Clinical use of psychostimulants in children and adolescents**

<b>Medication</b>	<b>Dose strengths</b>	<b>Typical starting dosage</b>	<b>FDA max/day</b>	<b>Off-label max/day</b>
<b>Amphetamine preparations</b>				
Adderall	5, 7.5, 10, 12.5, 15, 20, 30 mg	3–5 yr: 2.5 mg qd  ≥6 yr: 5 mg qd–bid	40 mg	≥50 kg: 60 mg
Dexedrine	5 mg	3–5 yr: 2.5 mg qd  ≥6 yr: 5 mg qd–bid	40 mg	≥50 kg: 60 mg
Dextrostat	5, 10 mg	3–5 yr: 2.5 mg qd	40 mg	≥50 kg: 60 mg

*Note.* bid=twice daily; CD=controlled delivery (extended release); ER=extended release; FDA=U.S. Food and Drug Administration; LA=long acting (extended release); qam=every morning; qd=once daily; SR=sustained release; XR=extended release.



<b>Medication</b>	<b>Dose strengths</b>	<b>Typical starting dosage</b>	<b>FDA max/day</b>	<b>Off-label max/day</b>
		≥6 yr: 5 mg qd-bid		
Dexedrine Spansule	5, 10, 15 mg	≥6 yr: 5-10 mg qd-bid	40 mg	≥50 kg: 60 mg
Adderall XR	5, 10, 15, 20, 25, 30 mg	≥6 yr: 10 mg qd	30 mg	≥50 kg: 60 mg
Vyvanse	30, 50, 70 mg	30 mg qd	70 mg	Not determined
<b>Methylphenidate preparations</b>				
Focalin	2.5, 5, 10 mg	2.5 mg bid	20 mg	50 mg
Focalin XR	5, 10, 15, 20 mg	5 mg qam	30 mg	50 mg
Methylin	5, 10, 20 mg	5 mg bid	60 mg	≥50 kg: 100 mg
Metadate ER	10, 20 mg	10 mg qam	60 mg	≥50 kg: 100 mg
Methylin ER	10, 20 mg	10 mg qam	60 mg	≥50 kg: 100 mg
Ritalin SR	20 mg	10 mg qam	60 mg	≥50 kg: 100 mg

---

*Note.* bid=twice daily; CD=controlled delivery (extended release); ER=extended release; FDA=U.S. Food and Drug Administration; LA=long acting (extended release); qam=every morning; qd=once daily; SR=sustained release; XR=extended release.

---

<b>Medication</b>	<b>Dose strengths</b>	<b>Typical starting dosage</b>	<b>FDA max/day</b>	<b>Off-label max/day</b>
Metadate CD	10, 20, 30, 40, 50, 60 mg	20 mg qam	60 mg	≥50 kg: 100 mg
Ritalin LA	20, 30, 40 mg	20 mg qam	60 mg	Not yet known
Concerta	18, 27, 36, 54 mg	18 mg qam	72 mg	108 mg
Daytrana patch	10-, 15-, 20-, 30-mg patches	Begin with 10-mg patch qd; then titrate up by patch strength	30 mg	Not yet known
Quillivant XR	25 mg/5 mL	2 mL qam	12 mL	Not yet known
Aptensio XR	10, 15, 20, 30, 40, 50, 60 mg	10 mg qam	60 mg	Not yet known

---

*Note.* bid=twice daily; CD=controlled delivery (extended release); ER=extended release; FDA=U.S. Food and Drug Administration; LA=long acting (extended release); qam=every morning; qd=once daily; SR=sustained release; XR=extended release.

---

## Side Effects

Common side effects of psychostimulants are insomnia, diminished appetite, weight loss, irritability, abdominal pain, and headaches (Pliszka and AACAP Work Group on Quality Issues 2007). Rebound symptoms of worsening behavior may occur when the effects of the short-acting psychostimulants dissipate. Switching to sustained-release or longer-acting psychostimulants may ameliorate rebound symptoms.

Although earlier reports of a protective effect from psychostimulants were not borne out by a later study (Molina et al. 2009), there is no evidence that psychostimulants increase substance abuse in youth with ADHD. Motor tics may develop during treatment with stimulants, but one study reported no increase in tics for children with or without preexisting tics who received typical clinical dosages of methylphenidate compared with placebo (Law and Schachar 1999).

The FDA and its Pediatric Advisory Committee have reviewed data regarding psychiatric adverse events related to stimulant medication (U.S. Food and Drug Administration 2006). Data from controlled trials and postmarketing safety data from sponsors and the FDA Adverse Events Reporting System (AERS), also referred to as MedWatch, were reviewed. For most of the agents, psychiatric adverse events were slightly more common in the groups given active drug rather than placebo in the controlled trials, but these differences did not reach statistical significance (Mosholder 2006). Postmarketing safety data were also reviewed for reports of mania/psychotic symptoms, aggression, and suicidality (Gelperin 2006). Rare events of suicidal thoughts, manic-like activation, or psychosis were reported. At the time, the Pediatric Advisory Committee did not recommend a black box warning regarding psychiatric adverse events but did suggest clarifying labeling regarding these phenomena. No changes to the stimulant medication labeling were suggested regarding suicide or suicidal ideation.

There have been rare reports of sudden death in patients taking stimulant medication. Villalaba (2006) reported that the FDA has records of 20 cases of sudden death with amphetamine or dextroamphetamine (14 children, 6 adults), and of 14 pediatric and 4 adult cases of sudden death with methylphenidate. It is important to note that the rate of sudden death in the general pediatric

population has been estimated at 1.3–8.5 per 100,000 patient-years ([Liberthson 1996](#)). The rate of sudden death among individuals with a history of congenital heart disease can be as high as 6% by age 20 years ([Liberthson 1996](#)). [Villalaba \(2006\)](#) estimated the rate of sudden death in children treated for ADHD during the period encompassing January 1, 1992, to December 31, 2004, to be 0.2 per 100,000 patient-years for methylphenidate, 0.3 per 100,000 patient-years for amphetamine, and 0.5 per 100,000 patient-years for atomoxetine (the differences between the agents are not clinically meaningful). Because the rate of sudden death in children taking ADHD medications does not appear to exceed the base rate of sudden death in the general population, cardiac monitoring of healthy children during treatment with stimulants is not required. Children with preexisting heart disease (or significant symptoms suggesting the condition) should obtain a cardiology consultation prior to taking a stimulant.

[Poulton \(2005\)](#) reviewed growth data and concluded that stimulant treatment may be associated with a reduction in expected height gain, at least in the first 1–3 years of treatment. The National Institute of Mental Health (NIMH) Multimodal Treatment of ADHD (MTA) study showed reduced growth rates in patients with ADHD after 2 years of stimulant treatment compared with patients who received no medication ([MTA Cooperative Group 2004](#)), and these deficits persisted at 36 months ([Swanson et al. 2007](#)). The Preschool ADHD Treatment Study (PATs) followed a group of 140 preschoolers who received methylphenidate for ADHD for up to a year ([Swanson et al. 2006](#)). The subjects had less than expected mean gains in height (–1.38 cm) and weight (–1.3 kg). [Charach et al. \(2006\)](#) found that higher dosages of stimulants correlated with reduced gains in height and weight and that the effect did not become significant until the dosage in methylphenidate equivalents was >2.5 mg/kg/day for 4 years. [Pliszka et al. \(2006b\)](#) did not find that children with ADHD treated with monotherapy with either amphetamine or methylphenidate showed any failure to achieve expected height; furthermore, the two stimulant classes did not have a differential effect on height, although amphetamine had a somewhat greater effect on weight than did methylphenidate. The subjects in this study had drug holidays averaging 31% of the time during their treatment

course, which may have contributed to the lack of effect of the stimulant on height.

In assessing for clinically significant growth reduction, it is recommended to use serial plotting of height and weight on growth charts labeled with lines showing the major percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) ([Mei et al. 2004](#)). This should occur one to two times per year and more frequently if practical. A change in height or weight that crosses two percentile lines suggests an aberrant growth trajectory. In these cases, a drug holiday should be considered if return of symptoms during weekends or summers does not lead to marked impairment of functioning. The clinician should also consider switching the patient to another ADHD medication. It is important for the clinician to carefully balance the benefits of medication treatment with the risks of small reductions in height gain, which as of yet have not been shown to be related to reductions in adult height ([Klein and Mannuzza 1988](#); [Kramer et al. 2000](#); [Weiss and Hechtman 2003](#)).

## CHAPTER 56

# Treatment During Late Life

Steven P. Roose, M.D.

Bruce G. Pollock, M.D., Ph.D.

D. P. Devanand, M.D.

Adverse events caused by medication are a significant cause of morbidity and mortality in the elderly. In a large study of ambulatory Medicare enrollees, 38% of adverse drug events were serious, life-threatening, or fatal and 28% were considered preventable ([Gurwitz et al. 2003](#)). Moreover, psychotropics are among the most common medications associated with preventable adverse drug events in elderly patients in long-term care settings ([Gurwitz et al. 2000](#)).

---

# Pharmacokinetics of Psychotropic Medications in the Elderly

---

In general, age-associated pharmacokinetic changes result in higher and more variable drug concentrations. Nonetheless, specific information on the pharmacokinetics of most psychoactive medications is inadequate, particularly with regard to medical comorbidities and potential drug interactions. The limited information that does exist for older subjects is largely derived from classical pharmacokinetic modeling. Traditional pharmacokinetic studies require a large number of plasma drug samples obtained from a small number (i.e., 6–12) of volunteers. These single-dosage pharmacokinetic studies usually are not adequate to rule out the possibility of nonlinear kinetics. Moreover, age or illness-associated differences in pharmacodynamics are not interpretable in the absence of drug concentration data. Population pharmacokinetics provides a means for addressing heterogeneous drug exposure for elders using minimal sampling methods ([Bigos et al. 2006](#)). For example, using this approach, we have examined age and cytochrome P450 (CYP) genotype effects for citalopram, escitalopram, and paroxetine ([Bies et al. 2004](#); [Feng et al. 2006](#); [Jin et al. 2010](#)).

Although individuals older than 65 years account for more than one-third of prescription drug expenditures in the United States, they are often excluded from clinical and regulatory trials. In addition, the trials that do include elders rarely include the “oldest old” (i.e., 85+ years), those having multiple comorbidities, or those taking multiple

medications. These exclusions raise questions about the generalizability of psychotropic data to the frail elderly.

Age-associated pharmacokinetic differences may be due to changes in absorption, distribution, metabolism, or elimination of a drug (Table 56-1). The multidimensional changes associated with aging are heterogeneous, and only generalizations can be made (Lotrich and Pollock 2005).

**TABLE 56-1. Physiological changes in the elderly associated with altered pharmacokinetics**

Organ system	Change	Pharmacokinetic consequence
Gastrointestinal tract	Decreased intestinal and splanchnic blood flow	Decreased rate of drug absorption
Circulatory	Decreased concentration of plasma albumin and increased $\alpha_1$ -acid glycoprotein	Increased or decreased free concentration of drugs in plasma
Kidney	Decreased glomerular filtration rate	Decreased renal clearance of active metabolites



<b>Organ system</b>	<b>Change</b>	<b>Pharmacokinetic consequence</b>
Muscle	Decreased lean body mass and increased adipose tissue	Altered volume of distribution of lipid-soluble drugs, leading to increased elimination half-life
Liver	Decreased liver size; decreased hepatic blood flow; minimal effects on cytochrome P450 enzyme activity	Decreased hepatic clearance

## Absorption

Although absorption of nutrients is often impaired in the elderly, the rate and extent of passive drug absorption are not affected by normal aging. Antacids, high-fiber supplements, and cholestyramine may significantly diminish the absorption of medications.

## Distribution

For most psychotropics that are lipid soluble, the loss of lean body mass with aging will lead to increases in their volumes of distribution, resulting in longer half-lives and

drug accumulation. This is because a drug's half-life is directly proportional to its apparent volume of distribution. Conversely, for water-soluble drugs such as lithium and digoxin, volumes of distribution will be diminished in older patients, reducing the margin of safety after acute increases in plasma drug concentration.

Reductions in serum albumin with age and possible increases in  $\alpha_1$ -acid glycoprotein with illness may affect the extent of drug bound to plasma proteins. However, it is now recognized that changes in plasma protein binding are of clinical significance only when therapeutic drug monitoring is used to adjust dosing, because total drug concentrations (free+protein bound) are usually reported ([Benet and Hoener 2002](#)). Total drug levels may be interpreted as too low if a drug's free fraction is increased by diminished plasma proteins or drug displacement. The use of free drug levels in older patients has been found to be useful for lidocaine, theophylline, phenytoin, and digitoxin.

## Metabolism

Available evidence suggests that there is no uniform age-associated decline in liver metabolism by CYP enzymes ([Pollock et al. 1992b](#); [Schmucker 2001](#)). Nonetheless, reductions in hepatic mass and blood flow with aging place greater emphasis on interindividual differences in drug metabolic capacity. These metabolic differences may be either genetic or the result of interactions from multiple medications. Enzyme specificity suggests that inhibition or induction of a given CYP enzyme will affect all drugs metabolized by that specific enzyme. Updated information on CYP-mediated drug-drug interactions is available at the

University of Indiana School of Medicine's "Drug Interactions" Web page (see [Flockhart 2007](#)).

CYP2D6 is the enzyme responsible for metabolizing tricyclic antidepressants (TCAs) and venlafaxine as well as several older antipsychotics and risperidone. Among the white population, 5%-10% are genetically poor CYP2D6 metabolizers.

Drugs metabolized by CYP3A4, such as alprazolam, triazolam, sertraline, and mirtazapine, appear to be cleared less well in elderly patients ([Greenblatt et al. 1991](#); [Ronfeld et al. 1997](#); [Timmer et al. 1996](#)). However, this may be because metabolism of CYP3A4 drugs is typically perfusion limited (i.e., dependent on hepatic blood flow, which is known to decline substantially with age) ([Wynne et al. 1990](#)). CYP3A4 makes up 30% of total hepatic CYP and nearly all of drug-metabolizing enzyme in the small bowel, and therefore is substantially responsible for "first-pass" or presystemic drug disposition ([Shimada et al. 1994](#)). Serious toxicity has occurred when the 3A4-mediated clearance of terfenadine, astemizole, cisapride, cerivastatin, midazolam, and triazolam was inhibited ([Dresser et al. 2000](#)). CYP3A4 activity may be inhibited by grapefruit juice, protease inhibitors, macrolide antibiotics, and triazole antifungals. Among antidepressants, fluvoxamine is the most potent inhibitor of CYP3A4, followed by fluoxetine, through its demethylated metabolite. The very long half-life of norfluoxetine may result in interactions occurring many weeks after the initiation of fluoxetine treatment. The 3A4 enzyme is also potently induced by other drugs, such as carbamazepine, phenytoin, topiramate, modafinil, barbiturates, steroids, and St. John's wort. CYP3A4 induction will increase the likelihood of therapeutic failure for concurrently prescribed 3A4 substrate drugs. Many

CYP3A4 inhibitors (e.g., diltiazem) and inducers (e.g., St. John's wort) also have been found to inhibit or induce the *P*-glycoprotein drug transporter, amplifying their effects on 3A4 ([Yu 1999](#)).

CYP1A2 metabolizes clozapine, olanzapine, fluvoxamine, and theophylline and contributes to the demethylation of some tertiary TCAs. This enzyme is induced by cigarette smoking, cruciferous vegetables, and charcoaled meats. CYP 2C9 metabolizes several drugs with a narrow therapeutic index (i.e., phenytoin, tolbutamide, ibuprofen, and warfarin). It is therefore important to recognize that this enzyme may be inhibited by fluvoxamine and fluoxetine.

## Excretion

Age-associated decline in renal clearance may affect excretion of psychotropic drug metabolites and lithium in older patients. The magnitude of this decline varies greatly among the aged ([Pollock et al. 1992b](#)), being exacerbated by concomitant conditions (e.g., diabetes and hypertension) and medications (e.g., nonsteroidal anti-inflammatory drugs). Accumulation of active TCA metabolites in the elderly was previously a subject of concern ([Pollock et al. 1992a](#)). Higher concentrations of bupropion and venlafaxine metabolites also have been observed in older patients and those with renal impairment, with uncertain clinical consequences.

---

## Pharmacodynamics of Psychotropic Medications in the

# Elderly

---

Interindividual differences in pharmacodynamics become evident when those with similar plasma drug concentrations experience different effects. In general, older patients are more sensitive to adverse effects of psychotropics at lower concentrations. Homeostatic mechanisms, such as postural control, water balance, orthostatic circulatory responses, and thermoregulation, are frequently less robust in the aged. This factor may interfere with the ability to physiologically adapt to medication. For example, all psychotropics, including selective serotonin reuptake inhibitors (SSRIs), may increase the risk of falls and hip fractures ([Liu et al. 1998](#)). Similarly, the syndrome of inappropriate antidiuretic hormone secretion has been reported as an age-associated adverse effect of all SSRIs and of venlafaxine ([Kirby and Ames 2001](#)).

Reductions in dopamine or acetylcholine function with age may increase sensitivity to antipsychotics and SSRIs (which indirectly reduce dopamine outflow) as well as medications with antimuscarinic effects ([Gerretsen and Pollock 2011](#); [Graff-Guerrero et al. 2015](#)). Even low serum anticholinergic levels may be associated with cognitive impairment in depressed and nondepressed elderly persons ([Mulsant et al. 2003](#); [Nebes et al. 2012](#)). Unfortunately, anticholinergic drugs continue to be widely prescribed in older patients ([Chew et al. 2008](#); [Roe et al. 2002](#)).

Anticoagulant-antidepressant interactions may be both pharmacokinetic and pharmacodynamic. Fluvoxamine and fluoxetine pose the greatest risk of pharmacokinetic interactions through CYP2C9 inhibition, reducing the

clearance of warfarin's active *S*-enantiomer. However, increased bleeding times with SSRIs alone or in combination with anticoagulants or nonsteroidal anti-inflammatory drugs also may be possible as a result of depleting platelets of serotonin and attenuating their aggregation ([Pollock et al. 2000b](#); [Shin et al. 2015](#)).

At present, there is only limited evidence that genetic differences may influence pharmacodynamics in older patients. Depressed elderly patients with the long-long (LL) serotonin transporter promoter genotype were found to have a more rapid initial response to paroxetine ([Pollock et al. 2000a](#)). This is consistent with results obtained with other SSRIs in younger patients ([Serretti et al. 2006](#)). Another study in geriatric major depression found that carriers of the short (S) allele experienced more severe adverse events during paroxetine treatment ([Murphy et al. 2004](#)). Interestingly, findings in Koreans with late-life depression were in the opposite direction—that is, better responses among carriers of the S allele ([Kim et al. 2006](#)).

---

## **Antidepressants in the Elderly**

---

### **Treatment of Late-Life Depression**

The combined prevalence of major depressive disorder and dysthymia in late life is 5%–12% in epidemiological studies; this rate is similar to the rate in the younger adult population. However, the symptom pattern and frequency of specific depressive subtypes appear to be different; older patients have more somatic symptoms, and both the melancholic and the delusional subtypes of depression

increase in frequency in older populations. In addition, some degree of cognitive impairment, whether manifesting only concurrently with the depressive episode or as a function of age, is common.

As in younger patients, untreated depression in late life causes significant social, vocational, and interpersonal morbidity, and depression in late life is associated with a significant risk of mortality. Comorbid depression adversely affects the course of several disease processes; this has been best documented for ischemic heart disease. Patients with unstable angina, post-myocardial infarction, or congestive heart failure who are depressed have a higher cardiac mortality rate than do medically comparable patients who are not depressed ([Musselman et al. 1998](#)). Furthermore, the suicide rate in men (in the United States, specifically white men) increases dramatically after age 60 years and continues to rise significantly as a function of age.

## Studies of Antidepressant Treatment in Older Patients

Considering the physiological changes associated with aging and the differences in the phenomenology and possible etiology of depression in late life compared with earlier in life, it is expected that clinical trials of antidepressants in late life will have a unique set of patient moderators and study design mediators that may significantly affect results. Variability in results of randomized controlled trials of antidepressants in late-life depression may result from heterogeneity in the patient population. Treatment moderators that have been identified as significant for late-life depression include the following:

- Subtype (e.g., melancholic or atypical)
- Severity
- Medical burden
- Social support
- Abnormalities on magnetic resonance scans indicating vascular disease
- Pattern of neurocognitive abnormalities labeled “executive dysfunction”

With respect to mediators of treatment response, the standard considerations in study design—namely, randomization, placebo versus comparator control, dosage, duration, and criteria for response and remission—are all important, but specifically the value of placebo-controlled trials versus comparator trials and optimal duration of treatment have been systematically reexamined. [Sneed et al. \(2008\)](#) conducted a meta-analysis of all studies published in peer-reviewed journals from 1985 to 2006 that were randomized placebo-controlled or comparator (a comparison of two active conditions) trials of antidepressants for the treatment of late-life depression. The intent of the meta-analysis was to determine whether rates of response to medications in comparator trials are significantly higher than rates of response to comparable medications in placebo-controlled trials—that is, whether study design significantly affects treatment outcome. Sixteen studies (9 comparator trials and 7 placebo-controlled trials) met the rigorous inclusion criteria for the meta-analysis. As hypothesized, antidepressant response rates were significantly higher in the comparator trials compared to placebo-controlled trials; the estimated probability of antidepressant response in a placebo-controlled trial was 46% as compared with 60% in a



comparator trial. One possible explanation for the higher response rate to the same medication in a comparator trial is that patient, doctor, and even research rater expectations of response are higher when it is known that the subject is receiving an active medication. Irrespective of the reason that response rates are higher in comparator trials, the results of the study suggest that when clinicians want to make evidence-based treatment decisions and communicate likelihood of response to patients, data from comparator trials may be more appropriate than results of placebo-controlled trials, since comparator trials more closely approximate the clinical situation in that both patient and doctor know that an active medication is being prescribed.

## Tricyclic Antidepressants

Most of the placebo-controlled trials involving TCAs were done before the use of plasma-level measurements to ensure optimal TCA treatment. Later randomized controlled trials that compared TCAs with SSRIs were invariably supported by the pharmaceutical industry, which had no desire to compare their new compound against optimal TCA treatment. Consequently, the preponderance of studies of TCA treatment in late-life depression reported inadequate dosages of the tertiary-amine TCAs amitriptyline and imipramine. Nonetheless, the results of these studies established that TCAs are an effective treatment for depression in geriatric patients.

**Nortriptyline.** Of the TCAs, nortriptyline has been found to induce the least orthostatic hypotension and has a documented “therapeutic window” that permits optimal dosing ([Roose et al. 1981](#)). Consequently, nortriptyline has

emerged as the choice of this class of medications issued to treat late-life depression. However, there are no rigorous placebo-controlled trials of nortriptyline in late-life depression; thus, the relative effectiveness of this medication is inferred from two open trials and three randomized comparator trials.

In a study reported by [Flint and Rifat \(1996\)](#), 101 patients meeting DSM-III-R ([American Psychiatric Association 1987](#)) criteria for major depressive disorder were treated openly with nortriptyline. The dosing schedule was as follows: all patients achieved a daily dosage of 75 mg by the end of week 1, and then the dosage was adjusted if necessary to achieve a plasma level within the therapeutic window of 50–150 ng/mL. The treatment duration was 6 weeks, and the remission criterion was a final Hamilton Rating Scale for Depression (Ham-D; 17-item) score of 10 or less; 60% of the intent-to-treat sample and 75% of the completers met the remission criterion. To establish speed of response, the authors determined the week of treatment that the 61 patients who met the criterion for remission at the end of the study first achieved sustained remission. Not surprisingly, at the end of week 1, no patient met the criterion for remission, and thus the cumulative response rate was 0%. At week 2, 11% of the sample met the remission criterion, and at week 3, 33% met the remission criterion (thus, the cumulative rate at the end of week 3 was 11%+33%, or 44%). At weeks 4 and 5, 25% and 20%, respectively, met the remission criterion. Thus, the accumulated remission rate at the end of week 5 was 89%. Although it is widely believed that late-life depression patients should have longer treatment trials, specifically 12 weeks, this study found that 89% of the patients who eventually recovered did so by the end of week 5. A second

open study of a therapeutic plasma level of nortriptyline reported on 42 inpatients (mean age: 70 years) with cardiac disease and melancholic depression who also were treated for 6 weeks ([Roose et al. 1994](#)). The remission criterion was a final Ham-D (21-item) score of 8 or less; the intent-to-treat remission rate was 67%, the completer remission rate was 82%, and the dropout rate was 19%.

Three randomized controlled trials compared nortriptyline with an SSRI; two studies compared a therapeutic plasma level of nortriptyline with paroxetine, and one study compared flexible-dose nortriptyline with sertraline. [Mulsant et al. \(2001a\)](#) compared nortriptyline with paroxetine in 116 inpatients and outpatients (mean age: 72 years) in a 12-week trial. Patients were considered to be in remission if the final Ham-D (17-item) score was 10 or less; the intent-to-treat remission rate was 57% for the nortriptyline group and 55% for the paroxetine group. The rate of dropout due to side effects in the nortriptyline group was significantly higher than that in the paroxetine group (33% vs. 16%;  $P=0.04$ ).

A second randomized controlled trial comparing nortriptyline (targeted to a therapeutic plasma level) with paroxetine is included in this chapter, although technically it should not be considered a geriatric study because the mean age of the patients was 58 years ([Nelson et al. 1999](#)). However, it is the only other study comparing a therapeutic plasma level of a TCA with an SSRI, and the results are consistent with those of the [Mulsant et al. \(2001a\)](#) study. In this trial, 81 outpatients with ischemic heart disease were treated with medication for 6 weeks. The remission criterion was a final Ham-D (17-item) score of 8 or less; in the intent-to-treat analysis, 63% of the nortriptyline group and 61% of the paroxetine group were remitters. The

dropout rate for nortriptyline (35%) was significantly higher than the dropout rate for paroxetine (10%) ( $P<0.05$ ). The rate of remission in study completers was 85% for nortriptyline and 68% for paroxetine, which was not a statistically significant difference, although the power of this comparison was limited by the small size of the completer group.

The randomized controlled trial comparing sertraline with nortriptyline included 210 patients (mean age: 68 years) randomly assigned to 12 weeks of medication treatment ([Bondareff et al. 2000](#)). This study did not report remission rates but only response rates, defined as a 50% reduction in Ham-D (24-item) score from baseline. The response rates for nortriptyline and sertraline were 41% and 52%, respectively.

**TCA side effects and safety.** Unfortunately, despite their robust effectiveness, the clinical utility of TCAs in the late-life population is limited by their side-effect and safety profiles. TCAs have significant anticholinergic effects that result in dry mouth, constipation, urinary retention, and confusional states.

The major safety problem with respect to the TCAs is cardiovascular effects ([Glassman et al. 1993](#)). TCAs are lethal in overdose, and as little as three times the daily dosage can result in death from heart block or arrhythmias. The TCAs have type 1A antiarrhythmic activity similar to that of moricizine and quinidine and consequently are presumed to confer an increased risk of sudden cardiovascular death if given to patients with ischemic heart disease. Given the prevalence of occult and manifest ischemic heart disease in both men and women older than

60 years, the use of TCAs in this population must reflect a careful consideration of the risk-benefit ratio.

## Selective Serotonin Reuptake Inhibitors

As in younger depressed patients, the SSRIs are the most prescribed class of antidepressants for late-life depression. Within this class, the various SSRIs appear to have equivalent efficacy and side-effect profiles. There are differences in pharmacokinetics and potential for drug-drug interactions, which are of importance in the geriatric population and have been discussed earlier in this chapter.

**Fluoxetine.** Four large studies of fluoxetine in late-life depression have been conducted: 1) a placebo-controlled study; 2) a three-cell study comparing venlafaxine, placebo, and fluoxetine; 3) a randomized controlled trial with a comparator drug; and 4) open treatment. In the first study, fluoxetine was compared with placebo in 671 patients ([Tollefson et al. 1995](#)). The dosing schedule was fluoxetine 20 mg/day for 6 weeks, and the remission criterion was a Ham-D (17-item) score of 7 or less after 4 weeks. The intent-to-treat analysis remission rate was 23% for fluoxetine and 13% for placebo; in the completer analysis, the remission rate was 27% for fluoxetine and 16% for placebo. Although fluoxetine was significantly more effective than placebo in both the intent-to-treat and the completer analyses, this was the first large SSRI trial in a geriatric population, and in comparison to the clinical experience with therapeutic plasma levels of TCAs, the remission rates in this study were disappointingly low.

In the comparator randomized clinical trial, patients were randomly assigned to receive either fluoxetine 20–40 mg/day or sertraline 50–100 mg/day for 12 weeks

([Newhouse et al. 2000](#)). The sample of 225 patients (mean age: 68 years) was somewhat unusual because the mean duration of the current episode of major depression was 9 years. The intent-to-treat remission rate was 46% for fluoxetine and 45% for sertraline, the completer remission rate was 60% for fluoxetine and 59% for sertraline, and the dropout rate was 33% for fluoxetine and 32% for sertraline. This study also reported an intriguing analysis of the response pattern of a subsample of 75 patients (42 treated with sertraline, 33 treated with fluoxetine) with a mean age of 75 years. For both sertraline and fluoxetine, 95% of the patients who achieved a 50% reduction in baseline Ham-D score did so by the end of week 8. As with the [Flint and Rifat \(1996\)](#) study of a therapeutic plasma level of nortriptyline, these data challenge the clinical wisdom that antidepressant trials in late-life depression must be extended to 12 weeks.

Finally, 308 patients meeting DSM-III ([American Psychiatric Association 1980](#)) criteria for major depressive disorder (mean age: 66 years) were treated openly with 20 mg/day of fluoxetine for 8 weeks ([Mesters et al. 1992](#)). The remission criterion was a final Ham-D (24-item) score of 10 or less; the intent-to-treat remission rate was 35%, the completer remission rate was 50%, and the dropout rate was 29%.

**Sertraline.** In addition to the two randomized controlled comparator trials previously described, nortriptyline versus sertraline and fluoxetine versus sertraline, a large rigorous placebo-controlled trial of sertraline in late-life depression was completed ([Schneider et al. 2003](#)). In this study, 716 patients (mean age: 70 years) were randomly assigned to flexible-dosage sertraline (50–100 mg/day) or placebo in an

8-week clinical trial. The criterion for remission was a final Ham-D (17-item) score of 10 or less; the intent-to-treat remission rate was 29% in the sertraline group, compared with 23% in the placebo group ( $P<0.05$ ).

**Paroxetine.** In addition to the two previously described trials that compared nortriptyline at a therapeutic plasma level with paroxetine, and in which the intent-to-treat remission rates (final 17-item Ham-D score  $\leq 10$ ) were 55% and 61%, respectively, a third trial compared mirtazapine with paroxetine ([Schatzberg et al. 2002](#)). In this study, 255 patients (mean age: 72 years) were randomly assigned to receive mirtazapine 30–45 mg/day or paroxetine 30–40 mg/day in an 8-week clinical trial. The criterion for remission was a final Ham-D (17-item) score of 7 or less; the intent-to-treat remission rates were 38% for mirtazapine and 28% for paroxetine and were not statistically different.

**Citalopram and escitalopram.** Many of the studies of citalopram in a geriatric population included patients with depression and dementia or significant cognitive impairment; therefore, the results of these studies are not comparable to those of other antidepressant trials in late-life depression ([Gottfries 1996](#)). However, two studies have provided information on citalopram in this population; the first was a single-blind comparison between citalopram and a therapeutic plasma level of nortriptyline, and the second was a comparison of citalopram with placebo in depressed patients older than 75 years.

In the first study, 58 patients (mean age: 71 years) were randomly assigned to treatment with a citalopram dosage of 30–40 mg/day or a therapeutic plasma level of



nortriptyline in a 12-week clinical trial ([Navarro et al. 2001](#)). The criterion for remission was a final Ham-D (17-item) score of 7 or less; the intent-to-treat remission rates were 69% for citalopram and 93% for nortriptyline. The remission rates for both medications were strikingly high in comparison with those in other trials; whether this result derived from differences in patient population or in study design is not obviously apparent.

The second trial is unique in the literature because it is the only study to focus on treatment of depression in the “old-old.” In this study, 174 patients were randomly assigned to treatment with either citalopram 20–40 mg/day or placebo in an 8-week clinical trial ([Roose et al. 2002](#)). The population was 58% female, with a mean age of 80 years and a mean baseline Ham-D (24-item) score of 24. The intent-to-treat response rate (50% reduction from baseline Ham-D score) was 41% in the citalopram group and 39% in the placebo group. The sample was divided for secondary analyses into patients with “severe” and “not severe” depression, which were defined as being either above or below the mean Ham-D score, respectively. The “not severe” group had a baseline Ham-D score of 22 and included 47 patients randomly assigned to receive citalopram and 59 patients randomly assigned to receive placebo. The criterion for remission was a final Ham-D score of 10 or less. In this group, the intent-to-treat remission rate was 34% for citalopram and 41% for placebo. The “severe” patient group had a mean baseline Ham-D score of 28 and included 37 patients randomly assigned to citalopram and 31 patients randomly assigned to placebo. In this group, the intent-to-treat remission rate was 36% for citalopram and 19% for placebo ( $P<0.05$ ). Thus, citalopram was significantly more effective than



placebo in the “severe” patient population, but this difference resulted not from an increased efficacy of citalopram compared with “not severe” patients but rather from a decreased efficacy of placebo.

A third study—an 8-week randomized controlled trial—compared citalopram (flexible dosage of 10–20 mg/day) and venlafaxine (flexible dosage of 75–150 mg/day) in the treatment of late-life depression ([Allard et al. 2004](#)). The study included 151 patients (mean age: 73 years; 73% female) with a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score of  $27 \pm 4$ . The response rates for venlafaxine versus citalopram were 75% and 73%, respectively, and the remission rates were 19% and 23%, respectively. The differences between the response rates and the remission rates were quite striking; it is unusual to see such a differential.

There has been one randomized controlled trial of escitalopram in the treatment of late-life depression ([Kasper et al. 2005](#)). In this study, 517 patients (mean age: 75 years; 75% female; mean baseline MADRS score:  $28 \pm 4$ ) were randomly assigned to escitalopram (10 mg/day), fluoxetine (20 mg/day), or placebo. There was no significant difference in response rates across the three treatment conditions (response rates: escitalopram 46%, fluoxetine 37%, and placebo 47%).

**SSRI side effects and safety.** As a group of medications, the SSRIs have the same side-effect profile in older patients as in younger patients: specifically, gastrointestinal distress, agitation, insomnia, and sexual dysfunction. Discontinuation rates for SSRIs are not statistically different from the discontinuation rates

reported for a therapeutic plasma level of nortriptyline in the geriatric samples.

With respect to safety, the SSRIs offer a significant advantage over the TCAs. SSRIs are relatively benign in overdose ([Barbey and Roose 1998](#)) and do not have an effect on blood pressure, heart rate, cardiac conduction, or cardiac arrhythmias ([Glassman et al. 2002](#); [Roose et al. 1998](#)). SSRIs block the uptake of serotonin into platelets and significantly reduce platelet function. SSRIs are associated with upper gastrointestinal bleeding, intracerebral hemorrhage, and postoperative bleeding complications ([Musselman et al. 1998](#)).

## Other Antidepressants

**Venlafaxine.** One study reported meaningful information about venlafaxine in a geriatric population ([Schatzberg and Cantillon 2000](#)). In this 8-week randomized controlled clinical trial, 204 patients (mean age: 71 years) were randomly assigned to treatment with venlafaxine (75–225 mg/day), fluoxetine (20–60 mg/day), or placebo. Remission was defined as a Ham-D (24-item) score less than 8; the intent-to-treat remission rate was 42% for venlafaxine, 29% for fluoxetine, and 38% for placebo (no statistically significant differences). Significantly more patients treated with venlafaxine (27%) and fluoxetine (19%) discontinued study participation because of side effects than did those given placebo (9%) ( $P<0.05$ ). Cardiovascular measures, including heart rate and measures of cardiac conduction (including pulse rate, QRS, and QTc intervals), were assessed, and neither medication induced a significant change compared with placebo in any of these measures.

**Duloxetine.** There has been one randomized controlled trial of duloxetine for the treatment of late-life depression. In this study, 311 patients (mean baseline Ham-D score:  $22 \pm 4$ ) were randomly assigned in a 2-to-1 allocation favoring duloxetine ([Raskin et al. 2007](#)). The response and remission (final Ham-D score:  $\leq 7$ ) rates were significantly greater for duloxetine than for placebo (response rates: duloxetine 37%, placebo 27% [ $P < 0.001$ ]; remission rates: duloxetine 19%, placebo 15% [ $P = 0.002$ ]). However, as with many other trials of antidepressant medication for the treatment of late-life depression, the remission rates are distressingly low.

**Mirtazapine.** As previously discussed, in one randomized controlled comparator trial of mirtazapine versus paroxetine in a geriatric population, the intent-to-treat remission rates were 38% for the mirtazapine group and 28% for the paroxetine-treated patients ([Schatzberg et al. 2002](#)). In this study, the rate of discontinuation due to adverse events was similar in both groups: 33% for mirtazapine and 29% for paroxetine.

**Bupropion.** One randomized controlled comparator trial of bupropion versus paroxetine in late-life depression has been published, and this represents the only data available on bupropion in this population ([Weihs et al. 2000](#)). In this 6-week clinical trial, 100 patients (mean age: 70 years), with a baseline Ham-D (24-item) score of 27, were randomly assigned to treatment with either bupropion (100–300 mg/day) or paroxetine (10–40 mg/day). Rates of response (defined as a 50% reduction from baseline Ham-D score) in the intent-to-treat analysis were 71% in the bupropion group and 77% in the paroxetine group.

Remission data were not reported. Discontinuation rates were 17% in the bupropion group and 15% in the paroxetine group.

## **Antipsychotic Augmentation of Antidepressant Treatment**

The use of atypical antipsychotics as an augmentation strategy in adults whose symptoms have not responded to antidepressants has been shown to be effective in many placebo-controlled studies. Concerns have been raised about whether the same approach would be effective and safe in the late-life population. In a recently completed study involving 181 depressed patients older than 60 years who had not responded to an open trial of venlafaxine, patients were randomly assigned to receive the addition of either aripiprazole or placebo for a 12 weeks ([Lenze et al. 2015](#)). The response rate with aripiprazole augmentation was significantly higher than that with placebo (44% vs. 29%). Aripiprazole treatment was associated with akathisia and parkinsonism, but these side effects resolved if the medication was discontinued.

---

## **Antipsychotics in the Elderly**

---

No class of medication, including antipsychotics, is approved by the U.S. Food and Drug Administration (FDA) to treat psychosis or agitation in patients with dementia, although risperidone is approved in Germany and a few other countries for this purpose. Nonetheless, antipsychotics and other psychotropic medications are used widely in the management of dementia-related psychosis or

agitation because there are no treatment alternatives; evidence for the effectiveness of nonpharmacological behavioral approaches is limited and may apply mainly to patients with mild behavioral symptoms ([Brodaty and Arasaratnam 2012](#)).

In the elderly, antipsychotic use in neurodegenerative disorders exceeds antipsychotic use in schizophrenia because of the difference in disease prevalence rates ([Colenda et al. 2002](#)). In this population, the prevalence of schizophrenia remains below 1%, whereas the prevalence of dementia is approximately 2%–5% for people older than 60 years, and the prevalence increases to 15%–40% for people older than 85 years ([Thomas et al. 2001](#)). Psychosis and behavioral dyscontrol occur in the majority of patients with dementia during the course of illness ([Devanand et al. 1997](#); [Lyketsos et al. 2000](#)). Consequently, use of antipsychotics is greater in elderly patients with dementia (prescribed off-label) than in those with schizophrenia.

## Special Safety Considerations in Older Patients

### **Antipsychotic Side Effects**

Older patients are more sensitive to the side effects of antipsychotics, which can include sedation, cardiac effects (e.g., tachycardia, orthostatic hypotension), anticholinergic side effects (e.g., dry mouth, blurred vision, constipation, urinary retention), neuroleptic malignant syndrome with hyperpyrexia, autonomic instability and tachycardia, pigmentary retinopathy, weight gain and associated

metabolic changes, allergic reactions, and seizures ([Arana 2000](#)).

The antipsychotics most likely to cause orthostatic hypotension are low-potency conventional (or typical) antipsychotics such as chlorpromazine and thioridazine and the atypical antipsychotics clozapine, risperidone, olanzapine, and quetiapine ([Tandon 1998](#)). Low-potency conventional antipsychotics and clozapine have the greatest potential to cause anticholinergic effects. At comparable dosages, low-potency conventional antipsychotics are less likely than high-potency conventional antipsychotics such as haloperidol to cause extrapyramidal side effects (EPS), but up to 50% of patients 60–80 years of age receiving conventional antipsychotics develop either EPS or tardive dyskinesia (TD) ([Jeste et al. 1999](#)). [Saltz et al. \(1991\)](#) reported an incidence of TD of 31% after 43 weeks of conventional antipsychotic treatment in a sample of elderly patients, and antipsychotic-induced TD is five to six times more prevalent in elderly than in younger patients ([Jeste 2000](#)). The susceptibility of older patients to the side effects of typical antipsychotics, particularly the neurological side effects of EPS and TD, requires the use of dosages lower than those commonly used in young adults. Atypical antipsychotics have a lower potential for TD compared with typical antipsychotics ([Jeste 2000](#)).

To varying degrees, the metabolic syndrome with glucose dysregulation is a potential side effect of all antipsychotic medications. New-onset type 2 diabetes mellitus or diabetic ketoacidosis may be more common with clozapine and olanzapine compared with other antipsychotics, and blood glucose levels need to be monitored in elderly patients ([Jin et al. 2004](#)). Weight gain is a problematic side effect of

several antipsychotics, particularly olanzapine and clozapine.

Sedation is one of the most common side effects of antipsychotic medications, with low-potency conventional antipsychotics being potent sleep inducers. In addition, low-potency antipsychotics have a greater propensity to cause anticholinergic side effects, which can lead to daytime confusion and disorientation in the elderly.

An Ontario, Canada, study that examined the medical records of 97,777 patients found an association between antipsychotic use and abnormal kidney function tests, although the mechanism underlying this effect was not clear ([Hwang et al. 2014](#)). There have been reports of an association between antipsychotic use and deep vein thrombosis in patients with dementia, which may be related to the decrease in mobility that is a common side effect of several antipsychotics ([Parker et al. 2010](#)).

Elderly patients are often taking a large number of medications, and drug interactions need to be considered when prescribing antipsychotics. Specifically, adding fluoxetine to risperidone raises risperidone levels ([Bondolfi et al. 2002](#)), and similar effects have been reported when fluoxetine is combined with typical antipsychotics ([Solai et al. 2001](#)).

## **Antipsychotic Mortality Risks**

The use of antipsychotics is associated with an increased risk of sudden cardiac death ([Ray et al. 2001](#)). Among the antipsychotics, thioridazine appears to carry the highest risk of sudden unexplained death that is believed to be due to cardiac causes ([Reilly et al. 2002](#)). Risperidone prolongs the QTc interval but has no effect on QT dispersion ([Yerrabolu et al. 2000](#)). Prolongation of the QTc interval,

which is associated with the development of torsades de pointes and sudden death, is known to occur with several antipsychotics, including the atypical antipsychotic ziprasidone, but aripiprazole may reduce the QTc interval ([Goodnick et al. 2002](#)).

Based on a review of double-blind, placebo-controlled trials of atypical antipsychotics in patients with dementia, the FDA concluded that there was a significantly greater mortality risk (1.6–1.7 times) for patients treated with these medications compared with those treated with placebo, and that all antipsychotic medications must carry a black box warning to this effect ([Jeste et al. 2008](#); [Schneider et al. 2005](#)). There is no clear explanation as to why the use of atypical antipsychotics is associated with an increased mortality risk in patients with dementia. There may be a small increase in the risk of stroke ([Brodaty et al. 2003](#)), but the increase in stroke risk does not by itself account for the increased mortality risk ([Jeste et al. 2008](#)). In a large-scale medical records study involving more than 75,000 nursing home patients receiving antipsychotics, haloperidol was associated with the greatest increase in mortality risk, risperidone and olanzapine with intermediate risk, and quetiapine with the lowest increase in mortality risk ([Huybrechts et al. 2012](#)). In a large U.S. Department of Veterans Affairs (VA) study, the association between antipsychotic use and mortality was highest for haloperidol, with the caveat that some patients receiving higher dosages of haloperidol were being treated for delirium, which may have artificially increased the mortality rate observed because of the known association between delirium and increased mortality ([Maust et al. 2015](#)). Another review suggested that the mortality risk associated with antipsychotics may not be as large as believed, possibly



because the FDA black box warning has led to a decrease in antipsychotic prescribing for elderly patients with dementia who also have serious medical illness ([Hulshof et al. 2015](#)).

## **Pharmacokinetic and Pharmacodynamic Issues**

Age-related decreases in gut motility and the anticholinergic effects of antipsychotics may decrease absorption rates. Antipsychotic drugs undergo biotransformation primarily in the liver, with the gastrointestinal tract, lungs, and kidneys being secondary sites. Antipsychotics have slightly longer half-lives in the elderly than in the rest of the adult population, thereby prolonging side effects ([Hicks and Davis 1980](#)). The concomitant use of antacids may lower antipsychotic blood levels ([Fann et al. 1973](#)).

Dopamine neurons degenerate with aging, particularly after age 70 years, and decreases in the number of cholinergic receptors occur in Alzheimer's disease ([Davies and Maloney 1976](#); [Perry et al. 1977](#)). The decrease in the number of available dopaminergic receptors reduces the tolerance of elderly patients to antipsychotics, thus increasing the likelihood of neurological side effects, including EPS and TD.

Blockade of dopamine type 2 (D<sub>2</sub>) receptors is believed to be the primary mechanism of action of antipsychotics. Atypical antipsychotics are more potent antagonists at the serotonin type 2A (5-HT<sub>2A</sub>) receptor than at the D<sub>2</sub> receptor, resulting in fewer EPS and less TD compared with typical antipsychotics ([Jeste et al. 1999](#)).

# Antipsychotics in Management of Behavioral Complications of Dementia

Patients with dementia often develop behavioral disturbances (e.g., agitation, aggression) or psychotic features (e.g., delusions, hallucinations). As used here, the term *behavioral complications* denotes both behavioral disturbances and psychotic features. Behavioral complications occur in most forms of dementia, lead to considerable burden for caregivers, and are common precipitants of institutionalization.

Personality changes occur early in dementia and include apathy, anhedonia, irritability, inability to pay attention, depression, and loss of emotional connection ([Rubin and Kinscherf 1989](#)). In later stages, varying degrees of agitation may occur in more than half of Alzheimer's disease patients in outpatient clinics ([Devanand et al. 1997](#)) and nursing homes ([Cohen-Mansfield et al. 1989](#)), with aggressive behavior also becoming common ([Devanand et al. 1997](#); [Swearer et al. 1988](#)). Other disinhibited behaviors include pacing, wandering, verbal and physical aggression, repetitive calling out and screaming, and (rarely) self-mutilating behaviors. Catastrophic reactions, including bursts of anger and even violent behavior, can occur when patients are required to perform tasks beyond their cognitive capacities ([Devanand et al. 1992a](#)). Stubbornness, or refusal to complete essential activities of daily life, can be particularly frustrating for caregivers.

The prevalence of delusions ranges from 0% to 50% in different samples of Alzheimer's disease patients

([Devanand et al. 1997](#); [Lyketsos et al. 2000](#); [Reisberg et al. 1989](#)). Isolated delusional thoughts are more common than diagnosable psychotic disorders, and paranoid delusions of theft and suspicion are the most frequent types of delusions. Systematized complex delusions and grandiose delusions are relatively rare in Alzheimer's disease and other dementias. Delusional processes in dementia can be chronic or intermittent, a feature that distinguishes them from delusions in schizophrenia. Hallucinations, which can be visual or auditory, occur in 5%–15% of patients with dementia. In Alzheimer's disease, a typical hallucination is the conviction that someone else is in the house (i.e., phantom boarder syndrome). Diagnostic criteria for psychosis in Alzheimer's disease have been developed ([Jeste and Finkel 2000](#)).

In a series of 235 patients with mild to moderate Alzheimer's disease who were followed prospectively for up to 5 years, approximately half of the patients who manifested paranoid delusions or hallucinations at baseline were likely to manifest the same symptom 6 months later ([Devanand et al. 1997](#)), a finding consistent with other reports ([Ballard et al. 1997](#); [Paulsen et al. 2000](#)). However, paranoid delusions or hallucinations were evident at three out of four consecutive visits (over a period of 2 years) in only 10%–15% of patients, which raises the question of how long patients need to continue taking antipsychotics after treatment response. Psychosis and behavioral dyscontrol often coexist in Alzheimer's disease, and treatment with antipsychotics is often prescribed for one or both sets of symptoms.

## **Assessment of Psychopathology in Alzheimer's Disease**

In elderly patients, assessment and treatment of psychopathology should occur after reversible medical conditions (e.g., occult urinary tract infection, metabolic imbalance, iatrogenic or medication-induced symptoms) have been ruled out. Because of the impairment induced by Alzheimer's disease and other dementias, most rating scales have been developed as informant-based interviews. Commonly used rating scales for measurement of neuropsychiatric symptoms of Alzheimer's disease include the Neuropsychiatric Inventory (NPI; [Cummings et al. 1994](#)), the Neuropsychiatric Inventory—Nursing Home Version ([Wood et al. 2000](#)), the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD; [Reisberg et al. 1987](#)), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavior Rating Scale ([Tariot et al. 1995](#)), the Cohen-Mansfield Agitation Inventory (CMAI; [Cohen-Mansfield et al. 1989](#)), and the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD; [Devanand et al. 1992b](#)). The NPI, which uses a quantitative time-efficient decision-tree approach, is the most widely used scale for evaluating the effects of antipsychotic treatment in patients with dementia. Recently, international consensus criteria were developed for the syndrome of agitation in dementia and other neurocognitive disorders in older adults, and these criteria are being used in treatment trials for agitation in dementia, including the most common form, Alzheimer's disease ([Cummings et al. 2015](#)).

## **Neurobiological Mechanisms of Psychosis in Dementia**

Alzheimer's disease patients with psychosis have been found to have significantly more plaques and tangles in the medial temporal-prosubicular area and the middle frontal cortex (Zubenko et al. 1991) and four to five times higher levels of abnormal paired helical filament (PHF)-tau protein in the entorhinal and temporal cortices (Mukaetova-Ladinska et al. 1993). A decrease in serotonin in the prosubiculum of the cerebral cortex has been reported in patients with psychotic compared with nonpsychotic dementia (Lawlor et al. 1995; Zubenko et al. 1991). Decreases in acetylcholine have been correlated with increases in thought disorder (Sunderland et al. 1997). Cholinergic agents, including the acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) that are used to treat cognitive impairment in Alzheimer's disease, may also reduce behavioral symptoms (Bodick et al. 1997; Kaufer et al. 1996; Raskind 1999). Higher levels of norepinephrine in the substantia nigra (Zubenko et al. 1991) and higher levels of  $\beta$ -adrenergic receptors (Russo-Neustadt and Cotman 1997) in multiple brain regions have been reported in psychotic compared with nonpsychotic patients with Alzheimer's disease. These data suggest an enhanced responsiveness of catecholamines that may be associated with increased psychosis in Alzheimer's disease (Peskind et al. 1995). Homozygosity of the 1 and 2 alleles of the dopamine receptor *DR3* gene (Holmes et al. 2001; Sweet et al. 1998) and homozygosity for the C102 allele of the 5-HT<sub>2A</sub> receptor gene (Nacmias et al. 2001) may be associated with psychosis in Alzheimer's disease. However, the precise pathophysiology underlying psychosis in Alzheimer's disease is still unknown.

## Psychotropic Medication Use in Dementia

Studies in the 1970s and early 1980s indicated that nearly half of inpatients with dementia in VA hospitals ([Prien et al. 1975](#)) and in other settings ([Michel and Kolakowska 1981](#)) received psychotropic medications, primarily antipsychotics and benzodiazepines ([Ray et al. 1980](#)). Growing awareness of the neurological side effects of typical antipsychotics, particularly in dementia patients in nursing homes, led to the promulgation of the Omnibus Budget Reconciliation Act (OBRA) of 1987 ([Elon and Pawlson 1992](#)), which became effective in 1990. OBRA required identification of target symptoms, justification for the use of antipsychotics, and mandatory attempts to decrease or stop the antipsychotic medication every 3 months. Nonetheless, antipsychotic medications have remained the treatment of choice for behavioral complications in dementia ([Devanand et al. 1998](#); [Katz et al. 1999](#); [Schneider et al. 1990](#); [Street et al. 2000](#)), and drug utilization studies show that antipsychotics are used in 30%–50% of elderly institutionalized patients ([Giron et al. 2001](#); [Lantz et al. 1990](#)), although their use may have decreased in recent years after the FDA black box warning on increased mortality in patients with dementia receiving antipsychotics.

## **Studies of Antipsychotics in Dementia**

The results of a 1990 meta-analysis of placebo-controlled treatment trials indicated that typical antipsychotic treatment in dementia was significantly more efficacious than placebo, with the magnitude of the advantage over placebo averaging 18% ([Schneider et al. 1990](#)). In later placebo-controlled clinical trials with typical or atypical antipsychotics, response rates have varied between 45% and 60% for active medication and between 20% and 45% for placebo ([De Deyn et al. 1999](#); [Devanand et al. 1998](#);

Katz et al. 1999; Street et al. 2000), with an overall advantage for antipsychotic over placebo in the range of 18%–26% (Kindermann et al. 2002; Lanctôt et al. 1998). Clinically, a complete “cure” of the target psychotic and behavioral symptoms is uncommon.

In schizophrenia, antipsychotics are often assumed to be specific to the treatment of psychosis, and improvement in behavioral dyscontrol is believed to be secondary to improvement in psychosis. However, in patients with dementia, placebo-controlled studies consistently show comparable advantages for antipsychotics over placebo for symptoms of both psychosis and behavioral dyscontrol (Brodaty et al. 2003; De Deyn et al. 1999; Devanand et al. 1998; Katz et al. 1999; Street et al. 2000).

**Typical antipsychotics.** Early placebo-controlled studies of typical antipsychotics used in the management of behavioral complications of dementia showed moderate efficacy with a high placebo response rate, and considerable EPS occurred even at moderate dosages (Barnes et al. 1982; Finkel et al. 1995; Petrie et al. 1982; Rada and Kellner 1976). In a double-blind, placebo-controlled, randomized comparison of standard-dosage (2–3 mg/day) and low-dosage (0.50–0.75 mg/day) haloperidol in 71 outpatients with Alzheimer’s disease (Devanand et al. 1998), standard-dosage haloperidol was efficacious and superior to both low-dosage haloperidol and placebo for symptoms of both psychosis and agitation (Devanand et al. 1998). EPS tended to be greater for haloperidol (2–3 mg/day) than for the other two conditions. Low-dosage haloperidol did not differ from placebo on any measure of efficacy or side effects.

In another study that compared the SSRI citalopram, the typical antipsychotic perphenazine, and placebo, citalopram was comparable to perphenazine in efficacy and significantly superior to placebo, with an advantageous side-effect profile ([Pollock et al. 2002](#)).

**Atypical antipsychotics.** Because of their more favorable safety profile, the atypical antipsychotics have gradually replaced typical antipsychotics in the treatment of behavioral complications in dementia. Atypical antipsychotics can be safely administered with cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine), which are used to treat the cognitive impairment of dementia ([Weiser et al. 2002](#)). The choice of atypical antipsychotic depends on the patient's clinical profile and the medication's side-effect profile (e.g., a patient prone to falls should receive a medication that is not likely to cause orthostatic hypotension). Clozapine, risperidone, paliperidone and iloperidone (risperidone metabolites), olanzapine, quetiapine, aripiprazole, ziprasidone, lurasidone, asenapine, and cariprazine are the atypical antipsychotics that are currently available. There are as yet no published studies examining ziprasidone, lurasidone, asenapine, or cariprazine in the treatment of psychosis or agitation in patients with dementia.

*Clozapine.* Clozapine was the first atypical antipsychotic to become available in the United States. Clozapine causes substantial serotonergic blockade and has antiadrenergic and antimuscarinic properties ([Lieberman 1998](#)). Clozapine may be more efficacious than other antipsychotics in schizophrenia, and it carries essentially no risk of TD ([Kane et al. 1988](#)). Circulating levels of clozapine rise with dosage



and age and may be slightly higher in women than in men; sedation is common, and seizure potential is elevated (Centorrino et al. 1994; Kurz et al. 1998). Clozapine's anticholinergic properties can lead to dry mouth and constipation and can adversely affect cognition in the elderly. Also, intensive monitoring is required for blood dyscrasias, particularly agranulocytosis, which is reported to occur in 0.38% of patients (Kane et al. 1988). These factors, as well as the increased risk of falls and fractures related to the side effect of orthostatic hypotension, limit the use of clozapine in the elderly. The few retrospective reviews and case reports available indicate moderate efficacy but significant adverse events, suggesting very low tolerability in elderly patients with dementia (Chengappa et al. 1995; Oberholzer et al. 1992; Pitner et al. 1995). Therefore, clozapine is rarely used in patients with dementia.

*Risperidone.* Risperidone has serotonin 5-HT<sub>2</sub> and dopamine D<sub>2</sub> blocking properties,  $\alpha_1$ - and  $\alpha_2$ -adrenergic blocking properties, minimal histaminergic (H<sub>1</sub>) blocking properties, and little affinity for cholinergic receptors (Janssen et al. 1988). Its elimination half-life is between 20 and 22 hours, allowing for once-a-day dosing (Byerly and DeVane 1996).

In young adults with schizophrenia, risperidone 6 mg/day has the best therapeutic profile compared with lower and higher dosages, with a low propensity for EPS (Chouinard et al. 1993). By contrast, the optimal risperidone dosage range is much lower for elderly patients (Katz et al. 1999). Compared with the other atypical antipsychotics, risperidone may be more likely to lead to EPS and TD, although its risk is still considerably lower than that

associated with typical antipsychotics such as haloperidol; in one study, risperidone's 1-year cumulative incidence of TD was a relatively low 2.6% in institutionalized patients with dementia ([Jeste et al. 2000](#)). Risperidone is mildly sedating and has the potential to cause orthostatic hypotension, although the latter effect is uncommon when low dosages are used in the elderly ([Katz et al. 1999](#)).

In a multicenter study, 625 nursing home patients (mean age: 83 years) with dementia (73% Alzheimer's disease, 15% vascular dementia, 12% mixed dementia; mean 30-item Mini-Mental State Examination [MMSE] score: 6.6) who had behavioral complications were randomly assigned to receive risperidone—at 0.5 mg/day, 1.0 mg/day, or 2.0 mg/day—or placebo for 12 weeks ([Katz et al. 1999](#)). At study endpoint, response rates for risperidone 1 mg/day (45%) and 2 mg/day (50%) were significantly superior to rates for placebo and risperidone 0.5 mg/day, which showed similar response rates (33%). Patients receiving risperidone 2 mg/day were more likely than those receiving risperidone 0.5 mg/day or 1 mg/day to develop EPS and sedation, suggesting a relatively narrow therapeutic window. Therefore, a risperidone starting dosage of 0.5 mg/day, with gradual upward dosage titration to 1–2 mg/day, is recommended. A meta-analysis of four placebo-controlled trials with risperidone found that it was superior to placebo in treating psychosis and agitation, particularly in severely disturbed patients ([Katz et al. 2007](#)). Although a long-acting injectable risperidone preparation is available, that formulation has not been studied in the treatment of behavioral complications of dementia.

Paliperidone and iloperidone are chemically related to risperidone and are approved for the treatment of schizophrenia ([Davidson et al. 2007](#); [Marder et al. 2007](#))

but have not been studied systematically in the treatment of behavioral complications in dementia.

*Olanzapine.* Olanzapine blocks multiple receptor sites, including serotonin 5-HT<sub>2A/2C</sub> and dopamine D<sub>4/3/2/1</sub> (serotonin-to-dopamine receptor binding ratio of 8:1), histaminergic H<sub>1</sub> receptors, muscarinic acetylcholine receptors, and noradrenergic  $\alpha_1$  receptors ([Bymaster et al. 1996](#)). Olanzapine is well absorbed and, is unaffected by food, and because of its mean half-life of 30 hours, it can be used once a day ([Fulton and Goa 1997](#)).

Sedation and weight gain are prominent side effects of olanzapine, and its use has been associated with the development of metabolic syndrome. Orthostatic hypotension is not common when low dosages are used in elderly patients ([Street et al. 2000](#)). Intramuscular olanzapine is a useful alternative to intramuscular haloperidol in the treatment of acutely psychotic, agitated patients with schizophrenia ([Breier et al. 2002a](#)) and may be a useful alternative to intramuscular lorazepam in patients with dementia ([Meehan et al. 2002](#)).

In a double-blind, placebo-controlled multicenter clinical trial, 206 nursing home patients (mean age: 83 years) with Alzheimer's disease (mean MMSE score: 6.9) and behavioral complications were randomly assigned to placebo or fixed-dosage olanzapine (5 mg/day, 10 mg/day, or 15 mg/day) for 6 weeks. Olanzapine 5 mg/day was significantly more efficacious than placebo, but the 10-mg/day and 15-mg/day dosages were not superior to placebo. The prominent side effects of sedation and weight gain were limiting factors at the higher dosages ([Street et al. 2000](#)). Clinically, a starting dosage of 2.5 mg/day with gradual upward titration is recommended.

*Quetiapine.* Quetiapine acts as an antagonist at multiple neurotransmitter receptors in the brain, including dopamine D<sub>1</sub> and D<sub>2</sub>, serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2</sub>, histamine H<sub>1</sub>, and  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors. D<sub>2</sub> receptor affinity is less than 5-HT<sub>2</sub> receptor affinity. Quetiapine has no appreciable binding affinity at cholinergic muscarinic or benzodiazepine receptors (Casey 1996). Although it has a short half-life (approximately 3–6 hours; Fulton and Goa 1997), quetiapine's efficacy has been documented with twice-daily administration (McManus et al. 1999).

The incidence of EPS is very low with quetiapine. In a study of 284 elderly patients with dementia, quetiapine (average dosage 96.9 mg/day) and haloperidol (average dosage 1.9 mg/day) were indistinguishable from placebo on most measures of efficacy, although haloperidol led to more EPS (Tariot et al. 2006). The optimal dosage for quetiapine is undetermined because dosage comparison studies have not been conducted in patients with dementia. Wide dosage ranges (from 12.5 to 800 mg/day) are used in clinical practice. Physicians often prescribe quetiapine because of its relatively benign side-effect profile and to take advantage of its main side effect, sedation, in patients who have insomnia.

*Aripiprazole.* A placebo-controlled study of aripiprazole in 208 outpatients with behavioral complications of Alzheimer's disease showed no advantage for aripiprazole on the main outcome measure (NPI score), but there was superiority on secondary outcome measures (Brief Psychiatric Rating Scale [BPRS] psychosis and BPRS Core subscale scores). The average dosage used was 10 mg/day, which was generally well tolerated (De Deyn et al. 2005).

These limited data suggest that aripiprazole has a role as a second-line atypical antipsychotic treatment in Alzheimer's disease patients with behavioral complications and that low starting dosages of 2–5 mg/day can be used.

**Comparisons among antipsychotics.** Head-to-head comparison studies have shown few differences between typical antipsychotics in the treatment of behavioral complications in dementia ([Barnes et al. 1982](#); [Carlyle et al. 1993](#); [Petrie et al. 1982](#); [Smith et al. 1974](#); [Tsuang et al. 1971](#)).

In a study comparing a typical with an atypical antipsychotic, patients with dementia and behavioral complications were randomly assigned to receive flexible-dose risperidone, haloperidol, or placebo ([De Deyn et al. 1999](#)). In 344 patients, risperidone (average dosage: 1.1 mg/day), haloperidol (average dosage: 1.2 mg/day), and placebo produced improvement rates of 54%, 63%, and 47%, respectively, at week 12 ( $P=0.25$ ). No significant differences in improvement were seen between the groups on psychosis scores. In post hoc analyses, both haloperidol and risperidone were significantly better than placebo in reducing BEHAVE-AD total scores and CMAI aggression cluster scores ( $P=0.01$ ), and risperidone was superior to haloperidol on the CMAI aggression cluster score ( $P=0.05$ ). Patients taking haloperidol had significantly higher EPS scores at endpoint than did patients taking either risperidone or placebo, with no significant difference in EPS scores between patients receiving risperidone and those receiving placebo ([De Deyn et al. 1999](#)). Overall, risperidone's efficacy was comparable to that of haloperidol, but with a superior side-effect profile. In smaller studies in patients with dementia, comparisons of

haloperidol and risperidone have yielded equivocal results ([Chan et al. 2001](#); [Suh et al. 2004](#)).

In adults with schizophrenia, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed only marginal superiority in antipsychotic effectiveness for olanzapine compared with typical and other atypical antipsychotics ([Lieberman et al. 2005](#)). In England, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) of 227 patients with schizophrenia did not show any differences in treatment response for atypical versus typical antipsychotics ([Jones et al. 2006](#)).

In the 421 elderly patients who participated in the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD), which compared risperidone, olanzapine, quetiapine, and placebo (first randomized phase), there were no significant differences in time to discontinuation because the superior efficacy of risperidone and olanzapine was compromised by their increased propensity to side effects; quetiapine was indistinguishable from placebo ([Schneider et al. 2006](#)). These findings indicate that efficacy must be weighed against side effects when prescribing risperidone or olanzapine in a patient with dementia and that quetiapine may not be as effective.

**Comparisons of antipsychotics versus benzodiazepines.** The few early studies that compared antipsychotics with benzodiazepines suffered from methodological flaws, particularly in sample selection and study design ([Burgio et al. 1992](#); [Covington 1975](#); [Kirven and Montero 1973](#); [Stotsky 1984](#); [Tewfik et al. 1970](#)). The data available from these studies did not indicate superiority for benzodiazepines over antipsychotics in the

treatment of behavioral complications in patients with dementia.

Benzodiazepines are known to have deleterious effects on learning and memory both in healthy younger subjects ([Ghoneim et al. 1981](#); [Jones et al. 1978](#); [Liljequist et al. 1978](#)) and in the elderly, even without baseline cognitive impairment ([Pomara et al. 1991, 2015](#)). Benzodiazepines can lead to tolerance and dependence, and worsening of cognition is a concern. Therefore, benzodiazepines should be used at low dosages, and use should be restricted to short-term crisis management of agitated and anxious behaviors if antipsychotics or other medications are ineffective.

**Studies of anticonvulsants and other agents.** A small-sample study by [Tariot et al. \(1998\)](#) suggested that carbamazepine was effective in the treatment of behavioral complications of Alzheimer's disease, and there were suggestions that valproate was efficacious in a single-site study by the same research group ([Porsteinsson et al. 2001](#)). However, valproate at an average dosage of 800 mg/day did not show superiority over placebo in a larger study of 153 nursing home patients who participated in a double-blind, placebo-controlled trial ([Tariot et al. 2005](#)). Nonetheless, anticonvulsants such as valproate are routinely prescribed in nursing homes.

Studies of other medications, such as buspirone ([Lawlor et al. 1994](#)), trazodone ([Sultzer et al. 1997](#); [Teri et al. 2000](#)), lithium ([Holton and George 1985](#)), and propranolol ([Shankle et al. 1995](#); [Weiler et al. 1988](#)), have involved case series or small samples, usually without placebo controls. These medications can be considered as therapeutic options only after antipsychotic treatment has failed.



In a 12-week placebo-controlled trial in patients with dementia and agitation, citalopram showed a small but significant advantage over placebo in some but not all measures of efficacy ([Porsteinsson et al. 2014](#)). However, the majority of patients received citalopram 30 mg/day, which is higher than the FDA dosage limit of 20 mg/day, which was instituted because of QT prolongation on the electrocardiogram at higher dosages.

## Choice of Antipsychotic

The potential side-effect profile should determine the choice of antipsychotic for individual patients ([Ellingrod et al. 2002](#)). Clozapine should be reserved for those patients who do not respond to the other available antipsychotics. Patients prone to orthostatic hypotension (e.g., patients receiving  $\beta$ -blockers) may develop this side effect while taking risperidone or olanzapine, although postural hypotension is uncommon at low dosages ([Katz et al. 1999](#); [Street et al. 2000](#)). Olanzapine causes weight gain and is strongly sedating, but the latter side effect may be advantageous in patients with prominent insomnia. The metabolic syndrome can occur with all antipsychotics but is most likely to occur with olanzapine. Quetiapine is generally well tolerated, but it can be sedating. Among the atypical antipsychotics, risperidone is the most likely to cause EPS, so olanzapine or quetiapine should be preferred in elderly patients who have parkinsonian features. The incidence of TD is much lower with atypical antipsychotics than with the typical antipsychotic haloperidol ([Jeste et al. 2000](#)). In a study of 35 agitated patients with dementia who were switched from haloperidol to risperidone, the crossover was generally safe and effective ([Lane et al. 2002](#)). Overall, the decreased likelihood of neurological side effects, both short-



term and long-term, makes atypical antipsychotics the treatment of choice in these patients.

### **Optimal Antipsychotic Dosing Strategy**

The studies with haloperidol and risperidone produced similar results: very low dosages were ineffective, whereas high dosages led to side effects, suggesting a relatively narrow therapeutic window for these medications in dementia patients who develop behavioral complications. The optimal dosage for olanzapine appears to be 5 mg/day, based on the study comparing 5, 10, and 15 mg/day ([Street et al. 2000](#)). The optimal quetiapine dosage remains uncertain.

In patients with Alzheimer's disease, risperidone should be started at 0.25–0.50 mg/day at bedtime (or twice-daily dosing), with a 0.5-mg/day increase per week to a maximum of 2 mg/day (or possibly 3 mg/day). Olanzapine should be started at 2.5 mg/day or 5.0 mg/day at bedtime and slowly increased to a target daily dosage of 5–10 mg. Quetiapine should be started at 25 mg twice daily, with dosage increases as tolerated up to 300 mg twice daily, based solely on clinical response and side effects, because the optimal dosage range for quetiapine has not been identified. If a typical antipsychotic is used, a starting dosage equivalent to haloperidol 0.5 mg/day is advisable, with subsequent individualized titration to achieve an optimal trade-off between efficacy and side effects.

### **Use of Concomitant Psychotropics**

Use of anticholinergic agents to treat EPS should be avoided, particularly in Alzheimer's disease, in which a cholinergic deficit is believed to underlie much of the

cognitive impairment. In some patients, concomitant use of a hypnotic (e.g., zolpidem 5-10 mg/day or zaleplon 5-10 mg/day) may be required. Trazodone at dosages of 25-200 mg/day can also be used as a hypnotic in these patients. As noted earlier, benzodiazepine use should be limited to short-term crisis management of anxiety or agitation.

## **Optimal Duration of Antipsychotic Treatment**

A trial of 6-12 weeks usually is sufficient to determine the outcome of an antipsychotic treatment trial. If the optimal antipsychotic dosage is reached quickly, clinical response may occur within the first 1 or 2 weeks. On the other hand, the need to adjust the dosage because of side effects may require a relatively prolonged trial period.

The expected natural course of target symptoms during the course of dementia should be considered in determining the duration of antipsychotic treatment. Delusions and hallucinations are not very persistent, whereas agitation usually persists for several months to years during the course of Alzheimer's disease ([Devanand et al. 1997](#)).

Conflicting evidence exists regarding how long antipsychotic medications should be continued in these patients. One report suggested that antipsychotics and other psychotropics can be discontinued in nursing home patients with dementia without increased risk of behavioral symptom relapse ([Cohen-Mansfield et al. 1999](#)), but other reports indicate a moderate to high rate of relapse after discontinuation ([Avorn et al. 1992](#); [Fitz and Mallya 1992](#); [Horwitz et al. 1995](#)). A British study suggested that antipsychotic withdrawal leads to a moderately increased risk of relapse ([Ballard et al. 2004](#)), but multiple

antipsychotics were withdrawn, and the results were not clear-cut.

In the largest study to examine relapse risk after antipsychotic discontinuation ([Devanand et al. 2012](#)), 180 Alzheimer's disease patients with psychosis or agitation/aggression received 16 weeks of open treatment with risperidone (mean dosage 0.97 mg/day). Responders were then randomly assigned, in a double-blind manner, to one of three arms: 1) continuation risperidone for 32 weeks, 2) risperidone for 16 weeks followed by placebo for 16 weeks, or 3) placebo for 32 weeks. In the initial open-label treatment phase, psychosis and agitation improved, with mild increases in EPS; 112 patients met criteria for response to treatment, and 110 of these responders entered the random-assignment portion of the study. In the first 16 weeks after randomization, patients who discontinued to placebo (Arm 3) showed greater rates of relapse than those who continued on risperidone (Arms 1 and 2) (hazard ratio=1.94, 95% confidence interval [CI]=1.09-3.45,  $P=0.022$ ), for a relapse rate of 60% (24/40) for placebo versus 32.9% (23/70) for risperidone ( $P=0.004$ ). During the second 16 weeks, relapse rates were again greater with discontinuation to placebo (Arm 2) compared with continuation risperidone (Arm 1) (hazard ratio=4.88, 95% CI=1.08-21.98,  $P=0.023$ ), for a relapse rate of 48.1% (13/27) for placebo versus 15.4% (2/13) for risperidone ( $P=0.017$ ). Postrandomization adverse events and deaths did not differ significantly, although comparisons were based on small numbers of patients, especially during the final 16 weeks. The results showed that among Alzheimer's disease patients with psychosis or agitation who maintained response to risperidone for 4-8 months, risperidone discontinuation was associated with an

increased risk of relapse ([Devanand et al. 2012](#)). The authors' clinical recommendation, which applies to the issue of antipsychotic withdrawal in nursing homes as per federal guidelines, is that if a patient has shown a clear response to antipsychotic treatment, that patient should be continued on treatment for several months (up to 8 months based on this study) as long as side effects are not prominent. In contrast, if a patient's symptoms do not clearly respond to antipsychotic treatment, it is advisable to withdraw the treatment in order to reduce the likelihood of persistent side effects or the development of future complications, including an increased risk of mortality.

## **Antipsychotic Effects on Cognition and Activities of Daily Living**

The anticholinergic activity of antipsychotics may further compromise the already damaged central cholinergic projections in Alzheimer's disease. The level of cognitive impairment may be increased by the use of antipsychotics with strong anticholinergic properties or by the addition of anticholinergic agents to treat drug-induced EPS. Therefore, if EPS develops following antipsychotic treatment in a patient with dementia, switching to an antipsychotic that is less likely to cause EPS is preferable to adding an anticholinergic medication to treat the EPS. At another level, the sedation produced by antipsychotics may worsen the degree of disorientation and cognitive impairment in Alzheimer's disease.

## **Antipsychotic Blood-Level Monitoring**

Few studies have examined the utility of monitoring antipsychotic blood levels in patients with dementia. In a

study that compared haloperidol 2–3 mg/day, haloperidol 0.5–0.75 mg/day, and placebo, plasma haloperidol levels were detectable in all patients at the 2–3 mg daily dosage, and blood levels showed stronger correlations with efficacy and EPS than did oral dosages ([Pelton et al. 2003](#)). In this series of predominantly drug-naïve Alzheimer's disease patients, therapeutic effects occurred at haloperidol blood levels that were invariably below the postulated therapeutic window of 5–15 ng/mL in schizophrenia ([Van Putten et al. 1992](#); [Volavka et al. 1992](#)). Also, EPS developed in some patients at these low blood levels, suggesting that the increased sensitivity to antipsychotics seen in dementia is not likely to be attributable to pharmacokinetic changes. A pharmacodynamic explanation (e.g., loss of dopamine receptors leading to greater sensitivity to even low oral dosages of antipsychotic medication) is more likely. In contrast to the associations observed with the typical antipsychotic haloperidol, clinically relevant associations between blood levels of atypical antipsychotics such as risperidone and either efficacy or side effects have not been demonstrated ([Jeste 2000](#)).

## **Treatment Monitoring of Target Behavioral Symptoms**

The heterogeneous nature of behavioral complications suggests that specific target symptoms should be identified before initiating antipsychotic treatment, and these target symptoms should be monitored serially during the course of treatment. A scale such as the NPI can also be used. In addition to neurological and other common antipsychotic side effects, cognition and activities of daily living need to be monitored, preferably with brief instruments such as the

MMSE. In patients who are being maintained on antipsychotics for extended periods, assessment for TD using the Abnormal Involuntary Movement Scale should be conducted at regular intervals.

## Antipsychotics in Other Neurodegenerative Disorders in the Elderly

The relative efficacy of antipsychotics in other subtypes of dementia (e.g., vascular dementia or mixed dementia, frontotemporal dementia) has not been studied extensively. Antipsychotic treatment trials that included patients with vascular, mixed, and other forms of dementia did not reveal any differences in treatment response among the diagnostic subtypes of dementia ([De Deyn et al. 1999](#); [Katz et al. 1999](#)). With the exceptions of diffuse Lewy body disease (DLBD) and Parkinson's disease, in which EPS are likely to worsen with antipsychotics, the recommendations for the use of antipsychotics in Alzheimer's disease generally apply to their use in other types of dementia.

DLBD is a subtype of dementia characterized by prominent EPS, fluctuating clinical course, hallucinations, and extreme sensitivity to the neurological side effects of antipsychotics ([McKeith 2006](#)). DLBD has features that overlap with those of Alzheimer's disease and Parkinson's disease, and the boundaries of DLBD as a diagnostic entity remain controversial. Sensitivity to typical antipsychotics is one of the defining criteria for DLBD ([McKeith 2006](#)), and atypical antipsychotics may be safer to use in these patients. A post hoc analysis of the olanzapine dosage

comparison study in Alzheimer's disease suggested that olanzapine was safe and effective for the subgroup of patients who met diagnostic criteria for DLBD ([Cummings et al. 2002](#)). Patients with Parkinson's disease can develop iatrogenic psychosis caused by the levodopa-carbidopa combination (Sinemet) or dopamine agonists. Lowering the dosage of the dopaminergic agent will often lead to remission of psychotic symptoms, but the price paid may be an unacceptable increase in parkinsonian symptoms ([Breier et al. 2002b](#)). In such cases, antipsychotics with a very low propensity to cause EPS can be considered. However, two double-blind, placebo-controlled trials did not find an advantage for olanzapine over placebo in these patients ([Breier et al. 2002b](#)). Clozapine may be of some value in patients with Parkinson's disease ([J.H. Friedman and Fernandez 2002](#)), but quetiapine may be the preferred antipsychotic in this disorder. Long-term quetiapine use is generally well tolerated in patients with Parkinson's disease or DLBD ([Fernandez et al. 2002](#)). Pimavanserin, a selective inverse agonist at the serotonin 5-HT<sub>2A</sub> receptor, has been shown to be efficacious in treating psychosis in Parkinson's disease ([Cummings et al. 2014](#)).

In patients with delirium, short-term administration of antipsychotics—particularly antipsychotic agents with low anticholinergic properties, such as haloperidol—is a standard treatment strategy ([Tune 2002](#)). Atypical antipsychotics are useful in the management of delirium, and olanzapine has been reported to be safe and efficacious for the treatment of symptoms of delirium in hospitalized patients ([Breitbart et al. 2002](#)).

# Antipsychotics in Late-Life Schizophrenia

The majority of elderly schizophrenic patients were first diagnosed as young adults, but a minority of patients are first diagnosed with schizophrenia later in life. The International Late-Onset Schizophrenia Group reached a consensus that the diagnoses of late-onset schizophrenia (onset after age 40 years) and very-late-onset schizophrenia (onset after age 60 years) have face validity and clinical utility ([Howard et al. 2000](#)). Although age at onset affects the clinical presentation to some extent ([Sable and Jeste 2002](#)), it does not appreciably influence the likelihood of response to antipsychotics or the occurrence of side effects ([Sable and Jeste 2002](#)).

## Studies in Elderly Patients With Schizophrenia

Tapering and stopping antipsychotic medications in schizophrenia is associated with a high risk of relapse ([Csernansky and Schuchart 2002](#)). This risk has made it difficult to conduct placebo-controlled trials in samples of elderly schizophrenic patients ([Sable and Jeste 2002](#)). In elderly schizophrenic patients, switching from typical antipsychotics to risperidone has been reported to be effective and well tolerated ([Barak et al. 2002](#)). Atypical antipsychotics appear to be at least as efficacious as and better tolerated than typical antipsychotics in the elderly, and a study of veterans suggested that adherence to atypical antipsychotics is slightly higher than adherence to typical antipsychotics ([Dolder et al. 2002](#)).

In a 4-month comparison trial of flexible-dose risperidone ( $n=175$ ) versus quetiapine ( $n=553$ ) in 728 mixed-age



patients with a variety of psychotic disorders, quetiapine was as effective as risperidone and was less likely to require adjustment of concomitant antiparkinsonian medication. However, quetiapine was associated with more sedation, dry mouth, and dizziness ([Mullen et al. 2001](#)). Quetiapine was evaluated in a sample of 151 elderly psychotic patients (mean age: 77 years), among whom 40% had schizophrenia, bipolar disorder, or psychotic depression; 50% had psychosis associated with Alzheimer's disease; and 10% had psychosis associated with Parkinson's disease. The median quetiapine dosage was 100 mg/day (range = 100–400 mg/day). Significant improvement was seen in the primary outcome measure of psychosis as measured by the BPRS ( $P<0.0001$ ) and Clinical Global Impression Scale ( $P<0.01$ ). The prominent side effects included somnolence in 32%, dizziness or postural hypotension in 13%, and EPS in 6% ([McManus et al. 1999](#)).

In 184 elderly patients (mean age: 76.1 years), 72% with Alzheimer's disease and 28% with other psychoses (mainly schizophrenia), open-label quetiapine was administered over 52 weeks. Quetiapine at a median dosage of 137.5 mg/day was effective, with 49% of the patients showing a 20% or greater decline in BPRS scores. The main side effects were sedation (31%), dizziness (17%), and postural hypotension (15%) ([Tariot et al. 2000](#)). EPS-related adverse events occurred in 13% of patients, but overall ratings on an EPS scale showed a small improvement from baseline, and new-onset TD did not develop in any patient over the 1-year period. Although limited by the lack of placebo control or comparison with another antipsychotic to establish efficacy, the relatively benign side-effect profile of quetiapine is noteworthy. The CATIE studies in patients with Alzheimer's disease suggested that quetiapine's lack of

efficacy compared with olanzapine and risperidone (quetiapine did not separate from placebo) should be an equally important consideration ([Schneider et al. 2006](#)).

In all age groups, it has been difficult to demonstrate that the atypical antipsychotics approved for use in the United States improve negative symptoms (e.g., anhedonia, apathy), even though this putative effect was one of the factors driving the development of these compounds. However, medications approved in Europe (e.g., amisulpride) have been shown to be efficacious in improving the negative symptoms of schizophrenia in controlled studies ([Möller 2001](#)).

## **Treatment and Dosing**

In elderly patients with schizophrenia, a thorough evaluation followed by treatment with low dosages of atypical antipsychotics is the optimal strategy. When appropriate, antipsychotic treatment may need to be combined with psychosocial intervention ([Sable and Jeste 2002](#)).

The dosages of typical antipsychotics used in elderly patients with schizophrenia need to be lower than the dosages used in young adults ([Jeste 2000](#)). Abrupt withdrawal of atypical antipsychotics, particularly quetiapine, has not been shown to cause major adverse effects, but nonetheless, gradual withdrawal over a few days is advisable for all antipsychotics ([Cutler et al. 2002](#)). Although atypical antipsychotics can be safely combined with cholinesterase inhibitors in schizophrenia, a study in patients receiving risperidone found no cognitive benefit from adding donepezil compared with adding placebo ([J.I. Friedman et al. 2002](#)).

# Antipsychotics in Other Psychotic Disorders in the Elderly

Late-onset delusional disorder is uncommon. As is the case in young adults, delusional disorder in elderly individuals is difficult to treat, and the delusions often do not remit even with adequate antipsychotic treatment. The diagnosis of paraphrenia overlaps considerably with current nomenclature for late-onset schizophrenia, and atypical antipsychotics are the treatment of choice for this disorder ([Howard et al. 2000](#)).

Psychotic depression is an uncommon but clinically important diagnosis in the elderly. Based on studies in mixed-age samples, antipsychotics combined with antidepressants are the pharmacological treatment of choice in psychotic depression, but electroconvulsive therapy (ECT) is still considered the most effective treatment for this disorder ([Mulsant et al. 2001b](#); [Sackeim et al. 1995](#); [Spiker et al. 1985](#)). Expert consensus guidelines suggest that antipsychotic medication should be continued for 6 months following treatment response in psychotic depression ([Alexopoulos et al. 2001](#)). A double-blind trial of combination pharmacotherapy for psychotic depression showed that treatment with olanzapine plus sertraline was superior to treatment with olanzapine plus placebo in both older ( $\geq 60$  years) and younger adult patients, a finding that highlights the importance of combination antipsychotic and antidepressant treatment ([Meyers et al. 2009](#)).

Antipsychotics are used widely in the treatment of the manic phase of bipolar disorder across the life span ([Levine et al. 2000](#)). In bipolar disorder, there is ample evidence for

the efficacy of typical and atypical antipsychotics, both individually and in combination with mood stabilizers ([Sachs et al. 2002](#); [Tohen et al. 2002](#)). However, there is a surprising lack of data on the use of antipsychotics in geriatric patients with bipolar disorder. Lithium's toxicity, particularly in the neurological domain, is problematic in the elderly ([McDonald 2000](#)). Hence, anticonvulsants and atypical antipsychotics are frequently used to treat mania in elderly patients. However, in the absence of controlled data, the optimal choice of antipsychotic and the optimal dosage to use in these patients are open questions that need to be answered in future research.

Although obsessive-compulsive disorder is not considered a psychotic illness, there is evidence that atypical antipsychotics are useful adjunctive medications in adults with this disorder ([Denys et al. 2002](#)). However, comparable data are lacking in geriatric patients.

---

## Conclusion

---

Clearly, antipsychotic medications, particularly atypical antipsychotics, have an important role to play in the treatment of psychosis and behavioral dyscontrol in Alzheimer's disease, other types of dementia, and other neurodegenerative conditions. Antipsychotics remain the first-line treatment for schizophrenia and other psychotic disorders across the life span. When antipsychotic medications are used in elderly patients, monitoring of target symptoms, somatic side effects, potential drug interactions, cognition, and activities of daily living is necessary.

---

# References

---

- Alexopoulos GS, Katz IR, Reynolds CF 3rd, et al; Expert Consensus Panel for Pharmacotherapy of Depressive Disorders in Older Patients: The expert consensus guideline series. Pharmacotherapy of depressive disorders in older patients (Special Report). Postgrad Med Spec No Pharmacotherapy(October):1-86, 2001 17205639
- Allard P, Gram L, Timdahl K, et al: Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: a double-blind, randomised 6-month comparative trial with citalopram. Int J Geriatr Psychiatry 19(12):1123-1130, 2004 15526307
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987
- Arana GW: An overview of side effects caused by typical antipsychotics. J Clin Psychiatry 61 (suppl 8):5-11, discussion 12-13, 2000 10811237
- Avorn J, Soumerai SB, Everitt DE, et al: A randomized trial of a program to reduce the use of psychoactive drugs in nursing homes. N Engl J Med 327(3):168-173, 1992 1608408
- Ballard C, O'Brien J, Coope B, et al: A prospective study of psychotic symptoms in dementia sufferers: psychosis in dementia. Int Psychogeriatr 9(1):57-64, 1997 9195279
- Ballard CG, Thomas A, Fossey J, et al: A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor

of clinical outcome. J Clin Psychiatry 65(1):114-119, 2004 14744180

Barak Y, Shamir E, Weizman R: Would a switch from typical antipsychotics to risperidone be beneficial for elderly schizophrenic patients? A naturalistic, long-term, retrospective, comparative study. J Clin Psychopharmacol 22(2):115-120, 2002 11910255

Barbey JT, Roose SP: SSRI safety in overdose. J Clin Psychiatry 59 (suppl 15):42-48, 1998 9786310

Barnes R, Veith R, Okimoto J, et al: Efficacy of antipsychotic medications in behaviorally disturbed dementia patients. Am J Psychiatry 139(9):1170-1174, 1982 7114310

Benet LZ, Hoener BA: Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther 71(3):115-121, 2002 11907485

Bies RR, Feng Y, Lotrich FE, et al: Utility of sparse concentration sampling for citalopram in elderly clinical trial subjects. J Clin Pharmacol 44(12):1352-1359, 2004 15545305

Bigos KL, Bies RR, Pollock BG: Population pharmacokinetics in geriatric psychiatry. Am J Geriatr Psychiatry 14(12):993-1003, 2006 17138806

Bodick NC, Offen WW, Shannon HE, et al: The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease. Alzheimer Dis Assoc Disord 11 (suppl 4):S16-S22, 1997 9339268

Bondareff W, Alpert M, Friedhoff AJ, et al: Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. Am J Psychiatry 157(5):729-736, 2000 10784465

Bondolfi G, Eap CB, Bertschy G, et al: The effect of fluoxetine on the pharmacokinetics and safety of risperidone in psychotic patients. Pharmacopsychiatry 35(2):50-56, 2002 11985287

- Breier A, Meehan K, Birkett M, et al: A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry* 59(5):441-448, 2002a 11982448
- Breier A, Sutton VK, Feldman PD, et al: Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. *Biol Psychiatry* 52(5): 438-445, 2002b 12242060
- Breitbart W, Tremblay A, Gibson C: An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics* 43(3):175-182, 2002 12075032
- Brodaty H, Arasaratnam C: Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. *Am J Psychiatry* 169(9):946-953, 2012 22952073
- Brodaty H, Ames D, Snowden J, et al: A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* 64(2):134-143, 2003 12633121
- Burgio LD, Reynolds CFI, Janosky JE, et al: A behavioral microanalysis of the effects of haloperidol and oxazepam in demented psychogeriatric inpatients. *Int J Geriatr Psychiatry* 7:253-262, 1992
- Byerly MJ, DeVane CL: Pharmacokinetics of clozapine and risperidone: a review of recent literature. *J Clin Psychopharmacol* 16(2):177-187, 1996 8690833
- Bymaster FP, Calligaro DO, Falcone JF, et al: Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 14(2):87-96, 1996 8822531
- Carlyle W, Ancill RJ, Sheldon L: Aggression in the demented patient: a double-blind study of loxapine versus haloperidol. *Int Clin Psychopharmacol* 8(2):103-108, 1993 8345158

- Casey DE: Extrapyramidal syndromes and new antipsychotic drugs: findings in patients and non-human primate models. *Br J Psychiatry Suppl* (29):32-39, 1996 8733821
- Centorrino F, Baldessarini RJ, Kando JC, et al: Clozapine and metabolites: concentrations in serum and clinical findings during treatment of chronically psychotic patients. *J Clin Psychopharmacol* 14(2):119-125, 1994 8195452
- Chan WC, Lam LC, Choy CN, et al: A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. *Int J Geriatr Psychiatry* 16(12):1156-1162, 2001 11748775
- Chengappa KNR, Baker RW, Kreinbrook SB, Adair D: Clozapine use in female geriatric patients with psychoses. *J Geriatr Psychiatry Neurol* 8(1):12-15, 1995 7710640
- Chew ML, Mulsant BH, Pollock BG, et al: Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc* 56(7):1333-1341, 2008 18510583
- Chouinard G, Jones B, Remington G, et al: A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 13(1):25-40, 1993 7683702
- Cohen-Mansfield J, Marx MS, Rosenthal AS: A description of agitation in a nursing home. *J Gerontol* 44(3):M77-M84, 1989 2715584
- Cohen-Mansfield J, Lipson S, Werner P, et al: Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study. *Arch Intern Med* 159(15):1733-1740, 1999 10448776
- Colenda CC, Mickus MA, Marcus SC, et al: Comparison of adult and geriatric psychiatric practice patterns:



- findings from the American Psychiatric Association's Practice Research Network. *Am J Geriatr Psychiatry* 10(5):609-617, 2002 12213696
- Covington JS: Alleviating agitation, apprehension, and related symptoms in geriatric patients: A double-blind comparison of a phenothiazine and a benzodiazepien. *South Med J* 68(6):719-724, 1975 1094544
- Csernansky JG, Schuchart EK: Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. *CNS Drugs* 16(7): 473-484, 2002 12056922
- Cummings JL, Mega M, Gray K, et al: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44(12):2308-2314, 1994 7991117
- Cummings JL, Street J, Masterman D, Clark WS: Efficacy of olanzapine in the treatment of psychosis in dementia with lewy bodies. *Dement Geriatr Cogn Disord* 13(2):67-73, 2002 11844887
- Cummings J, Isaacson S, Mills R, et al: Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet* 383(9916):533-540, 2014 24183563
- Cummings J, Mintzer J, Brodaty H, et al; International Psychogeriatric Association: Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *Int Psychogeriatr* 27(1): 7-17, 2015 25311499
- Cutler AJ, Goldstein JM, Tumas JA: Dosing and switching strategies for quetiapine fumarate. *Clin Ther* 24(2):209-222, 2002 11911552
- Davidson M, Emsley R, Kramer M, et al: Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. *Schizophr Res* 93(1-3):117-130, 2007 17466492

- Davies P, Maloney AJF: Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* 2(8000):1403, 1976 63862
- De Deyn PP, Rabheru K, Rasmussen A, et al: A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology* 53(5):946-955, 1999 10496251
- De Deyn P, Jeste DV, Swanink R, et al: Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study. *J Clin Psychopharmacol* 25(5):463-467, 2005 16160622
- Denys D, van Megen H, Westenberg H: Quetiapine addition to serotonin reuptake inhibitor treatment in patients with treatment-refractory obsessive-compulsive disorder: an open-label study. *J Clin Psychiatry* 63(8):700-703, 2002 12197450
- Devanand DP, Brockington CD, Moody BJ, et al: Behavioral syndromes in Alzheimer's disease. *Int Psychogeriatr* 4 (suppl 2): 161-184, 1992a 1288661
- Devanand DP, Miller L, Richards M, et al: The Columbia University Scale for Psychopathology in Alzheimer's disease. *Arch Neurol* 49(4):371-376, 1992b 1558517
- Devanand DP, Jacobs DM, Tang M-X, et al: The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry* 54(3):257-263, 1997 9075466
- Devanand DP, Marder K, Michaels KS, et al: A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. *Am J Psychiatry* 155(11): 1512-1520, 1998 9812111
- Devanand DP, Mintzer J, Schultz SK, et al: Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med* 367(16):1497-1507, 2012 23075176
- Dolder CR, Lacro JP, Dunn LB, Jeste DV: Antipsychotic medication adherence: is there a difference between

- typical and atypical agents? *Am J Psychiatry* 159(1):103-108, 2002 11772697
- Dresser GK, Spence JD, Bailey DG: Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 38(1):41-57, 2000 10668858
- Ellingrod VL, Schultz SK, Ekstam-Smith K, et al: Comparison of risperidone with olanzapine in elderly patients with dementia and psychosis. *Pharmacotherapy* 22(1):1-5, 2002 11794418
- Elon R, Pawlson LG: The impact of OBRA on medical practice within nursing facilities. *J Am Geriatr Soc* 40(9):958-963, 1992 1512394
- Fann WE, Davis JM, Janowsky DS, et al: Chlorpromazine: effects of antacids on its gastrointestinal absorption. *J Clin Pharmacol* 13(10):388-390, 1973 4355737
- Feng Y, Pollock BG, Ferrell RE, et al: Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling. *Br J Clin Pharmacol* 61(5):558-569, 2006 16669849
- Fernandez HH, Trieschmann ME, Burke MA, Friedman JH: Quetiapine for psychosis in Parkinson's disease versus dementia with Lewy bodies. *J Clin Psychiatry* 63(6):513-515, 2002 12088163
- Finkel SI, Lyons JS, Anderson RL, et al: A randomized, placebo-controlled trial of thiothixene in agitated, demented nursing home patients. *Int J Geriatr Psychiatry* 10:129-136, 1995
- Fitz D, Mallya A: Discontinuation of a psychogeriatric program for nursing home residents: psychotropic medication changes and behavioral reactions. *J Appl Gerontol* 11(1):50-63, 1992 10116945
- Flint AJ, Rifat SL: The effect of sequential antidepressant treatment on geriatric depression. *J Affect Disord* 36(3-4):95-105, 1996 8821312

- Flockhart DA: Drug Interactions: Cytochrome P450 Drug Interaction Table. Indianapolis, Indiana University School of Medicine, 2007. Available at: <http://medicine.iupui.edu/clinpharm/ddis/clinical-table/>. Accessed February 28, 2016.
- Friedman JH, Fernandez HH: Atypical antipsychotics in Parkinson-sensitive populations. *J Geriatr Psychiatry Neurol* 15(3): 156-170, 2002 12230086
- Friedman JI, Adler DN, Howanitz E, et al: A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for the cognitive impairment of schizophrenia. *Biol Psychiatry* 51(5):349-357, 2002 11904128
- Fulton B, Goa KL: Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. *Drugs* 53(2):281-298, 1997 9028746
- Gerretsen P, Pollock BG: Drugs with anticholinergic properties: a current perspective on use and safety. *Expert Opin Drug Saf* 10(5):751-765, 2011 21635190
- Ghoneim MM, Mewaldt SP, Berie JL, Hinrichs JV: Memory and performance effects of single and 3-week administration of diazepam. *Psychopharmacology (Berl)* 73(2):147-151, 1981 6785805
- Giron MS, Forsell Y, Bernstein C, et al: Psychotropic drug use in elderly people with and without dementia. *Int J Geriatr Psychiatry* 16(9):900-906, 2001 11571771
- Glassman AH, Roose SP, Bigger JT Jr: The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. *JAMA* 269(20):2673-2675, 1993 8487453
- Glassman AH, O'Connor CM, Califf RM, et al; Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group: Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 288(6):701-709, 2002 12169073

- Goodnick PJ, Jerry J, Parra F: Psychotropic drugs and the ECG: focus on the QTc interval. *Expert Opin Pharmacother* 3(5):479-498, 2002 11996627
- Gottfries CG: Scandinavian experience with citalopram in the elderly. *Int Clin Psychopharmacol* 11 (suppl 1):41-44, 1996 8732444
- Graff-Guerrero A, Rajji TK, Mulsant BH, et al: Maintenance antipsychotic dose can be decreased in late-life schizophrenia: a prospective dopamine D2/3 receptor occupancy study with [11C]-raclopride. *JAMA Psychiatry* 72:927-934, 2015 26131622
- Greenblatt DJ, Harmatz JS, Shader RI: Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly. Therapeutic considerations (Part I). *Clin Pharmacokinet* 21(3):165-177, 1991 1684924
- Gurwitz JH, Field TS, Avorn J, et al: Incidence and preventability of adverse drug events in nursing homes. *Am J Med* 109(2):87-94, 2000 10967148
- Gurwitz JH, Field TS, Harrold LR, et al: Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 289(9):1107-1116, 2003 12622580
- Hicks R, Davis J: Pharmacokinetics in geriatric psychopharmacology, in *Psychopharmacology of Aging*. Edited by Eisdorfer C, Fann W. New York, Spectrum Publications, 1980, pp 169-212
- Holmes C, Smith H, Ganderton R, et al: Psychosis and aggression in Alzheimer's disease: the effect of dopamine receptor gene variation. *J Neurol Neurosurg Psychiatry* 71(6):777-779, 2001 11723200
- Holton A, George K: The use of lithium in severely demented patients with behavioural disturbance. *Br J Psychiatry* 146:99-100, 1985 3978352
- Horwitz GJ, Tariot PN, Mead K, et al: Discontinuation of antipsychotics in nursing home patients with dementia. *Am J Geriatr Psychiatry* 3:290-299, 1995

- Howard R, Rabins PV, Seeman MV, Jeste DV; The International Late-Onset Schizophrenia Group: Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. *Am J Psychiatry* 157(2):172-178, 2000 10671383
- Hulshof TA, Zuidema SU, Ostelo RW, Luijendijk HJ: The mortality risk of conventional antipsychotics in elderly patients: a systematic review and meta-analysis of randomized placebo-controlled trials. *J Am Med Dir Assoc* 16(10):817-824, 2015 25933724
- Huybrechts KF, Gerhard T, Crystal S, et al: Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ* 344:e977, 2012 22362541
- Hwang YJ, Dixon SN, Reiss JP, et al: Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. *Ann Intern Med* 161(4):242-248, 2014 25133360
- Janssen PA, Niemegeers CJ, Awouters F, et al: Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S2 and dopamine-D2 antagonistic properties. *J Pharmacol Exp Ther* 244(2):685-693, 1988 2450200
- Jeste DV: Tardive dyskinesia in older patients. *J Clin Psychiatry* 61 (suppl 4):27-32, 2000 10739328
- Jeste DV, Finkel SI: Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. *Am J Geriatr Psychiatry* 8(1):29-34, 2000 10648292
- Jeste DV, Lacro JP, Palmer B, et al: Incidence of tardive dyskinesia in early stages of low-dose treatment with typical neuroleptics in older patients. *Am J Psychiatry* 156(2):309-311, 1999 9989570
- Jeste DV, Okamoto A, Napolitano J, et al: Low incidence of persistent tardive dyskinesia in elderly patients with

- dementia treated with risperidone. *Am J Psychiatry* 157(7):1150-1155, 2000 10873925
- Jeste DV, Blazer D, Casey D, et al: ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology* 33(5):957-970, 2008 17637610
- Jin H, Meyer JM, Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res* 71(2-3):195-212, 2004 15474892
- Jin Y, Pollock BG, Frank E, et al: Effect of age, weight, and CYP2C19 genotype on escitalopram exposure. *J Clin Pharmacol* 50(1):62-72, 2010 19841156
- Jones DM, Lewis MJ, Spriggs TLB: The effects of low doses of diazepam on human performance in group administered tasks. *Br J Clin Pharmacol* 6(4):333-337, 1978 698029
- Jones PB, Barnes TR, Davies L, et al: Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 63(10):1079-1087, 2006 17015810
- Kane J, Honigfeld G, Singer J, Meltzer H: Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45(9):789-796, 1988 3046553
- Kasper S, de Swart H, Friis Andersen H: Escitalopram in the treatment of depressed elderly patients. *Am J Geriatr Psychiatry* 13(10):884-891, 2005 16223967
- Katz IR, Jeste DV, Mintzer JE, et al; Risperidone Study Group: Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. *J Clin Psychiatry* 60(2):107-115, 1999 10084637
- Katz I, de Deyn PP, Mintzer J, et al: The efficacy and safety of risperidone in the treatment of psychosis of

- Alzheimer's disease and mixed dementia: a meta-analysis of 4 placebo-controlled clinical trials. *Int J Geriatr Psychiatry* 22(5):475-484, 2007 17471598
- Kaufer DI, Cummings JL, Christine D: Effect of tacrine on behavioral symptoms in Alzheimer's disease: an open-label study. *J Geriatr Psychiatry Neurol* 9(1):1-6, 1996 8679057
- Kim H, Lim SW, Kim S, et al: Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression. *JAMA* 296(13):1609-1618, 2006 17018806
- Kindermann SS, Dolder CR, Bailey A, et al: Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. *Drugs Aging* 19(4):257-276, 2002 12038878
- Kirby D, Ames D: Hyponatraemia and selective serotonin re-uptake inhibitors in elderly patients. *Int J Geriatr Psychiatry* 16(5):484-493, 2001 11376464
- Kirven LE, Montero EF: Comparison of thioridazine and diazepam in the control of nonpsychotic symptoms associated with senility: double-blind study. *J Am Geriatr Soc* 21(12):546-551, 1973 4584169
- Kurz M, Hummer M, Kemmler G, et al: Long-term pharmacokinetics of clozapine. *Br J Psychiatry* 173:341-344, 1998 9926040
- Lancôt KL, Best TS, Mittmann N, et al: Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. *J Clin Psychiatry* 59(10):550-561, quiz 562-563, 1998 9818639
- Lane H-Y, Chang Y-C, Chiu C-C, et al: Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. *Am J Psychiatry* 159(9):1593-1595, 2002 12202283
- Lantz MS, Louis A, Lowenstein G, Kennedy GJ: A longitudinal study of psychotropic prescriptions in a



- teaching nursing home. *Am J Psychiatry* 147(12):1637-1639, 1990 2244642
- Lawlor BA, Radcliffe J, Molchan SE, et al: A pilot placebo-controlled study of trazodone and buspirone in Alzheimer's disease. *Int J Geriatr Psychiatry* 9:55-59, 1994
- Lawlor BA, Ryan TM, Bierer LM, et al: Lack of association between clinical symptoms and postmortem indices of brain serotonin function in Alzheimer's disease. *Biol Psychiatry* 37(12):895-896, 1995 7548465
- Lenze E, Mulsant B, Blumberger D, et al: Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. *Lancet* 386(10011):2394, 2015 26423182
- Levine J, Chengappa KN, Brar JS, et al: Psychotropic drug prescription patterns among patients with bipolar I disorder. *Bipolar Disord* 2(2):120-130, 2000 11252651
- Lieberman JA: Maximizing clozapine therapy: managing side effects. *J Clin Psychiatry* 59 (suppl 3):38-43, 1998 9541337
- Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353(12):1209-1223, 2005 16172203
- Liljequist R, Linnoila M, Mattila MJ: Effect of diazepam and chlorpromazine on memory functions in man. *Eur J Clin Pharmacol* 13(5):339-343, 1978 352709
- Liu B, Anderson G, Mittmann N, et al: Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet* 351(9112):1303-1307, 1998 9643791
- Lotrich FE, Pollock BG: Aging and clinical pharmacology: implications for antidepressants. *J Clin Pharmacol* 45(10):1106-1122, 2005 16172176

- Lyketsos CG, Steinberg M, Tschanz JT, et al: Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 157(5):708-714, 2000 10784462
- Marder SR, Kramer M, Ford L, et al: Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. *Biol Psychiatry* 62(12):1363-1370, 2007 17601495
- Maust DT, Kim HM, Seyfried LS, et al: Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry* 72(5):438-445, 2015 25786075
- McDonald WM: Epidemiology, etiology, and treatment of geriatric mania. *J Clin Psychiatry* 61 (suppl 13):3-11, 2000 11153809
- McKeith IG: Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. *J Alzheimers Dis* 9 (3 suppl):417-423, 2006 16914880
- McManus DQ, Arvanitis LA, Kowalczyk BB: Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. Seroquel Trial 48 Study Group. *J Clin Psychiatry* 60(5):292-298, 1999 10362435
- Meehan KM, Wang H, David SR, et al: Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. *Neuropsychopharmacology* 26(4):494-504, 2002 11927174
- Mesters P, Ansseau M, Brasseur R, et al: An open multicentre study to evaluate the efficacy and tolerance of fluoxetine 20 mg in depressed ambulatory patients. *Acta Psychiatr Belg* 92(4):232-245, 1992 1345403
- Meyers BS, Flint AJ, Rothschild AJ, et al; STOP-PD Group: A double-blind randomized controlled trial of olanzapine

plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). *Arch Gen Psychiatry* 66(8):838-847, 2009 19652123

Michel K, Kolakowska T: A survey of prescribing psychotropic drugs in two psychiatric hospitals. *Br J Psychiatry* 138:217-221, 1981 7272613

Möller HJ: Amisulpride: efficacy in the management of chronic patients with predominant negative symptoms of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 251(5):217-224, 2001 11829208

Mukaetova-Ladinska EB, Harrington CR, Roth M, Wischik CM: Biochemical and anatomical redistribution of tau protein in Alzheimer's disease. *Am J Pathol* 143(2): 565-578, 1993 8342603

Mullen J, Jibson MD, Sweitzer D: A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: the quetiapine experience with safety and tolerability (QUEST) study. *Clin Ther* 23(11):1839-1854, 2001 11768836

Mulsant BH, Pollock BG, Nebes R, et al: A twelve-week, double-blind, randomized comparison of nortriptyline and paroxetine in older depressed inpatients and outpatients. *Am J Geriatr Psychiatry* 9(4):406-414, 2001a 11739067

Mulsant BH, Sweet RA, Rosen J, et al: A double-blind randomized comparison of nortriptyline plus perphenazine versus nortriptyline plus placebo in the treatment of psychotic depression in late life. *J Clin Psychiatry* 62(8):597-604, 2001b 11561930

Mulsant BH, Pollock BG, Kirshner M, et al: Serum anticholinergic activity in a community-based geriatric sample: relationship with cognitive performance. *Arch Gen Psychiatry* 60(2):198-203, 2003 12578438

- Murphy GM Jr, Hollander SB, Rodrigues HE, et al: Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry* 61(11):1163-1169, 2004 15520364
- Musselman DL, Evans DL, Nemeroff CB: The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 55(7): 580-592, 1998 9672048
- Nacmias B, Tedde A, Forleo P, et al: Association between 5-HT(2A) receptor polymorphism and psychotic symptoms in Alzheimer's disease. *Biol Psychiatry* 50(6): 472-475, 2001 11566166
- Navarro V, Gastó C, Torres X, et al: Citalopram versus nortriptyline in late-life depression: a 12-week randomized single-blind study. *Acta Psychiatr Scand* 103(6):435-440, 2001 11401657
- Nebes RD, Pollock BG, Perera S, et al: The greater sensitivity of elderly APOE  $\epsilon$ 4 carriers to anticholinergic medications is independent of cerebrovascular disease risk. *Am J Geriatr Pharmacother* 10(3): 185-192, 2012 22534472
- Nelson JC, Kennedy JS, Pollock BG, et al: Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. *Am J Psychiatry* 156(7):1024-1028, 1999 10401446
- Newhouse PA, Krishnan KRR, Doraiswamy PM, et al: A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. *J Clin Psychiatry* 61(8):559-568, 2000 10982198
- Oberholzer AF, Hendriksen C, Monsch AU, et al: Safety and effectiveness of low-dose clozapine in psychogeriatric patients: a preliminary study. *Int Psychogeriatr* 4(2):187-195, 1992 1477306
- Parker C, Coupland C, Hippisley-Cox J: Antipsychotic drugs and risk of venous thromboembolism: nested case-

- control study. *BMJ* 341:c4245, 2010 20858909
- Paulsen JS, Salmon DP, Thal LJ, et al: Incidence of and risk factors for hallucinations and delusions in patients with probable AD. *Neurology* 54(10):1965-1971, 2000 10822438
- Pelton GH, Devanand DP, Bell K, et al: Usefulness of plasma haloperidol levels for monitoring clinical efficacy and side effects in Alzheimer patients with psychosis and behavioral dyscontrol. *Am J Geriatr Psychiatry* 11(2):186-193, 2003 12611748
- Perry EK, Gibson PH, Blessed G, et al: Neurotransmitter enzyme abnormalities in senile dementia. Choline acetyltransferase and glutamic acid decarboxylase activities in necropsy brain tissue. *J Neurol Sci* 34(2):247-265, 1977 144789
- Peskind ER, Raskind MA, Wingerson D, et al: Enhanced hypothalamic-pituitary-adrenocortical axis responses to physostigmine in normal aging. *J Gerontol A Biol Sci Med Sci* 50(2):M114-M120, 1995 7874590
- Petrie WM, Ban TA, Berney S, et al: Loxapine in psychogeriatrics: a placebo- and standard-controlled clinical investigation. *J Clin Psychopharmacol* 2(2):122-126, 1982 7042770
- Pitner JK, Mintzer JE, Pennypacker LC, Jackson CW: Efficacy and adverse effects of clozapine in four elderly psychotic patients. *J Clin Psychiatry* 56(5):180-185, 1995 7737956
- Pollock BG, Everett G, Perel JM: Comparative cardiotoxicity of nortriptyline and its isomeric 10-hydroxymetabolites. *Neuropsychopharmacology* 6(1):1-10, 1992a 1571065
- Pollock BG, Perel JM, Altieri LP, et al: Debrisoquine hydroxylation phenotyping in geriatric psychopharmacology. *Psychopharmacol Bull* 28(2):163-168, 1992b 1513919
- Pollock BG, Ferrell RE, Mulsant BH, et al: Allelic variation in the serotonin transporter promoter affects onset of

paroxetine treatment response in late-life depression. *Neuropsychopharmacology* 23(5):587-590, 2000a 11027924

Pollock BG, Laghrissi-Thode F, Wagner WR: Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. *J Clin Psychopharmacol* 20(2): 137-140, 2000b 10770450

Pollock BG, Mulsant BH, Rosen J, et al: Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. *Am J Psychiatry* 159(3):460-465, 2002 11870012

Pomara N, Deptula D, Singh R, et al: Cognitive toxicity of benzodiazepines in the elderly, in *Anxiety in the Elderly: Treatment and Research*. Edited by Salzman C, Lebowitz BD. New York, Springer, 1991, pp 175-196

Pomara N, Lee SH, Bruno D, et al: Adverse performance effects of acute lorazepam administration in elderly long-term users: pharmacokinetic and clinical predictors. *Prog Neuropsychopharmacol Biol Psychiatry* 56:129-135, 2015 25195839

Porsteinsson AP, Tariot PN, Erb R, et al: Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry* 9(1):58-66, 2001 11156753

Porsteinsson AP, Drye LT, Pollock BG, et al; CitAD Research Group: Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA* 311(7):682-691, 2014 24549548

Prien RF, Haber PA, Caffey EMJ Jr: The use of psychoactive drugs in elderly patients with psychiatric disorders: survey conducted in twelve s Administration hospitals. *J Am Geriatr Soc* 23(3):104-112, 1975 234489

Rada RT, Kellner R: Thiothixene in the treatment of geriatric patients with chronic organic brain syndrome. *J Am Geriatr Soc* 24(3):105-107, 1976 765388

- Raskin J, Wiltse CG, Siegal A, et al: Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry* 164(6):900-909, 2007 17541049
- Raskind MA: Evaluation and management of aggressive behavior in the elderly demented patient. *J Clin Psychiatry* 60 (suppl 15):45-49, 1999 10418815
- Ray WA, Federspiel CF, Schaffner W: A study of antipsychotic drug use in nursing homes: epidemiologic evidence suggesting misuse. *Am J Public Health* 70(5):485-491, 1980 6103676
- Ray WA, Meredith S, Thapa PB, et al: Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 58(12):1161-1167, 2001 11735845
- Reilly JG, Ayis SA, Ferrier IN, et al: Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry* 180:515-522, 2002 12042230
- Reisberg B, Borenstein J, Salob SP, et al: Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry* 48 (suppl):9-15, 1987 3553166
- Reisberg B, Franssen E, Sclan S, et al: Stage specific incidence of potentially remediable behavioral symptoms in aging and Alzheimer's disease: a study of 120 patients using the BEHAVE-AD. *Bull Clin Neurosci* 54:95-112, 1989
- Roe CM, Anderson MJ, Spivack B: Use of anticholinergic medications by older adults with dementia. *J Am Geriatr Soc* 50(5):836-842, 2002 12028169
- Ronfeld RA, Tremaine LM, Wilner KD: Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers. *Clin Pharmacokinet* 32 (suppl 1):22-30, 1997 9068932
- Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic

- hypotension: a meaningful difference. *J Clin Psychopharmacol* 1(5):316-319, 1981 6277997
- Roose SP, Glassman AH, Attia E, Woodring S: Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am J Psychiatry* 151(12):1735-1739, 1994 7977878
- Roose SP, Laghrissi-Thode F, Kennedy JS, et al: Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 279(4):287-291, 1998 9450712
- Roose S, Alexopoulos G, Burke W, et al: Treatment of depression in the "old-old": a randomized, double-blind, placebo-controlled trial of citalopram in patients at least 75 years of age, in New Research, American Association of Geriatric Psychiatry, Orlando, FL, March 2002
- Rubin EH, Kinscherf DA: Psychopathology of very mild dementia of the Alzheimer type. *Am J Psychiatry* 146(8):1017-1021, 1989 2750973
- Russo-Neustadt A, Cotman CW: Adrenergic receptors in Alzheimer's disease brain: selective increases in the cerebella of aggressive patients. *J Neurosci* 17(14):5573-5580, 1997 9204938
- Sable JA, Jeste DV: Antipsychotic treatment for late-life schizophrenia. *Curr Psychiatry Rep* 4(4):299-306, 2002 12126599
- Sachs GS, Grossman F, Ghaemi SN, et al: Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry* 159(7):1146-1154, 2002 12091192
- Sackeim HA, Devanand DP, Nobler MS: Electroconvulsive therapy, in *Psychopharmacology: The Fourth Generation of Progress*. Edited by Bloom F, Kupfer D. New York, Raven, 1995, pp 1123-1141
- Saltz BL, Woerner MG, Kane JM, et al: Prospective study of tardive dyskinesia incidence in the elderly. *JAMA*



266(17):2402-2406, 1991 1681122

Schatzberg AF, Cantillon M: Antidepressant early response and remission with venlafaxine or fluoxetine in depressed geriatric outpatients (poster presentation [S225-S226]), in Abstracts from 13th Congress of the European College of Neuropsychopharmacology. Munich, Germany, September 9-13, 2000. Eur Neuropsychopharmacol 10 (suppl 3):S107-S424, 2000 11039098

Schatzberg AF, Kremer C, Rodrigues HE, Murphy GM Jr; Mirtazapine vs. Paroxetine Study Group: Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. Am J Geriatr Psychiatry 10(5):541-550, 2002 12213688

Schmucker DL: Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging 18(11):837-851, 2001 11772124

Schneider LS, Pollock VE, Lyness SA: A metaanalysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 38(5):553-563, 1990 1970586

Schneider LS, Nelson JC, Clary CM, et al; Sertraline Elderly Depression Study Group: An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. Am J Psychiatry 160(7): 1277-1285, 2003 12832242

Schneider LS, Dagerman KS, Insel P: Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 294(15):1934-1943, 2005 16234500

Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 355(15):1525-1538, 2006 17035647

Serretti A, Cusin C, Rausch JL, et al: Pooling pharmacogenetic studies on the serotonin transporter: a

- mega-analysis. *Psychiatry Res* 145(1):61-65, 2006 17069894
- Shankle WR, Nielson KA, Cotman CW: Low-dose propranolol reduces aggression and agitation resembling that associated with orbitofrontal dysfunction in elderly demented patients. *Alzheimer Dis Assoc Disord* 9(4):233-237, 1995 8749613
- Shimada T, Yamazaki H, Mimura M, et al: Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 270(1):414-423, 1994 8035341
- Shin JY, Park MJ, Lee SH, et al: Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study. *BMJ* 351:h3517, 2015 26173947
- Smith GR, Taylor CW, Linkous P: Haloperidol versus thioridazine for the treatment of psychogeriatric patients: a double-blind clinical trial. *Psychosomatics* 15:134-138, 1974
- Sneed JR, Rutherford BR, Rindskopf D, et al: Design makes a difference: a meta-analysis of antidepressant response rates in placebo-controlled versus comparator trials in late-life depression. *Am J Geriatr Psychiatry* 16(1):65-73, 2008 17998306
- Solai LK, Mulsant BH, Pollock BG: Selective serotonin reuptake inhibitors for late-life depression: a comparative review. *Drugs Aging* 18(5):355-368, 2001 11392444
- Spiker DG, Weiss JC, Dealy RS, et al: The pharmacological treatment of delusional depression. *Am J Psychiatry* 142(4):430-436, 1985 3883815
- Stotsky B: Multicenter study comparing thioridazine with diazepam and placebo in elderly, nonpsychotic patients

- with emotional and behavioral disorders. Clin Ther 6(4):546-559, 1984 6380725
- Street JS, Clark WS, Gannon KS, et al; The HGEU Study Group: Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 57(10):968-976, 2000 11015815
- Suh GH, Son HG, Ju YS, et al: A randomized, double-blind, crossover comparison of risperidone and haloperidol in Korean dementia patients with behavioral disturbances. Am J Geriatr Psychiatry 12(5): 509-516, 2004 15353389
- Sultzer DL, Gray KF, Gunay I, et al: A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. Am J Geriatr Psychiatry 5(1):60-69, 1997 9169246
- Sunderland T, Molchan SE, Little JT, et al: Pharmacologic challenges in Alzheimer disease and normal controls: cognitive modeling in humans. Alzheimer Dis Assoc Disord 11 (suppl 4):S23-S26, 1997 9339269
- Swearer JM, Drachman DA, O'Donnell BF, Mitchell AL: Troublesome and disruptive behaviors in dementia. Relationships to diagnosis and disease severity. J Am Geriatr Soc 36(9):784-790, 1988 3411060
- Sweet RA, Nimgaonkar VL, Kamboh MI, et al: Dopamine receptor genetic variation, psychosis, and aggression in Alzheimer disease. Arch Neurol 55(10):1335-1340, 1998 9779662
- Tandon R: Impact of antipsychotic treatment on long-term course of schizophrenic illness: an introduction. J Psychiatr Res 32(3-4):119-120, 1998 9793864
- Tariot PN, Mack JL, Patterson MB, et al: The CERAD Behavior Rating Scale for Dementia (BRSD). Am J Psychiatry 152:1349-1357, 1995 7653692
- Tariot PN, Erb R, Podgorski CA, et al: Efficacy and tolerability of carbamazepine for agitation and

aggression in dementia. *Am J Psychiatry* 155(1):54-61, 1998 9433339

Tariot PN, Salzman C, Yeung PP, et al: Long-Term use of quetiapine in elderly patients with psychotic disorders. *Clin Ther* 22(9): 1068-1084, 2000 11048905

Tariot PN, Raman R, Jakimovich L, et al; Alzheimer's Disease Cooperative Study; Valproate Nursing Home Study Group: Divalproex sodium in nursing home residents with possible or probable Alzheimer Disease complicated by agitation: a randomized, controlled trial. *Am J Geriatr Psychiatry* 13(11):942-949, 2005 16286437

Tariot PN, Schneider L, Katz IR, et al: Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. *Am J Geriatr Psychiatry* 14(9):767-776, 2006 16905684

Teri L, Logsdon RG, Peskind E, et al; Alzheimer's Disease Cooperative Study: Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. *Neurology* 55(9):1271-1278, 2000 11087767

Tewfik GI, Jain VK, Harcup M, Magowan S: Effectiveness of various tranquilisers in the management of senile restlessness. *Gerontol Clin (Basel)* 12(6):351-359, 1970 4926614

Thomas VS, Darvesh S, MacKnight C, Rockwood K: Estimating the prevalence of dementia in elderly people: a comparison of the Canadian Study of Health and Aging and National Population Health Survey approaches. *Int Psychogeriatr* 13 (suppl 1):169-175, 2001 11892964

Timmer CJ, Paanakker JE, Van Hal HJM: Pharmacokinetics of mirtazapine from orally administered tablets: influence of gender, age and treatment regimen. *Hum Psychopharmacol* 11:497-509, 1996

Tohen M, Baker RW, Altshuler LL, et al: Olanzapine versus divalproex in the treatment of acute mania. *Am J Psychiatry* 159(6):1011-1017, 2002 12042191

- Tollefson GD, Bosomworth JC, Heiligenstein JH, et al; The Fluoxetine Collaborative Study Group: A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. *Int Psychogeriatr* 7(1):89-104, 1995 7579025
- Tsuang MM, Lu LM, Stotsky BA, Cole JO: Haloperidol versus thioridazine for hospitalized psychogeriatric patients: double-blind study. *J Am Geriatr Soc* 19(7):593-600, 1971 4937658
- Tune L: The role of antipsychotics in treating delirium. *Curr Psychiatry Rep* 4(3):209-212, 2002 12003684
- Van Putten T, Marder SR, Mintz J, Poland RE: Haloperidol plasma levels and clinical response: a therapeutic window relationship. *Am J Psychiatry* 149(4):500-505, 1992 1554036
- Volavka J, Cooper T, Czobor P, et al: Haloperidol blood levels and clinical effects. *Arch Gen Psychiatry* 49(5):354-361, 1992 1586270
- Weihs KL, Settle EC Jr, Batey SR, et al: Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psychiatry* 61(3):196-202, 2000 10817105
- Weiler PG, Mungas D, Bernick C: Propranolol for the control of disruptive behavior in senile dementia. *J Geriatr Psychiatry Neurol* 1(4):226-230, 1988 3252890
- Weiser M, Rotmensch HH, Korczyn AD, et al; Rivastigmine-Risperidone Study Group: A pilot, randomized, open-label trial assessing safety and pharmacokinetic parameters of co-administration of rivastigmine with risperidone in dementia patients with behavioral disturbances. *Int J Geriatr Psychiatry* 17(4):343-346, 2002 11994888
- Wood S, Cummings JL, Hsu MA, et al: The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. *Am J Geriatr Psychiatry* 8(1):75-83, 2000 10648298

- Wynne HA, Goudevenos J, Rawlins MD, et al: Hepatic drug clearance: the effect of age using indocyanine green as a model compound. *Br J Clin Pharmacol* 30(4):634-637, 1990 2291878
- Yerrabolu M, Prabhudesai S, Tawam M, et al: Effect of risperidone on QT interval and QT dispersion in the elderly. *Heart Dis* 2(1):10-12, 2000 11728238
- Yu DK: The contribution of P-glycoprotein to pharmacokinetic drug-drug interactions. *J Clin Pharmacol* 39(12):1203-1211, 1999 10586385
- Zubenko GS, Moossy J, Martinez AJ, et al: Neuropathologic and neurochemical correlates of psychosis in primary dementia. *Arch Neurol* 48(6):619-624, 1991 1710105

## CHAPTER 57

# **Psychopharmacology During Pregnancy and Lactation**

Shona L. Ray-Griffith, M.D.

D. Jeffrey Newport, M.D.

Zachary N. Stowe, M.D.

The management of mental illness during pregnancy and lactation is a complicated clinical challenge encompassing two concomitant medical conditions (i.e., pregnancy and a psychiatric disorder) that requires consideration of the welfare of at least two patients (i.e., mother and child). Various nonpharmacological treatment options for maternal mental illnesses during the antepartum and postpartum periods are beyond the scope of this chapter. Viable treatment options must be available, accessible, affordable, and effective for the illness, and in many cases, this may involve pharmacotherapy.

Unfortunately, definitive treatment guidelines for perinatal psychotropic medications remain unavailable. In the two decades since the initial iteration of this chapter, there has been an enormous expansion in the reproductive safety literature focusing on psychotropic medications.

In this chapter, we posit that minimizing infant exposure to the purported risks of both maternal mental illness and psychotropic medications is the preeminent clinical objective. Investigations and reviews focusing on reproductive safety of psychotropic medications typically provide only cursory information about the effect of illness, rely on maternal self-report to address concomitant fetal exposures, and use extensive statistical interrogation that may not have meaningful clinical import.

Space limitations preclude a comprehensive review of each class of psychotropic medications; rather, we review the available data with an emphasis on providing the clinician with the requisite components to interpret and apply medication reproductive safety data in the clinical decision. Also included are data regarding pharmacokinetic alterations during pregnancy and lactation and the potential clinical relevance of these data for psychotropic dosage management. The chapter concludes with a series of potential modifications of previously suggested treatment guidelines to optimize clinical decisions and a list of resources.

---

## **Minimizing Exposure of Offspring: Primary Therapeutic Objective**

---



The clinical management of any medical condition during pregnancy and lactation must consider the reproductive safety of available therapies, the likelihood of illness recurrence without continued treatment, and the potential effect of untreated maternal illness. Minor ailments, such as headaches and nausea, are routinely treated during pregnancy with medications that often have limited reproductive safety data. Recent data indicate that 90% of pregnant women take one medication and that more than 50% take four or more medications ([Ayad and Costantine 2015](#); [Mitchell et al. 2011](#)), confounding the ability to isolate the effect of an individual medication. Women with mental illness are frequently encouraged to discontinue psychotropic medication during pregnancy, and pregnancy is associated with high rates of both antidepressant discontinuation ([Petersen et al. 2011](#)) and nonadherence to prescribed psychiatric medications ([Lupattelli et al. 2015](#)). The desire to avoid offspring exposure to psychotropic medication is laudable; however, recommendations to discontinue medication are often made with limited knowledge of the potential risk of recurrent illness and of the effect of maternal illness on obstetrical and child outcomes.

An assessment of the risks of offspring exposure to maternal psychiatric illness must consider both the likelihood that an episode of illness will occur and the evidence that the illness may be harmful to the child. The clinician can estimate a patient's likelihood of experiencing illness recurrence or exacerbation by carefully synthesizing prevalence data from epidemiological studies with evidence from the patient's own history. Patients with frequent episodes of psychiatric illness, a declining course, or a

history of perinatal illness are more likely to become ill in the current pregnancy or the postpartum period.

Investigations of the incidence and course of maternal mental illness have found no evidence that mental illness lies quiescent during pregnancy and considerable evidence that the postpartum period entails heightened vulnerability. The incidence of depression during the perinatal period is comparable to that in other populations ([Buesching et al. 1986](#); [Cutrona 1983](#); [Kumar and Robson 1984](#); [Manly et al. 1982](#); [O'Hara et al. 1982](#); [Watson et al. 1984](#)). Two large studies, collectively comprising 122,400 women, found a 14%–20% incidence of prenatal major depressive disorder (MDD) ([Marcus et al. 2003](#); [Oberlander et al. 2006](#)). In fact, 11% of women presenting for evaluation of postpartum depression report symptom onset before delivery ([Stowe et al. 2005](#)). Discontinuation of treatment during pregnancy in women with histories of MDD or bipolar disorder increases the risk of episodes during pregnancy ([Cohen et al. 2006](#); [Newport et al. 2008c](#); [Viguera et al. 2007b](#)). However, one group failed to identify an increase in depression with antidepressant discontinuation ([Yonkers et al. 2011](#)).

*Psychotic disorders* also may worsen during pregnancy ([Glaze et al. 1991](#); [McNeil et al. 1984a, 1984b](#)). The course of *obsessive-compulsive disorder* (OCD) appears to be variable during pregnancy, with 14%–33% of patients experiencing exacerbation ([Guglielmi et al. 2014](#); [Jenike et al. 1990](#); [Williams and Koran 1997](#)). Women with OCD who continued pharmacotherapy throughout the perinatal period did not have a significant change in symptoms ([House et al. 2016](#)). *Panic disorder* during gestation is also variable, with 19% of patients experiencing more frequent panic attacks and 30% having less frequent attacks ([Hertzberg and Wahlbeck 1999](#); [Wisner et al. 1996a](#)).

Finally, obstetrical trauma and pregnancy loss can precipitate *posttraumatic stress disorder* (PTSD) (Allen 1998; [Engelhard et al. 2001](#); [Fones 1996](#)), with PTSD symptoms following stillbirth persisting into the next pregnancy ([Turton et al. 2001](#)).

Postpartum mental illness has been documented for millennia and is substantiated by modern research. Early studies reported that psychiatric hospitalization rates increased during the first postpartum month ([Kendler et al. 1993](#)) and noted that up to 12.5% of all psychiatric admissions for women occurred during the first postpartum year ([Duffy 1983](#)). Postpartum depression affects 10%–22% of adult mothers and up to 26% of adolescent mothers ([Stowe and Nemeroff 1995](#); [Troutman and Cutrona 1990](#)). Women with bipolar disorder also face considerable postpartum risks ([Kendell et al. 1987](#); [Targum et al. 1979](#)). Postpartum OCD, often manifested by violence and contamination obsessions, may affect 9%–16% of new mothers ([Miller et al. 2013](#); [Zambaldi et al. 2009](#)), with one-third experiencing new-onset OCD symptoms during the postpartum period ([Miller et al. 2013](#)). Nearly one-half of women with preexisting OCD report an exacerbation of symptoms during the postnatal period ([Guglielmi et al. 2014](#)). Thankfully, postpartum psychosis, the most severe postpartum syndrome, is a rare condition; however, its prevalence is at least 100-fold higher among women with bipolar disorder than among those with other affective or psychotic disorders ([Brockington et al. 1982](#); [Kendell et al. 1987](#)).

---

# Effect of Maternal Psychiatric Disorders

---

Not only the likelihood but also the potential effect of maternal mental illness on maternal and child well-being must be considered. Most studies focusing on obstetrical and developmental outcomes have focused on the effect of maternal depression, anxiety, and stress. Often these terms are used interchangeably, with most previous investigations focusing on maternal symptoms rather than diagnosis. Given the high rate of comorbidity of mood and anxiety disorders in women, the distinction between maternal depression and maternal anxiety may not have clinical import. The effect of maternal unipolar versus bipolar depression during gestation remains unexplored. Maternal depression during pregnancy has been associated with slower fetal growth ([Hedegaard et al. 1996](#); [Schell 1981](#); [Uguz et al. 2013](#)); increased risk of preterm delivery and other obstetrical complications ([Korebrits et al. 1998](#); [Liu et al. 2016](#); [Oberlander et al. 2006](#); [Orr and Miller 1995](#); [Perkin et al. 1993](#); [Steer et al. 1992](#); [Uguz et al. 2013](#); [Venkatesh et al. 2016](#)); and long-standing cognitive, behavioral, and emotional changes in the offspring ([Luoma et al. 2001, 2004](#); [Meijer 1985](#); [Nulman et al. 2002](#); [O'Connor et al. 2003](#); [Søndergaard et al. 2003](#); [Stott 1973](#)). Similarly, prenatal panic disorder is associated with higher rates of preterm birth and low birth weight ([Uguz et al. 2013](#)), and maternal anxiety is associated with higher rates of attentional problems ([Van den Bergh and Marcoen 2004](#)). Depressed pregnant women are less compliant with prenatal vitamins and obstetrical care; receive poorer nutrition; and have greater use of prescription opiates,

hypnotics, alcohol, tobacco, and illicit substances ([Newport et al. 2012](#); [Zuckerman et al. 1989](#)). Finally, depressed pregnant women, and those with PTSD, often experience suicidal thoughts ([Newport et al. 2007b](#); [Smith et al. 2006](#)) and may engage in suicidal behavior.

Postpartum depression also carries deleterious consequences for infant development. As early as 3 months, infants of depressed mothers show less facial expression, less head orientation, less crying, and more fussiness compared with infants of nondepressed mothers ([Martinez et al. 1996](#)). As they age, the children of depressed mothers show ineffective emotional regulation ([Downey and Coyne 1990](#)), delayed motor development ([Galler et al. 2000](#)), poor interpersonal skills ([Jameson et al. 1997](#)), lower self-esteem ([Downey and Coyne 1990](#)), increased fear and anxiety ([Lyons-Ruth et al. 2000](#)), more aggression ([Jameson et al. 1997](#)), and more insecure and disorganized attachment behaviors ([Martins and Gaffan 2000](#)). Children of depressed mothers are ultimately more likely to experience emotional instability, to have behavior problems and suicidal behavior, and to require psychiatric treatment ([Lyons-Ruth et al. 2000](#); [Weissman et al. 1984](#)).

Antepartum exacerbation of schizophrenia and other psychotic illnesses also warrants concern. Women with schizophrenia have a higher prevalence of substance abuse during pregnancy ([Miller and Finnerty 1996](#); [Taylor et al. 2015](#)) and may have bizarre ideas about contraception, pregnancy, and child rearing that complicate their perinatal course ([McEvoy et al. 1983](#); [Riordan et al. 1999](#)). Maternal schizophrenia has been associated with elevated rates of obstetrical complications ([Bennedsen et al. 2001](#); [Miller and Finnerty 1996](#)) and fetal and neonatal death ([Rieder et al. 1975](#)).

The clinical data regarding the obstetrical and developmental consequences of maternal mental illness are supported by an extensive line of laboratory animal research. Preclinical studies across a variety of species indicate that stress during pregnancy and the early postpartum period adversely affects offspring growth, learning ability, and postnatal development, producing a range of biobehavioral aberrations that may persist into adulthood (for a review, see [Newport et al. 2002](#)).

---

## **Risks of Antepartum and Postpartum Exposure to Psychotropic Medication**

---

Clinical decisions during pregnancy and the postpartum period must consider the risks of fetal and neonatal medication exposure. These risks may be broadly classified as acute or developmental adverse effects ([Table 57-1](#)). *Acute effects* are typically immediately evident and are not dependent on the developmental window of exposure. Examples include drug toxicity, drug withdrawal, and drug-drug interactions. *Developmental effects* are, by definition, dependent on the developmental window of exposure and are often not evident until later. These effects include somatic teratogenesis (i.e., major and minor malformations) and neurobehavioral teratogenesis (i.e., alterations in brain development that affect the child's subsequent behavior, cognitive abilities, and emotional regulation). The window of vulnerability to somatic teratogenesis is limited to the embryonic phase of development, but because central

nervous system (CNS) development continues long after delivery, the fetus and breast-feeding infant are equally vulnerable to the theoretical risks of neurobehavioral teratogenesis.

**TABLE 57-1. Potential risks of medication exposure**

	<b>Acute</b>	<b>Developmental</b>
Pregnancy	Neonatal toxicity	Somatic teratogenesis
	Neonatal withdrawal	Neurobehavioral teratogenesis
	Drug-drug interactions	
Lactation	Infant toxicity	Neurobehavioral teratogenesis
	Drug-drug interactions	

A decision to use psychotropic medication during pregnancy and/or lactation will carry complicated clinical, ethical, and potentially legal consequences. Although a rapidly expanding base of reproductive safety data has begun to address many of these concerns, review of the current literature reveals numerous methodological problems. The most glaring deficiencies are a frequent lack of appropriate control groups and an overreliance on retrospective data collection—deficiencies shown to introduce systematic biases that potentially lead to overestimation of the effect of psychotropic exposure ([Newport et al. 2008a](#)). In particular, most studies report outcomes of “depressed-treated women compared with

nondepressed-untreated women,” eliminating any opportunity to disentangle treatment and illness effects on outcomes (McDonagh et al. 2014). Despite these limitations, ethical considerations preclude implementation of randomized controlled trials to evaluate psychotropic efficacy and safety during pregnancy and lactation. Therefore, the reproductive safety database for psychotropic medications is composed of a diverse conglomeration of case reports, case series by pharmaceutical companies and academic centers, birth registries, retrospective surveys, reports from teratology or poison control centers, clinical and preclinical pharmacokinetic investigations, review articles summarizing data from these sources, and the U.S. Food and Drug Administration (FDA) medication safety rating systems (Table 57-2).

**TABLE 57-2. U.S. Food and Drug Administration use-in-pregnancy ratings (prior to 2015)**

Category Interpretation	
A	<b>Controlled studies show no risk:</b> Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	<b>No evidence of risk in humans:</b> Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.

Source. Physicians’ Desk Reference 2007.



## Category Interpretation

---

- C      **Risk cannot be ruled out:** Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.
  - D      **Positive evidence of risk:** Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh risks.
  - X      **Contraindicated in pregnancy:** Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.
- 

*Source.* [Physicians' Desk Reference 2007](#).

In addition to the available reproductive safety data, the patient's clinical history is important in treatment selection. If the rationale for psychotropic therapy during pregnancy is to protect the mother and the child from the harmful sequelae of maternal mental illness, then a history of treatment response or nonresponse is critical. Regardless of the favorability of its reproductive safety profile, a medication that has been ineffective for or poorly tolerated by a particular patient is of little value during the reproductive period.

---

# FDA Reproductive Safety Ratings

---

On June 30, 2015, the FDA's new Pregnancy and Lactation Labeling Rule became effective, with a plan for staggered implementation over the following 3–5 years. The new labeling rule eliminates the pregnancy letter category previously used (see [Table 57-2](#)) and provides the following information for the use of medications in pregnancy and delivery when available: 1) pregnancy exposure registry, 2) narrative risk summary, 3) clinical considerations, and 4) data description of supporting evidence. Specifically, the clinical considerations are as follows: disease-associated maternal and embryo/fetal risk, dosage adjustment, maternal adverse reactions, fetal/neonatal adverse reactions, and labor or delivery. Two new sections also summarize evidence for lactation and evidence for males and females of reproductive potential. The labeling will be updated as evidence emerges but is required only for medications receiving FDA approval after June 30, 2001. Medications approved prior to this date are strongly encouraged to comply with the new recommendations but are not required to do so.

The result of these changes is two unintegrated systems for reproductive safety ratings that present a challenge for clinicians. Similarly, the rate of accrual for reproductive safety information in humans is variable and all obtained postmarketing. The new safety ratings will arguably have greater clinical import, because the older system often provided more favorable ratings to newer medications with very limited information and was often overvalued in clinical decisions. For example, a clinician may be tempted

to use buspirone (Category B) over clonazepam (Category D) for panic disorder despite the very limited information underlying buspirone's preferable pregnancy rating and its lack of efficacy for panic disorder. Similarly, lurasidone (Category B) may be used in lieu of lithium (Category D) for bipolar depression despite the virtual absence of human data on lurasidone's safety during gestation and the lack of published clinical experience in the antepartum and postpartum periods.

---

## Dosage Management: Perinatal Pharmacokinetics

---

Prescribing the *minimal effective dosage* is especially important during pregnancy and lactation. On learning that a patient is pregnant, clinicians and patients often instinctively lower psychotropic dosages in an effort to reduce fetal exposure, but indiscriminate dosage reduction may increase the vulnerability to relapse. If the therapeutic objective is to eliminate the child's exposure to maternal illness while minimizing the child's psychotropic exposure, then dosage management must be informed by an understanding of the factors governing the alterations in drug disposition across gestation, the placental passage, and excretion into breast milk.

Dosage adjustments may be required to maintain medication efficacy during pregnancy. For example, it may be necessary to increase the dosage of tricyclic antidepressants (TCAs) to approximately 1.6 times the preconception dosage to maintain therapeutic concentrations in late pregnancy ([Altshuler et al. 1996](#);

[Wisner et al. 1993](#)). Small studies examining selective serotonin reuptake inhibitors (SSRIs) have reported clearance changes over the course of pregnancy and the necessity for dosage adjustments in response to increased maternal symptoms ([Freeman et al. 2008](#); [Hostetter et al. 2000](#); [Sit et al. 2008](#)). However, the pattern of dosage adjustment during gestation is not uniform for all medications. For example, among anticonvulsant and mood-stabilizing medications, serum concentrations of lamotrigine ([Ohman et al. 2000](#); [Pennell et al. 2004](#); [Polepally et al. 2014](#); [Tran et al. 2002](#)) and valproate ([Otani 1985](#); [Philbert et al. 1985](#)) decline steadily across gestation, whereas carbamazepine concentrations ([Bardy et al. 1982b](#); [Battino et al. 1982](#); [Bologa et al. 1991](#); [Dam et al. 1979](#); [Lander et al. 1981](#); [Omtzigt et al. 1993](#); [Otani 1985](#); [Tomson et al. 1994](#); [Yerby et al. 1985](#)) undergo smaller changes that are primarily evident only in late pregnancy. These alterations in drug concentrations and dosing requirements likely result from effects of the physiological changes of pregnancy on the pharmacokinetics ([Boobis and Lewis 1983](#); [Frederiksen 2001](#); Little 1999; [Wyska and Jusko 2001](#)) and possibly the pharmacodynamics ([Wyska and Jusko 2001](#)) of psychotropic medications. Ultimately, an improved understanding of the factors governing perinatal pharmacokinetic and pharmacodynamic alterations may enable the development of personalized dosing strategies during gestation.

The level of fetal psychotropic exposure is another key consideration. All psychotropics studied to date cross the human placenta; yet there are significant differences in placental passage rates. Bidirectional placental transfer is mediated primarily by simple diffusion, and determinants of the transplacental diffusion rate include molecular weight,

lipid solubility, degree of ionization, and protein-binding affinity ([Audus 1999](#); W.M. [Moore et al. 1966](#); [Pacifici and Nottoli 1995](#)). In addition, placental P-glycoprotein (P-gp), which actively transports substrates from the fetal to the maternal circulation, is likely a key determinant of fetal psychotropic exposure. Consequently, medications with greater affinity for P-gp should be associated with lower fetal-to-maternal medication ratios, which, in fact, has been confirmed in an investigation of antipsychotic placental passage ([Newport et al. 2007a](#)). Furthermore, clarification of the factors governing placental passage may ultimately contribute to the development of psychotropic agents with minimal rates of placental transfer ([Wang et al. 2007](#)).

Fetal plasma concentrations are not, however, the ultimate measure of functional psychotropic exposure and may even underestimate the more critical measure of fetal brain concentration. Certain physiological attributes of the human fetus, including high cardiac output, increased blood-brain barrier permeability, low plasma protein concentrations and plasma protein binding affinities, and low hepatic enzyme activity ([Bertossi et al. 1999](#); [Morgan 1997](#); [Oesterheld 1998](#)), may produce higher-than-anticipated fetal CNS concentrations of psychotropic medications than might be anticipated from circulating levels. Preclinical investigations from our group have found that transplacental passage of psychotropic drugs results in high levels in fetal CNS tissues and significant binding at neurotransmitter receptor and transporter sites ([Capello et al. 2011](#)).

Similar considerations apply when endeavoring to minimize the psychotropic exposure of nursing infants. Because the neonate has relatively low hepatic enzyme activity ([Warner 1986](#)) and low glomerular filtration and

tubular secretion rates ([Welch and Findlay 1981](#)), psychotropic exposure may be higher than anticipated for breast-fed infants. A model to predict rates of breast-milk excretion from characteristics of the molecular structure of candidate medications has been proposed ([Agatonovic-Kustrin et al. 2002](#)). Such models may allow clinicians to estimate a nursing infant's exposure without subjecting the infant to invasive procedures.

---

## Antidepressants

---

The use of antidepressant medications in pregnancy has been extensively reviewed ([McDonagh et al. 2014](#); [Yonkers et al. 2014](#)), and multiple meta-analyses have found no association between antidepressant use in pregnancy and congenital malformations and/or major malformations ([Einarson and Einarson 2005](#); [Grigoriadis et al. 2013](#)). We include an overview of the individual categories of antidepressants in this section.

## Selective Serotonin Reuptake Inhibitors

Reproductive safety data on the SSRIs have rapidly accrued over the past two decades. A recent meta-analysis investigating SSRIs found no overall association with birth defects ([Reefhuis et al. 2015](#)). Despite overall reassuring data, some concerns with specific SSRIs have emerged. [Reefhuis et al. \(2015\)](#) found an increased risk of anencephaly, atrial septal defects, right ventricular outflow

tract obstruction, gastroschisis, and omphalocele with paroxetine and an increased risk of right ventricular outflow tract obstruction defects and craniosynostosis with fluoxetine. Analysis of a managed care database identified a higher odds ratio (OR) for cardiovascular malformations with exposure to paroxetine compared with other antidepressants ([GlaxoSmithKline 2005](#)). Three large case-control studies of SSRI exposures ([Alwan et al. 2007](#); [Bérard et al. 2007](#); [Louik et al. 2007](#)) reported largely reassuring results, although with some concerns. The first ([Alwan et al. 2007](#)) reported small increases in the risk of three uncommon malformations—anencephaly (OR=2.4), craniosynostosis (OR=2.5), and omphalocele (OR=2.8) associated with use of fluoxetine, sertraline, or paroxetine. The second study ([Louik et al. 2007](#)) reported an increased risk of omphalocele (OR=5.7) and septal defects (OR=2.0) with sertraline exposure and of right ventricular outflow tract obstruction defects (OR=3.3) with paroxetine exposure. The third study ([Bérard et al. 2007](#)) found no evidence of increased risk of cardiovascular or other malformations with SSRI use, unless women were taking paroxetine at daily dosages of 25 mg or greater, in which case their infants were at an increased risk of cardiovascular (OR=3.1) and overall malformations (OR=2.2). In the Medicaid Analytic eXtract (MAX) database, [Huybrechts et al. \(2014a\)](#) found an overall adjusted risk of 1.06 (95% confidence interval [CI]=0.93–1.22) for any cardiac defect with use of an SSRI in the first trimester; a risk of 1.07 (95% CI=0.59–1.93) for a right ventricular outflow tract obstruction with use of paroxetine; and a risk of 1.04 (95% CI=0.76–4.41) for a ventricular septal defect with use of sertraline.

A handful of studies have systematically assessed child development after prenatal exposure to antidepressants. Two studies ([Nulman et al. 1997a, 2002](#)) assessed children (ages 15–86 months) who had been prenatally exposed to fluoxetine ( $n=90$ ) or TCAs ( $n=126$ ), collectively comparing them with nonexposed children ( $n=120$ ). No differences were observed with respect to global cognitive, psychomotor, or language development. The same research group compared children exposed to SSRIs in utero with children of mothers without depression or SSRI use and found no difference in IQ or behavior ([Nulman et al. 2012](#)). A similar study that compared children (ages 6–40 months) with prenatal SSRI exposure ( $n=31$ ) and children without antidepressant exposure ( $n=13$ ) observed no differences in global cognition but reported lower psychomotor scores for the SSRI-exposed children ([Casper et al. 2003](#)).

Unfortunately, limitations of these studies render their implications speculative at best. Children were not age-matched in any of these studies, and the predictive validity of measured indices across child developmental stages has not been established ([Black and Matula 2000](#)). In addition, the [Casper et al. \(2003\)](#) study was confounded by the fact that 29% of the participants were enrolled after delivery, which could have resulted in an overrepresentation of children with developmental abnormalities.

A study of 69 (46 SSRI-exposed; 23 nonexposed) children that eliminated the age confound by examining the children at two fixed time points—ages 2 months and 8 months—reported no differences between the exposed and the nonexposed children in cognitive or motor development ([Oberlander et al. 2004](#)). Finally, an assessment of 4-year-old children found no evidence that prenatal SSRI exposure affected externalizing or attentional behaviors ([Oberlander](#)



et al. 2007). It is noteworthy that several of these developmental studies involved a significant overlap in the cohort of children, thereby limiting further the cumulative sample size of extant follow-up studies.

Multiple studies have examined the association between maternal antidepressant use and autism spectrum disorders in offspring. The results were mixed, with four studies finding an association between antidepressant exposure and autism (Boukhris et al. 2016; Croen et al. 2011; El Marroun et al. 2014; Gidaya et al. 2014) and six finding no such association (Castro et al. 2016; Clements et al. 2015; Harrington et al. 2014; Hviid et al. 2013; Rai et al. 2013; Sørensen et al. 2013). In addition, close inspection reveals evidence of probable detection bias in at least some of these studies, with nonminority children of well-educated mothers overrepresented in the autism case subjects (Croen et al. 2011). These discordant and arguably flawed data preclude definitive conclusions regarding any autism risk attributable to prenatal antidepressant exposure.

Data regarding the effect of prenatal antidepressant exposure on rates of miscarriage, preterm delivery, and low birth weight are decidedly mixed. Some investigators have reported an association between antidepressant exposure and such outcomes (Chambers et al. 1996; Chun-Fai-Chan et al. 2005; Oberlander et al. 2006; Pastuszak et al. 1993; Ross et al. 2013; Simon et al. 2002), whereas others have not (Einarson et al. 2001, 2003; Kulin et al. 1998; Sivojelezova et al. 2005; Venkatesh et al. 2016). Multiple recent meta-analyses found an association between prenatal antidepressant exposure and preterm delivery (Huang et al. 2014; Huybrechts et al. 2014b; Ross et al. 2013) and low birth weight (Huang et al. 2014; Ross et al. 2013). Interpretation is complicated by other reports that

link prenatal maternal stress and/or depression with prematurity and low birth weight ([Orr et al. 2002](#); [Steer et al. 1992](#)). As a result, no definitive conclusions can be drawn as to whether antidepressant use during gestation conveys an adverse effect on fetal growth or the timing of parturition.

Finally, concerns have been expressed regarding neonatal SSRI syndromes, typically manifested by transient symptoms including respiratory difficulty and tremulousness ([Moses-Kolko et al. 2005](#)). Most controlled prospective studies suggest that SSRI exposure is associated with poor neonatal adaptation ([Chambers et al. 1996](#); [Costei et al. 2002](#); [Källén 2004](#); [Laine et al. 2003](#); [Oberlander et al. 2004, 2006](#); [Sivojelezova et al. 2005](#); [Zeskind and Stephens 2004](#)), although one study found no such association ([Maschi et al. 2008](#)). Closer scrutiny of these reports identified a cadre of methodological shortcomings. Limited effort was made to mask those evaluating the neonates as to exposure status, only one study ([Oberlander et al. 2006](#)) controlled for the effect of maternal mental illness, and key confounding factors such as gestational age at delivery and maternal use of other medications and/or habit-forming substances were either ignored altogether or controlled only in a rudimentary manner.

A case-control study comparing the exposures of neonates who “required observation” with those of “healthy” neonates ([Misri et al. 2004](#)) underscores the importance of controlling for confounding factors. In this study of antidepressant-exposed neonates ( $n=46$ ) born to mothers with MDD, the mothers of infants who required observation had more severe symptoms of depression and anxiety, were more likely to have a comorbid anxiety

disorder, and were exposed to higher dosages of clonazepam.

Debate has also focused on a more serious neonatal concern—a possible connection between late-pregnancy SSRI exposure and persistent pulmonary hypertension of the neonate (PPHN). A case-control study ([Chambers et al. 2006](#)) of 1,213 neonates (377 with PPHN) reported data supporting an association between SSRI exposure and PPHN (OR=6.1). However, a similar study of 1,104 SSRI-exposed neonates and 1,104 matched control subjects found no association ([Andrade et al. 2009](#)). A case-control study ([Källén and Olausson 2008](#)) of more than 831,000 neonates (of whom 506 were diagnosed with PPHN) from the Swedish Medical Birth Register observed a more modest association (OR=2.9). The overall rate of PPHN in this population-wide study was approximately 1 in 2,000, and the rate of PPHN with SSRI exposure was approximately 1 in 600. In the largest study to date, involving more than 3 million women, the adjusted odds of PPHN, after controlling for depression, was 1.10 (95% CI=0.77-1.35) for SSRI use and 1.14 (95% CI=0.74-1.74) for non-SSRI antidepressant use ([Huybrechts et al. 2015](#)). Finally, a study concluded that PPHN was associated not with SSRI exposure but rather with cesarean delivery prior to onset of labor ([Wilson et al. 2011](#)), underscoring the importance of controlling for all potential confounding factors. Overall, the SSRI-PPHN data are mixed, with a very low absolute rate of PPHN.

Pharmacokinetic data regarding the placental passage of SSRI antidepressants remain limited. However, existing studies have found that mean fetal-to-maternal ratios for numerous SSRIs and their active metabolites are uniformly

less than 1.0, although considerable differences exist among agents ([Hendrick et al. 2003](#); [Rampono et al. 2009](#)).

Published reports pertaining to SSRIs and lactation now encompass the largest data set for medications during breast feeding, including infant serum measures, breast milk concentrations, and pharmacokinetic studies of excretion. There are now published investigations for all of the SSRIs, including sertraline ([Altshuler et al. 1995](#); [Birnbaum et al. 1999](#); [Dodd et al. 2000](#); [Epperson et al. 1997, 2001](#); [Hendrick et al. 2001a](#); [Kristensen et al. 1998](#); [Mammen et al. 1997](#); [Stowe et al. 1997, 2003](#); [Wisner et al. 1998](#)), fluoxetine ([Birnbaum et al. 1999](#); [Burch and Wells 1992](#); [Goldstein et al. 1997](#); [Hendrick et al. 2001b](#); [Kristensen et al. 1999](#); [Lester et al. 1993](#); [Suri et al. 2002](#); [Taddio et al. 1996](#); [Yoshida et al. 1998a](#)), paroxetine ([Birnbaum et al. 1999](#); [Hendrick et al. 2001a](#); [Ohman et al. 1999](#); [Spigset et al. 1996](#); [Stowe et al. 2000](#)), escitalopram ([Rampono et al. 2006](#)), fluvoxamine ([Hendrick et al. 2001a](#); [Piontek et al. 2001](#); [Wright et al. 1991](#)), and citalopram ([Heikkinen et al. 2002](#); [Jensen et al. 1997](#); [Schmidt et al. 2000](#); [Spigset et al. 1997](#)). Although infant follow-up data are limited, only a few isolated cases of adverse effects have been reported. Long-term neurobehavioral studies of infants exposed to SSRI antidepressants during lactation warrant continued examination. The pharmacokinetic profiles of breast milk excretion, including delineation of distribution gradients and time gradients, are best defined for sertraline ([Stowe et al. 1997, 2003](#)), paroxetine ([Stowe et al. 2000](#)), and fluoxetine ([Suri et al. 2002](#)). These studies indicate that quantitative infant SSRI exposure during lactation is considerably lower than transplacental exposure.

## Other Antidepressants

Reproductive safety data are more limited for other classes of antidepressants, including bupropion, desvenlafaxine, duloxetine, mirtazapine, nefazodone, trazodone, venlafaxine, vilazodone, and vortioxetine. Prospective reports of first-trimester use of these agents have included 2,550 bupropion exposures producing 56 (2.2%) children with major malformations ([Boshier et al. 2003](#); [Briggs et al. 2005](#); [Chun-Fai-Chan et al. 2005](#); [Cole et al. 2007](#); [GlaxoSmithKline 2005](#)), 862 venlafaxine exposures with 91 (10.6%) major malformations ([Einarson et al. 2001](#); [GlaxoSmithKline 2005](#); [Polen et al. 2013](#)), 404 trazodone exposures with 10 (2.5%) major malformations ([Briggs et al. 2005](#); [GlaxoSmithKline 2005](#); [McElhatton et al. 1996](#)), 140 nefazodone exposures with 2 (1.4%) major malformations ([GlaxoSmithKline 2005](#)), 508 mirtazapine exposures with 14 (2.8%) major malformations ([Djulus et al. 2006](#); [GlaxoSmithKline 2005](#); [Smit et al. 2015](#); [Winterfeld et al. 2015](#)), and a combined report of 121 nefazodone or trazodone exposures with 2 (1.7%) major malformations ([Einarson et al. 2003](#)). For duloxetine, there have been 165 exposures with 3 (1.8%) major malformations ([Einarson et al. 2012](#)). The only reported case of vilazodone use in pregnancy resulted in a full-term, healthy neonate ([Morrison 2014](#)). No published data are yet available for prenatal vortioxetine exposure.

A single study that followed an infant until 9 months after in utero exposure to duloxetine reported normal infant cognitive, language, motor, and psychomotor development ([Bellantuono et al. 2013](#)). Likewise, children exposed to venlafaxine in utero showed no differences in IQ or

behavior compared with children of nondepressed mothers (Nulman et al. 2012).

A recent study found that prenatal exposure to serotonin-norepinephrine reuptake inhibitor antidepressants after the 20th week of gestation was associated with an increased risk of hypertensive disorders of pregnancy (OR=2.57; 95% CI=1.34-4.93), with an even higher (sixfold) increase among those receiving venlafaxine at dosages exceeding 187.5 mg/day (Newport et al. 2016).

Prenatal pharmacokinetic data are limited. High rates of placental transfer (i.e., umbilical cord concentrations in excess of maternal concentrations) have been reported for venlafaxine (Hendrick et al. 2003) and for its active metabolite desvenlafaxine (Hendrick et al. 2003; Rampono et al. 2009). Duloxetine has a single case report of a cord-to-maternal serum concentration ratio of 0.12, which suggests a low rate of placental transfer (Boyce et al. 2011).

Lactation data also remain limited. Best studied are venlafaxine/desvenlafaxine, for which three studies (Ilett et al. 1998; Newport et al. 2009; Rampono et al. 2011) encompassing 26 mother-infant nursing dyads have reported infant dosages that were 6.8%-8.1% of maternal dosages, which is within the notional 10% presumed safety level (Hendrick et al. 2003; Rampono et al. 2009). A single case report and a small case series of six women receiving duloxetine therapy during lactation described relative infant doses of less than 1% (Boyce et al. 2011; Lobo et al. 2008). The sole report of bupropion in nursing infants noted that the drug could not be detected in the plasma of a nursing infant (Briggs et al. 1993). Five studies totaling 55 neonates exposed to mirtazapine have reported no adverse outcomes and a low relative infant dose (Aichhorn et al.

2004; [Klier et al. 2007](#); [Kristensen et al. 2007](#); [Smit et al. 2015](#); [Tonn et al. 2009](#)). No lactation data have been published for vilazodone or vortioxetine.

## Tricyclic Antidepressants

Before the introduction of the SSRIs, TCAs were widely used during pregnancy and lactation. No clear association has been established between TCA exposure and congenital malformations. Early studies raised concerns about limb anomalies ([Barson 1972](#); [Elia et al. 1987](#); [McBride 1972](#)), but a meta-analysis by [Altshuler et al. \(1996\)](#) identified a congenital malformation incidence of only 3.14% ( $n=13$ ) among 414 infants exposed to a TCA during the first trimester. A data review from the European Network of Teratology Information Services and the United Kingdom's General Practice Research Database found similar rates of malformation after TCA exposure ([McElhatton et al. 1996](#); [Vasilakis-Scaramozza et al. 2013](#)). Moreover, no adverse neurodevelopmental effects were reported in two studies involving 126 children with prenatal TCA exposure ([Nulman et al. 1997a, 2002](#)).

Few data exist regarding the acute effects of TCA exposure on fetal and neonatal well-being. There are case reports of fetal tachycardia and neonatal symptoms including tachypnea, tachycardia, cyanosis, irritability, hypertonia, clonus, and spasm ([Eggermont 1973](#); [ter Horst et al. 2012](#)). A small ( $n=18$ ) prospective study found no evidence of increased complications during labor and delivery but did report transient withdrawal symptoms among TCA-exposed neonates ([Misri and Sivertz 1991](#)).

TCAs have been widely used during lactation. The only adverse event reported to date is respiratory depression in a nursing infant exposed to doxepin, leading the authors to conclude that doxepin should be avoided but that most TCAs are safe for use during breast feeding ([Matheson et al. 1985](#)). This clinical finding is paralleled by pharmacokinetic data indicating that whereas all TCAs are excreted in breast milk, infant plasma concentrations are considerably higher for doxepin than for other TCAs (for a review, see [Wisner et al. 1996b](#)).

## Monoamine Oxidase Inhibitors

Although the monoamine oxidase inhibitors (MAOIs) were introduced almost 50 years ago, reproductive safety data are sparse. The utility of MAOIs during pregnancy and lactation is severely limited by the potential for hypertensive crisis, which necessitates dietary constraints and avoidance of numerous medications that are commonly used during pregnancy (e.g., pseudoephedrine) or labor and delivery (e.g., meperidine).

---

## Mood Stabilizers

---

### Lithium

Early retrospective data suggested that lithium exposure was associated with a 400-fold increase in cardiac malformations—specifically, a defect of the tricuspid valve known as Ebstein’s anomaly ([Nora et al. 1974](#); [Weinstein](#)



and Goldfield 1975). However, a subsequent meta-analysis calculated the risk ratio for cardiac malformations as 1.2–7.7 and the risk ratio for overall congenital malformations as 1.5–3.0 (Cohen et al. 1994). Altshuler et al. (1996) estimated that the risk of Ebstein’s anomaly after prenatal lithium exposure rises from 1 in 20,000 to 1 in 1,000. A recent study indicated that lithium exposure in utero is associated with a higher rate of cardiovascular malformations but not of all major congenital malformations (Diav-Citrin et al. 2014). Additional studies (albeit small ones) also failed to confirm the early estimates regarding lithium’s teratogenic potential (Friedman and Polifka 2000; Jacobson et al. 1992; Källén and Tandberg 1983). Laboratory animal studies had indicated that neurobehavioral alterations also might be a concern for prenatal lithium exposure, but two studies of school-age children exposed to lithium during gestation found no evidence of adverse neurobehavioral sequelae (Schou 1976; van der Lugt et al. 2012).

The continued recommendation for prenatal assessment for fetal anomalies in women taking lithium includes a fetal echocardiogram between weeks 18 and 20 of gestation. In the event of unplanned conception during lithium therapy, the decision to continue or discontinue lithium should be informed by the severity and course of the patient’s illness and the time point in gestation when the exposure comes to attention. Discontinuing lithium therapy after cardiogenesis is complete, at approximately 9–11 weeks’ gestation, may be ill advised.

Lithium’s low therapeutic index raises concerns about acute perinatal toxicities. Lithium exposure later in gestation can result in fetal and neonatal cardiac arrhythmias (Wilson et al. 1983), hypoglycemia and

nephrogenic diabetes insipidus ([Mizrahi et al. 1979](#)), thyroid dysfunction ([Karlsson et al. 1975](#)), polyhydramnios, premature delivery, and floppy infant syndrome ([Llewellyn et al. 1998](#)). Neonatal symptoms of lithium toxicity, including flaccidity, lethargy, and poor suck reflexes, may persist for more than 7 days ([Woody et al. 1971](#)).

In a pooled analysis of lithium placental passage and neonatal outcomes ([Newport et al. 2005](#)), we determined that 1) higher neonatal lithium concentrations were associated with significantly lower Apgar scores, longer hospital stays, and higher rates of CNS and neuromuscular complications; 2) umbilical cord (i.e., fetal) plasma concentrations were uniformly equivalent to maternal concentrations, suggesting that lithium rapidly equilibrates across the placenta; and 3) withholding lithium therapy for 24–48 hours prior to delivery resulted in a 0.28 mEq/L reduction in maternal (and presumably fetal) lithium concentrations, thereby likely improving neonatal outcomes.

The physiological alterations of pregnancy are of particular importance in the perinatal management of lithium. Changes in renal clearance over the course of pregnancy and the potential for abrupt volume changes during delivery as a result of copious diaphoresis and the loss of blood and amniotic fluid mandate careful monitoring of lithium levels during pregnancy and especially at delivery. Furthermore, nonsteroidal anti-inflammatory drugs, which inhibit renal clearance of lithium, should be avoided in mother and infant alike during the early postpartum period.

The existing database regarding lithium and lactation encompasses 25 mother–infant nursing dyads ([Bogen et al. 2012](#); [Fries 1970](#); [Schou and Amdisen 1973](#); [Skausig and](#)

Schou 1977; Sykes et al. 1976; Tunnessen and Hertz 1972; Viguera et al. 2007a; Weinstein and Goldfield 1969; Woody et al. 1971). Adverse events, including lethargy, hypotonia, hypothermia, cyanosis, electrocardiogram changes, poor feeding, slow growth, gross and fine motor delay, and elevated thyroid-stimulating hormone levels, were reported in five (16%) of these children (Bogen et al. 2012; Skausig and Schou 1977; Tunnessen and Hertz 1972; Viguera et al. 2007a; Woody et al. 1971), including one infant who developed frank lithium toxicity with a serum concentration of 1.4 mEq/L, which was double the maternal level (Skausig and Schou 1977). The American Academy of Pediatrics (American Academy of Pediatrics Committee on Drugs 2001) discourages the use of lithium during lactation. The largest pharmacokinetic study of lithium in lactation reported a milk-to-plasma ratio of 0.53 and an infant-to-maternal plasma ratio of 0.24 (Viguera et al. 2007a). In other studies, nursing infants have had lithium concentrations generally ranging from 5% to 65% of maternal levels (Bogen et al. 2012; Fries 1970; Kirksey and Groziak 1984; Schou and Amdisen 1973; Sykes et al. 1976; Tunnessen and Hertz 1972; Weinstein and Goldfield 1969), excluding the lone infant whose serum concentration was 200% of the maternal concentration (Skausig and Schou 1977). Because dehydration can increase vulnerability to lithium toxicity, the hydration status of nursing infants of mothers taking lithium should be carefully monitored (Llewellyn et al. 1998).

## Valproate (Valproic Acid)

Prenatal exposure to valproate has been associated with numerous congenital malformations (rate of 6.7% for overall congenital malformations; [Campbell et al. 2014](#)), including neural tube defects ([Bjerkedal et al. 1982](#); [Centers for Disease Control 1992](#); [Jäger-Roman et al. 1986](#); [Lindhout and Schmidt 1986](#)), craniofacial anomalies ([Assencio-Ferreira et al. 2001](#); [Lajeunie et al. 1998, 2001](#); [Paulson and Paulson 1981](#)), limb abnormalities ([Rodríguez-Pinilla et al. 2000](#)), cardiovascular anomalies ([Dalens et al. 1980](#); [Koch et al. 1983](#); [Sodhi et al. 2001](#); [Veiby et al. 2014](#)), and hypospadias ([Veiby et al. 2014](#)). Valproate exposure prior to neural tube closure, during the fourth week of gestation, confers a 1%–2% risk of spina bifida, which is 10–20 times greater than the risk in the general population ([Bjerkedal et al. 1982](#); [Centers for Disease Control 1992](#); [Rosa 1991](#)). One meta-analysis placed the risk of neural tube defects even higher, at 3.8%, with particular vulnerability for the infants of women whose daily dosage exceeded 1,000 mg ([Samrén et al. 1997](#)). Other studies support this dose-response relationship ([Canger et al. 1999](#); [Kaneko et al. 1999](#); [Omtzigt et al. 1992](#); [Samrén et al. 1999](#); [Tomson et al. 2011, 2015](#)), leading one group to recommend that daily dosages not exceed 1,000 mg and that maternal serum concentrations not exceed 70 µg/mL to reduce the risk of malformations ([Kaneko et al. 1999](#)). In a case-control study examining the incidence of limb malformations in a cohort of more than 44,000 children, 67 of whom were exposed to valproate in the first trimester, [Rodríguez-Pinilla et al. \(2000\)](#) reported an OR of 6.17 for limb abnormalities among children exposed to valproate and estimated the risk of limb abnormalities from valproate exposure at 0.42%.

A *fetal valproate syndrome* was initially reported by [DiLiberti et al. \(1984\)](#) and subsequently confirmed by other investigators ([Ardinger et al. 1988](#); [Martínez-Frías 1990](#); [Winter et al. 1987](#)). The phenotypic attributes of fetal valproate syndrome include stereotypical facial features such as bifrontal narrowing, midface hypoplasia, a broad nasal bridge, a short nose with anteverted nares, epicanthal folds, micrognathia, a shallow philtrum, a thin upper lip, and a thick lower lip ([McMahon and Braddock 2001](#); [S.J. Moore et al. 2000](#)). Many of the congenital malformations previously associated with valproate exposure have been recognized as attributes of fetal valproate syndrome ([McMahon and Braddock 2001](#)). Valproate's antagonism of folate activity may underlie the risk of both spina bifida and fetal valproate syndrome. A case-control study comparing 57 children with fetal anticonvulsant syndromes, 46 of whose mothers were given valproate, with 152 control children found a significantly higher rate of homozygosity for a mutation in the gene for methylenetetrahydrofolate reductase (*MTHFR*), a key enzyme in folate metabolism, in the valproate-exposed children ([Dean et al. 1999](#)).

Neurodevelopmental outcomes associated with prenatal valproate exposure are equally of concern. A review found that developmental delay was evident in 20% and intellectual disability in 10% of children exposed to valproate monotherapy prenatally ([Kozma 2001](#)). An interim report from a prospective multicenter investigation of the neurodevelopmental effects of prenatal antiepileptic drug exposure noted that 24% of 2-year-olds with prenatal valproate exposure had mental developmental indexes of less than 70, more than double the rate associated with other antiepileptic drugs ([Meador et al. 2006](#)). More recent studies have consistently shown deleterious

neurodevelopmental effects from prenatal valproate exposure ([Baker et al. 2015](#); [Cohen et al. 2013](#); [Meador et al. 2009, 2013](#); [Shallcross et al. 2011](#); [Veiby et al. 2013](#)), with particular consequences for verbal cognition ([McVearry et al. 2009](#); [Meador et al. 2011](#); [Nadebaum et al. 2011a, 2011b](#)). Retrospective reports indicate that varying degrees of cognitive impairment may be present in children manifesting the physical sequelae of fetal valproate syndrome ([Adab et al. 2001](#); [Gaily et al. 1990](#); [Moore et al. 2000](#)). Fetal valproate syndrome also has been associated with autism spectrum disorders ([Bescoby-Chambers et al. 2001](#); [Christensen et al. 2013](#); [Moore et al. 2000](#); [Williams and Hersh 1997](#); [Williams et al. 2001](#); [Wood et al. 2015](#)).

Valproate exposure during gestation is also associated with risks for numerous fetal and neonatal toxicities, including hepatotoxicity ([Kennedy and Koren 1998](#)), coagulopathies ([Mountain et al. 1970](#)), and neonatal hypoglycemia ([Ebbesen et al. 2000](#); [Thisted and Ebbesen 1993](#)). Ten of 13 infants who had neonatal hypoglycemia after prenatal valproate exposure developed withdrawal symptoms—including irritability, jitteriness, hypertonia, seizures, and vomiting—that began 12–24 hours after delivery and lasted up to 1 week ([Ebbesen et al. 2000](#)).

Pharmacokinetic studies in women with epilepsy have reported that maternal valproate concentrations steadily decline over the course of pregnancy, falling to levels as much as 50% lower than preconception concentrations ([Yerby et al. 1990, 1992](#)). Consistent findings from other studies indicate that valproate is more rapidly cleared during gestation, and especially during the final month of pregnancy ([Nau et al. 1982b](#); [Otani 1985](#); [Philbert et al. 1985](#)). Dosage increases during pregnancy therefore may be required to maintain therapeutic efficacy. Valproate

readily crosses the human placenta, with umbilical cord concentrations at delivery equal to or slightly higher than maternal concentrations ([Froescher et al. 1984b](#); [Philbert et al. 1985](#); [Yerby et al. 1990, 1992](#)).

The database regarding valproate and lactation includes 41 mother–infant nursing dyads ([Alexander 1979](#); [Bardy et al. 1982a](#); [Dickinson et al. 1979](#); [Froescher et al. 1981](#); [Nau et al. 1981](#); [Piontek et al. 2000](#); [Stahl et al. 1997](#); [Tsuru et al. 1988](#); [von Unruh et al. 1984](#); [Wisner and Perel 1998](#)). From these cases, only one adverse event, thrombocytopenia and anemia in an infant, has been reported ([Stahl et al. 1997](#)). The pharmacokinetic data indicate that valproate milk-to-plasma ratios are uniformly low and that serum concentrations of nursing infants are 2%–40% of maternal concentrations ([Alexander 1979](#); [Bardy et al. 1982a](#); [Piontek et al. 2000](#); [Stahl et al. 1997](#); [von Unruh et al. 1984](#); [Wisner et al. 1996b](#)). In a study of the neurobehavioral effects of valproate exposure during lactation, [Meador et al. \(2014\)](#) found no adverse effects on cognitive functions.

In summary, prenatal valproate use raises grave safety concerns. In women of childbearing age, valproate should never be used except as a treatment of last resort. If valproate must be used during pregnancy, its risk may be reduced by being careful not to exceed 1,000 mg/day or a serum concentration of 70 µg/mL. Folate supplementation (4–5 mg/day) is also recommended, although no definitive evidence indicates that it reduces the risk of valproate-associated anomalies. All women of childbearing potential who are treated with valproate should receive concomitant folate supplementation, regardless of whether they plan to conceive. The preliminary evidence that aspects of fetal valproate syndrome other than neural tube defects may be



associated with valproate's antagonism of folate metabolism suggests that folate supplementation should be administered not only in the first trimester but also throughout gestation. Because of the potential for valproate-associated neonatal coagulopathies, oral vitamin K supplementation (10–20 mg/day) may be considered during the final month of gestation. Prenatal surveillance for congenital abnormalities should include maternal serum  $\alpha$ -fetoprotein, fetal echocardiography, and a level 2 ultrasound at approximately 16–18 weeks' gestation. Finally, genetic screening of women taking valproate for mutations in the *MTHFR* gene warrants future consideration.

In contrast to the marked risks of its use during pregnancy, valproate therapy during lactation appears to be well tolerated by nursing infants. Nevertheless, periodic assays of platelet counts and serum liver enzymes in nursing infants are recommended because the neurodevelopmental effect of nursing exposure to valproate is unclear.

## Carbamazepine

Carbamazepine is associated with many of the same risks as valproate during gestation, although in many cases with less frequency or severity. For example, first-trimester carbamazepine exposure is associated with a 0.5%–1.0% risk of neural tube defects ([Rosa 1991](#)), which is approximately half that seen with valproate exposure ([Lindhout and Schmidt 1986](#); [Rosa 1991](#)). A meta-analysis of five prospective studies encompassing 1,255 prenatal exposures indicated that carbamazepine exposure in utero



is associated with an increased risk of neural tube defects, cleft palate, cardiovascular abnormalities, and urinary tract anomalies ([Matalon et al. 2002](#)). The European Surveillance of Congenital Anomalies (EUROCAT) study ([Jentink et al. 2010](#)), a large case-control investigation, reported that carbamazepine exposure was associated with an increased risk of spina bifida (OR=2.6) only. The Australian Register of Antiepileptic Drugs in Pregnancy showed that carbamazepine exposure in utero was associated with renal tract abnormalities ([Vajda et al. 2013](#)). An epidemiological study indicated that periconceptional folate supplementation was associated with a lower rate of neural tube defects among the children of women taking carbamazepine during pregnancy ([Hernández-Díaz et al. 2001](#)).

A *fetal carbamazepine syndrome*—manifested by a short nose, long philtrum, epicanthal folds, hypertelorism, upslanting palpebral fissures, and fingernail hypoplasia—has been described ([Jones et al. 1989](#)), and in one study, the phenotypic characteristics of this syndrome were observed in 6 of 47 children prenatally exposed ([Ornoy and Cohen 1996](#)). Other studies have confirmed the association with facial anomalies ([Moore et al. 2000](#); [Nulman et al. 1997b](#); [Scolnik et al. 1994](#); [Wide et al. 2000](#)), but one of these studies found similar facial abnormalities among children born to women with epilepsy who were untreated during pregnancy ([Nulman et al. 1997b](#)). There has been an isolated case report of phocomelia (i.e., absence or underdevelopment of limbs) in an infant with in utero exposure ([Dursun et al. 2012](#)).

Data regarding the neurodevelopmental sequelae of prenatal carbamazepine exposure have been mixed. Some studies reported developmental delay in up to 20% of

children with fetal carbamazepine syndrome (Jones et al. 1989; Meador et al. 2011; Moore et al. 2000; Ornoy and Cohen 1996; Veiby et al. 2013), but others did not find that association (Gaily et al. 1990; Scolnik et al. 1994; van der Pol et al. 1991; Wide et al. 2000). Recent systematic studies generally have found no evidence of developmental delay in children exposed to carbamazepine in utero (Baker et al. 2015; McVearry et al. 2009; Meador et al. 2006, 2009, 2011; Nadebaum et al. 2011b).

Potential fetal/neonatal toxicities associated with carbamazepine exposure include blood dyscrasias, coagulopathies, skin reactions, and hepatotoxicity. Most of these risks remain theoretical, although neonatal hepatotoxicity has been reported in a carbamazepine-exposed infant (Frey et al. 2002).

Pharmacokinetic studies of carbamazepine clearance during gestation have yielded mixed results. Some investigators have reported significant increases in carbamazepine clearance during the third trimester (Battino et al. 1982; Dam et al. 1979; Lander et al. 1981), but others have found no changes in clearance (Bardy et al. 1982b; Johnson et al. 2014; Otani 1985; Reisinger et al. 2013; Yerby et al. 1985). Placental pharmacokinetic studies indicate that the placental transfer of carbamazepine is lower than that of other anticonvulsants (Nau et al. 1982a; Yerby et al. 1990, 1992), with umbilical cord-to-maternal plasma ratios of 0.5–0.8 (Nau et al. 1982a).

The literature on carbamazepine and lactation encompasses 12 published reports and 144 mother-infant nursing pairs (Brent and Wisner 1998; Frey et al. 1990, 2002; Froescher et al. 1984a; Kaneko et al. 1982; Kok et al. 1982; Kuhnz et al. 1983; Merlob et al. 1992; Niebyl et al. 1979; Pynnönen and Sillanpää 1975; Pynnönen et al. 1977;

Wisner and Perel 1998), representing the most extensive data set for any mood stabilizer in lactation. Included are 8 reports of adverse events: 1 drowsy, irritable infant with an undetectable serum concentration of carbamazepine (Kok et al. 1982); 2 “hyperexcitable” infants in whom carbamazepine levels were not reported (Kuhnz et al. 1983); 2 infants with cholestatic hepatitis in whom carbamazepine levels were not reported (Frey et al. 1990, 2002); 1 infant with poor nursing effort (Froescher et al. 1984a); 1 infant with an increased serum concentration of  $\gamma$ -glutamyl transpeptidase (GGT) but no overt clinical sequelae whose serum concentration was 33% of the maternal concentration (Merlob et al. 1992); and 1 infant with a seizurelike phenomenon whose carbamazepine level was 8% of the maternal level (Brent and Wisner 1998). Serum carbamazepine concentrations in the 8 nursing infants in whom these levels were assessed ranged from undetectable to 65% of the maternal level (Brent and Wisner 1998; Kok et al. 1982; Merlob et al. 1992; Pynnönen and Sillanpää 1975; Pynnönen et al. 1977; Wisner and Perel 1998).

Although the risks associated with prenatal carbamazepine exposure are marginally better than those for valproate exposure, the clinical recommendations are quite similar. Carbamazepine should be avoided in pregnancy, especially during the first trimester. Folate supplementation (4–5 mg/day) is also recommended, not only during gestation but also throughout the reproductive years because of the high prevalence of inadvertent conception in the United States. Women taking carbamazepine during gestation should receive prenatal surveillance for congenital abnormalities, including maternal serum  $\alpha$ -fetoprotein, fetal echocardiography, and

a level 2 ultrasound at approximately 16–18 weeks' gestation. Carbamazepine has by far the most extensive database for mood stabilizers in lactation, but reports of hepatic dysfunction in nursing infants certainly raise concern. Thus, periodic assays of blood counts and serum liver enzymes of nursing infants are recommended.

## Lamotrigine

Reproductive safety data for lamotrigine have rapidly accrued during the past decade and compare favorably with safety data for other mood stabilizers. The overall risk of major fetal malformations following first-trimester prenatal exposure to lamotrigine is 2.6% (207 per 7,951 exposures) ([Campbell et al. 2014](#); [Cunnington et al. 2011](#); [Dominguez-Salgado et al. 2004](#); [GlaxoSmithKline 2007](#); [Holmes et al. 2006](#); [Meador et al. 2006](#); [Mølgaard-Nielsen and Hviid 2011](#); [Morrow et al. 2006](#); [Sabers et al. 2004](#); [Vajda et al. 2003](#)), a risk that is within the range associated with births not involving drug exposures. A report by the North American Pregnancy Registry ([Holmes et al. 2006](#)) noted a relatively high rate of midline facial clefts (0.89% of 564 exposures); however, the collective rate of orofacial clefts in the other registries was only 0.10% (3 per 2,956 exposures) ([Dominguez-Salgado et al. 2004](#); [GlaxoSmithKline 2007](#); [Meador et al. 2006](#); [Mølgaard-Nielsen and Hviid 2011](#); [Morrow et al. 2006](#); [Sabers et al. 2004](#); [Vajda et al. 2003](#)). Furthermore, the EUROCAT case-control study, encompassing 5,511 children with orofacial clefts and 80,052 children without clefts, reported an adjusted OR of 0.67 for clefts with lamotrigine exposure ([Dolk et al. 2008](#)). The U.K. Epilepsy and Pregnancy

Register reported a higher risk of malformations at maternal dosages exceeding 200 mg/day ([Morrow et al. 2006](#)), although this finding was not confirmed in subsequent analyses ([GlaxoSmithKline 2007](#); [Mølgaard-Nielsen and Hviid 2011](#)). Despite these reassuring findings, folate supplementation is recommended for all women of childbearing age taking any antiepileptic drug, including lamotrigine. Prospective neurodevelopmental data have been consistently favorable among children with prenatal lamotrigine exposure ([Baker et al. 2015](#); [McVearry et al. 2009](#); [Meador et al. 2006, 2009, 2011](#); [Nadebaum et al. 2011b](#)).

Numerous pharmacokinetic studies have reported that lamotrigine clearance steadily increases across gestation ([de Haan et al. 2004](#); [Fotopoulou et al. 2009](#); [Franco et al. 2008](#); [Pennell et al. 2004, 2008](#); [Petrenaite et al. 2005](#); [Polepally et al. 2014](#); [Reisinger et al. 2013](#); [Tran et al. 2002](#)). These studies are limited by polytherapy with other anticonvulsants, which are known to alter the metabolism of lamotrigine. It is unclear whether dosage changes would be necessary to maintain mood stability in patients with bipolar disorder and whether the adjunctive agents commonly used in the treatment of bipolar disorder would have similar effects on lamotrigine metabolism. Studies in patients taking lamotrigine also report that its rate of clearance abruptly declines after delivery ([Ohman et al. 2000](#); [Pennell et al. 2004](#); [Polepally et al. 2014](#); [Tran et al. 2002](#)). Therefore, dosage reductions may be necessary after delivery to avoid maternal symptoms of lamotrigine toxicity, such as dizziness, nausea and vomiting, and diplopia ([Tran et al. 2002](#)). Published reports on the placental passage of lamotrigine indicate that lamotrigine concentrations in fetal circulation at delivery are equal to

maternal concentrations ([Myllynen et al. 2003](#); [Ohman et al. 2000](#); [Paulzen et al. 2015](#); [Sathanandar et al. 2000](#); [Tomson et al. 1997](#)). There have been no reports of acute adverse events observed in neonates exposed to lamotrigine.

Reports regarding lamotrigine and lactation ([Clark et al. 2013](#); [GlaxoSmithKline 2007](#); [Liporace et al. 2004](#); [Newport et al. 2008c](#); [Nordmo et al. 2009](#); [Ohman et al. 2000](#); [Page-Sharp et al. 2006](#); [Rambeck et al. 1997](#); [Tomson et al. 1997](#)) collectively encompass 60 mother-infant nursing dyads. The only reported adverse event was an apneic episode in a nursing infant whose mother was taking lamotrigine 850 mg/day ([Nordmo et al. 2009](#)). Seven other infants were observed to have a benign thrombocytosis ([Newport et al. 2008b](#)). In the largest ( $n=30$ ) of these studies ([Newport et al. 2008b](#)), the mean milk-to-plasma ratio was 41.3%, the relative infant dose equaled 9.2%, and the infant-to-maternal plasma ratio equaled 18.3%. Long-term neurobehavioral outcomes have not been studied in nursing infants exposed to lamotrigine.

---

## Antipsychotics

---

### Second-Generation Antipsychotics

Commonly prescribed antipsychotic medications, as well as agents used to treat the side effects of first-generation antipsychotics (FGAs), are covered in [Chapters 24–35](#). The second-generation antipsychotics (SGAs) have supplanted the FGAs as first-line medications for psychotic disorders and are also used for other psychiatric indications,

including bipolar disorder, anxiety disorders, and treatment-resistant depression. Despite rapidly expanding use, the reproductive safety database regarding SGAs remains limited. A recent study that used a national pregnancy registry for SGAs reported an OR of 1.25 (95% CI=0.13–12.13) for major malformations in exposed infants compared with nonexposed infants ([Cohen et al. 2015](#)). A neurobehavioral outcome study identified a transient delay in cognitive, motor, social-emotional, and adaptive behavior in SGA-exposed infants that resolved by age 12 months ([Peng et al. 2013](#)).

Even though some data have been reassuring, the small volume of SGA data to date precludes definitive conclusions about their reproductive safety. Therefore, the routine use of SGAs during pregnancy and lactation cannot yet be recommended. Nonetheless, if a woman who is taking an SGA inadvertently conceives, a comprehensive risk–benefit assessment may indicate that continuing the SGA (to which the fetus has already been exposed) during gestation is preferable to switching to an FGA (to which the fetus has not yet been exposed).

## **Clozapine**

Reproductive safety data for clozapine, the oldest of the SGAs, are limited to case reports ([Barnas et al. 1994](#); [Di Michele et al. 1996](#); [Kornhuber and Weller 1991](#); [Moreno-Bruna et al. 2012](#); [Waldman and Safferman 1993](#)), case series ([McKenna et al. 2005](#); [Stoner et al. 1997](#); [Tenyi and Tixler 1998](#)), and a retrospective review ([Dev and Krupp 1995](#)), collectively encompassing 80 children exposed to clozapine during pregnancy and/or lactation. Adverse sequelae associated with in utero clozapine therapy include maternal gestational diabetes ([Dickson and Hogg 1998](#));



several minor anomalies, including cephalohematoma, hyperpigmentation folds, and a coccygeal dimple, in an infant (Stoner et al. 1997); delayed peristalsis (Moreno-Bruna et al. 2012); transient low-grade fever in an infant also exposed to lithium (Stoner et al. 1997); and floppy infant syndrome in a newborn also exposed to lorazepam (Di Michele et al. 1996). In a review of 61 children exposed to clozapine prenatally, Dev and Krupp (1995) reported 5 cases of congenital malformations and 5 cases of neonatal syndromes; however, many of these mothers were taking other psychotropic medications during pregnancy. A recent study of neurodevelopmental consequences of prenatal exposure to SGAs reported higher rates of developmental delay at ages 2 months and 6 months among clozapine-exposed infants compared with infants exposed to other SGAs (Shao et al. 2015). The only reported case of clozapine use during lactation noted no adverse effects on the nursing infant (Kornhuber and Weller 1991).

The only investigation of the perinatal pharmacokinetics of clozapine found elevated concentrations in fetal serum and breast milk compared with concentrations in maternal serum and amniotic fluid (Barnas et al. 1994), leading the authors to conclude that clozapine accumulates in fetal circulation and breast milk. Although no cases of agranulocytosis have been reported in clozapine-exposed infants, this potential risk and the requisite laboratory monitoring limit the utility of clozapine during the peripartum.

## **Olanzapine**

A published birth registry of 23 prospectively ascertained olanzapine-exposed pregnancies from the Lilly Worldwide Pharmacovigilance Safety Database reported no major



malformations, 13% spontaneous abortions, 5% preterm deliveries, and 5% fetal deaths ([Goldstein et al. 2000](#)). In a subsequent examination of the same database, 610 prospectively identified pregnancies exposed to olanzapine resulted in 10% premature births, 9% spontaneous abortions, 8% perinatal conditions (i.e., an adverse event occurring within 7 days of birth), and 4% congenital anomalies ([Brunner et al. 2013](#)). A prospective study comparing outcomes among 151 pregnant women with SGA exposure (olanzapine,  $n=60$ ; risperidone,  $n=49$ ; quetiapine,  $n=36$ ; clozapine,  $n=6$ ) with outcomes among 151 pregnant control subjects reported no differences in rates of spontaneous abortion, stillbirth, major malformations, prematurity, or low birth weight ([McKenna et al. 2005](#)). In this study, one SGA-exposed child (olanzapine) was observed to have major malformations (a series of midline defects including an oral cleft, encephalocele, and aqueductal stenosis). A recent meta-analysis reported a malformation rate of 3.5% among 1,090 olanzapine-exposed infants, a rate that compares favorably to rates with other SGAs ([Ennis and Damkier 2015](#)).

In a study of antipsychotic placental passage rates and neonatal outcomes ([Newport et al. 2007a](#)), umbilical cord concentrations in olanzapine-exposed neonates ( $n=14$ ) were 72.1% of maternal concentrations. In this study, there was a trend toward higher rates of low birth weight (30.8%;  $P<0.06$ ) and neonatal intensive care unit admission (30.8%;  $P<0.09$ ) among neonates exposed to olanzapine compared with those exposed to the other antipsychotics.

Case reports of 39 infants exposed to olanzapine during lactation with no evidence of infant toxicity currently appear in the literature ([Croke et al. 2002](#); [Friedman and Rosenthal 2003](#); [Gardiner et al. 2003](#); [Gilad et al. 2011](#);

[Goldstein et al. 2000](#); [Kirchheiner et al. 2000](#); [Whitworth et al. 2010](#)). The Lilly Safety Database reported on 62 breastfeeding mother-infant dyads with a 15.6% rate of adverse events, identified as somnolence, irritability, tremors, and insomnia ([Brunner et al. 2013](#)). Pharmacokinetic studies of olanzapine exposure during lactation have reported that plasma concentrations were undetectable in infants during nursing ([Gardiner et al. 2003](#); [Kirchheiner et al. 2000](#); [Stiegler et al. 2014](#)) and that the median infant daily dosage via breast feeding was approximately 0.7%–1.8% of the maternal dosage ([Ambresin et al. 2004](#); [Aydin et al. 2015](#); [Brunner et al. 2013](#); [Croke et al. 2002](#); [Gardiner et al. 2003](#)).

## **Risperidone**

Prospective data on pregnancy outcomes following first-trimester risperidone exposure include a collective study of outcomes for several SGAs ([McKenna et al. 2005](#)) reporting no major malformations among 49 risperidone-exposed infants and a recent meta-analysis reporting a 5.1% malformation rate among 432 risperidone-exposed infants ([Ennis and Damkier 2015](#)). An additional study in 68 women with first-trimester exposure and known outcomes reported 9 (13.2%) spontaneous abortions, 1 (1.5%) stillbirth, and 2 (2.9%) children with major malformations ([Coppola et al. 2007](#)). No data on the neurodevelopmental effects of risperidone exposure during pregnancy or lactation are available.

Pharmacokinetic studies have reported placental passage concentrations among neonates ( $n=6$ ) of 49.2% ([Newport et al. 2007a](#)), milk-to-plasma ratios of less than 0.5 for risperidone and less than 0.88 for 9-hydroxyrisperidone ([Hill et al. 2000](#); [Ilett et al. 2004](#); [Weggelaar et al. 2011](#)),

and infant plasma concentrations ranging from 2.3% to 4.7% of maternal levels ([Ilett et al. 2004](#); [Weggelaar et al. 2011](#)).

## Quetiapine

The reproductive safety literature for first-trimester quetiapine exposure is limited to a case series of two successive pregnancies ([Grover and Madan 2012](#)), which reported healthy, full-term deliveries, and the [McKenna et al. \(2005\)](#) study, which reported no major malformations among 36 infants exposed to quetiapine. In the [Newport et al. \(2007a\)](#) study of antipsychotic placental passage, quetiapine concentrations among neonates ( $n=21$ ) were 23% of maternal concentrations. To our knowledge, this is the lowest placental passage rate ever reported for a psychotropic agent. No data are available on the neurodevelopmental effects of quetiapine exposure during pregnancy or lactation.

Three cases of quetiapine use during lactation following use during pregnancy estimated the nursing infant dosage at 0.09%–7.3% of the maternal daily dosage ([Lee et al. 2004](#); [Van Boekholt et al. 2015](#)).

## Aripiprazole

Reproductive safety data for aripiprazole include a case series of 86 mother–infant dyads that showed an increased risk of premature birth and fetal growth retardation but no increased risk of congenital malformations, miscarriages, preeclampsia, or gestational diabetes ([Bellet et al. 2015](#)). In addition, a recent meta-analysis reported a 5.0% malformation rate among 100 infants with first-trimester aripiprazole exposure ([Ennis and Damkier 2015](#)). A single

case report indicated poor respiratory effort at birth ([Watanabe et al. 2011](#)), and two case reports and a case series showed no adverse obstetrical or neonatal outcomes ([Gentile et al. 2011](#); [Lutz et al. 2010](#); [Windhager et al. 2014](#)).

Of the three case reports of aripiprazole use during lactation, the milk excretion profiles were questionable in two ([Lutz et al. 2010](#); [Schlotterbeck et al. 2007](#)), and the other reported a milk-to-plasma ratio of 0.051 ([Watanabe et al. 2011](#)). Placental transfer was 53.3%–54.7%, as shown in two reports of four mother–infant dyads ([Watanabe et al. 2011](#); [Windhager et al. 2014](#)).

## Other SGAs

Information about the use of other SGAs is scant. Use of ziprasidone, brexpiprazole, lurasidone, iloperidone, or asenapine during pregnancy has not been reported. A lone case report of use of paliperidone palmitate, the long-acting injectable formulation of paliperidone, during pregnancy (haloperidol was also used) indicated no adverse obstetrical outcomes ([Özdemir et al. 2015](#)).

Data concerning lactation were limited to a single case report of ziprasidone use during lactation that reported a milk-to-plasma ratio of 0.06 ([Schlotterbeck et al. 2009](#)).

## First-Generation Antipsychotics

In contrast to the SGAs, the FGAs have an extensive reproductive safety database addressing both somatic and neurobehavioral teratogenicity. Furthermore, the historical use of phenothiazine antipsychotics to treat pregnancy-associated emesis aids in separating the effects of

psychiatric illness and antipsychotic drugs on pregnancy outcome. Chlorpromazine, haloperidol, and perphenazine have received the greatest scrutiny, with no significant associations between these compounds and major malformations ([Goldberg and DiMascio 1978](#); [Hill and Stern 1979](#); [Nurnberg and Prudic 1984](#)).

In a study of 100 women taking haloperidol (mean dosage=1.2 mg/day) for hyperemesis gravidarum, no differences in gestational duration, fetal viability, or birth weight were noted ([Van Waes and Van de Velde 1969](#)). In a prospective study encompassing nearly 20,000 women receiving primarily phenothiazines for emesis, [Milkovich and van den Berg \(1976\)](#) found no significant association with neonatal survival rates or severe anomalies after controlling for maternal age, medication, and gestational age at exposure. Similar results have been obtained in several retrospective studies of women taking trifluoperazine for repeated abortions and emesis ([Moriarty and Nance 1963](#); [Rawlings et al. 1963](#)). In contrast, [Rumeau-Rouquette et al. \(1977\)](#) reported a significant association of major anomalies with prenatal exposure to aliphatic phenothiazines but not to piperazine- or piperidine-class agents. Reanalysis of the data obtained by [Milkovich and van den Berg \(1976\)](#) did find a significant risk of malformations associated with phenothiazine exposure in weeks 4 through 10 of gestation ([Edlund and Craig 1984](#)).

Neurobehavioral outcome studies encompassing 203 children exposed to FGAs during gestation detected no significant differences in IQ scores at age 4 years ([Kris 1965](#); [Slone et al. 1977](#)), although relatively low antipsychotic dosages were used by many women in these studies. Conversely, several laboratory animal studies

(Hoffeld et al. 1968; Ordy et al. 1966; Robertson et al. 1980), although not all (Dalleymagne and Weiss 1982), have identified persistent deficits in learning and memory among offspring prenatally exposed to FGA medications.

Beyond the teratogenic potential of the FGAs lies the possibility of fetal and infant toxicities such as neuroleptic malignant syndrome (James 1988) and extrapyramidal side effects (EPS) manifested by heightened muscle tone and increased rooting and tendon reflexes persisting for several months (Cleary 1977; Hill et al. 1966; O'Connor et al. 1981). Furthermore, prenatal exposure to FGAs has been associated with neonatal jaundice (Scokel and Jones 1962) and postnatal intestinal obstruction (Faltermann and Richardson 1980).

In our study of antipsychotic placental passage, neonatal haloperidol ( $n=13$ ) concentrations were 66% of maternal concentrations (Newport et al. 2007a).

In lactation, chlorpromazine is the most widely studied typical antipsychotic, with 7 infants exposed to chlorpromazine during nursing showing no developmental deficits at 16-month and 5-year follow-up evaluations (Kris and Carmichael 1957). However, 3 infants in another study whose mothers were prescribed both chlorpromazine and haloperidol showed evidence of developmental delay at 12-18 months (Yoshida et al. 1998b). Pharmacokinetic investigations of FGAs during lactation, including haloperidol (Stewart et al. 1980; Whalley et al. 1981; Yoshida et al. 1998b), trifluoperazine (Wilson et al. 1980; Yoshida et al. 1998b), perphenazine (Wilson et al. 1980), thioxanthenes (Matheson and Skjaeraasen 1988), and chlorpromazine (Yoshida et al. 1998b), have uniformly reported milk-to-plasma ratios of less than 1.0, although adequate control for distribution and time gradients was

lacking in these studies. One group postulated that the physicochemical properties of perphenazine could lead it to become “trapped” in breast milk ([Wilson et al. 1980](#)); however, this speculation is unconfirmed.

Fetal and infant exposure to any of the various agents available for the management of EPS (e.g., diphenhydramine, benztropine, amantadine) also raises concern. Results of the Collaborative Perinatal Project indicated that first-trimester exposure to diphenhydramine, the best studied of these medications, was associated with major and minor congenital anomalies ([Miller 1991](#); [Wisner and Perel 1988](#)). A case-control study found a significantly higher rate of prenatal diphenhydramine exposure among 599 infants with oral clefts than among 590 control infants ([Saxén 1974](#)). Despite these data, diphenhydramine is routinely used during pregnancy. Clinical studies of the teratogenic potential of benztropine and amantadine are lacking, although laboratory animal studies indicated that amantadine is associated with an elevated risk of congenital malformations ([Hirsch and Swartz 1980](#)). Perinatal toxicities, including neonatal intestinal obstruction after gestational exposure to benztropine ([Falterman and Richardson 1980](#)) and a possible neonatal diphenhydramine withdrawal syndrome manifested by tremulousness and diarrhea ([Parkin 1974](#)), also warrant concern.

In summary, FGAs have been widely used for more than 40 years, and the paucity of data linking these agents to either teratogenic or toxic effects suggests that their risks are minimal. In particular, piperazine phenothiazines (e.g., trifluoperazine, perphenazine) may have especially low teratogenic potential ([Rumeau-Rouquette et al. 1977](#)). Given the greater fetal risks associated with anticholinergic medications (e.g., diphenhydramine), their use should be

avoided if possible. Consequently, FGAs used during the antepartum period should be kept at the lowest effective dosage to minimize the need for adjunctive medications to manage EPS.

---

## Anxiolytics

---

Pharmacotherapy for anxiety disorders includes antidepressants, benzodiazepines, buspirone, and certain atypical antipsychotics.

### Benzodiazepines

A retrospective analysis of more than 100,000 women found that at least 2% were prescribed a benzodiazepine during gestation ([Bergman et al. 1992](#)). The earliest benzodiazepine teratogenicity studies reported an increased risk of oral clefts after in utero diazepam exposure ([Aarskog 1975](#); [Saxén 1975](#); [Saxén and Saxén 1975](#)), but later studies failed to confirm this association ([Ban et al. 2014](#); [Entman and Vaughn 1984](#); [Rosenberg et al. 1983](#); [Shiono and Mills 1984](#)). Prospective studies of first-trimester alprazolam exposure encompassing approximately 1,300 pregnancies indicated no excess of oral clefts or other birth defects ([Barry and St Clair 1987](#); [Schick-Boschetto and Zuber 1992](#); [St Clair and Schirmer 1992](#)), and a recent study of first-trimester exposure to diazepam and temazepam echoed this finding ([Ban et al. 2014](#)). A meta-analysis found that prenatal benzodiazepine exposure does confer an increased risk of oral clefts, although the absolute risk increased by only 0.01%



([Altshuler et al. 1996](#)). This conclusion is consistent with the findings of a later case-control study that found no difference in rates of prenatal benzodiazepine exposure between more than 38,000 infants with congenital anomalies and nearly 23,000 control children ([Eros et al. 2002](#)).

Although benzodiazepine teratogenicity data are somewhat mixed, benzodiazepine neonatal syndromes are well documented. Numerous groups have described a floppy infant syndrome characterized by hypothermia, lethargy, poor respiratory effort, and feeding difficulties following benzodiazepine exposure in late pregnancy ([Erkkola et al. 1983](#); [Fisher et al. 1985](#); [Haram 1977](#); [Källén and Reis 2012](#); [Kriel and Cloyd 1982](#); [McAuley et al. 1982](#); [Sanchis et al. 1991](#); [Speight 1977](#); [Woods and Malan 1978](#)). In a study of 53 infants with late-pregnancy lorazepam exposure, term infants whose mothers had taken oral lorazepam showed no evidence of toxicity other than a brief delay in establishing feeding, whereas preterm infants and term infants whose mothers had received larger intravenous doses of lorazepam had symptoms consistent with floppy infant syndrome ([Whitelaw et al. 1981](#)). Neonatal withdrawal syndromes, characterized by restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, and vomiting, have been described in infants whose mothers were taking alprazolam ([Barry and St Clair 1987](#)), chlordiazepoxide ([Athinarayanan et al. 1976](#); [Bitnun 1969](#); [Stirrat et al. 1974](#)), or diazepam ([Backes and Cordero 1980](#); [Mazzi 1977](#)). Benzodiazepine neonatal syndromes have been reported to persist for as long as 3 months after delivery (for a review, see [Miller 1991](#)).

Pharmacokinetic studies during pregnancy indicate that benzodiazepines readily traverse the placenta and with prolonged administration may accumulate in the fetus ([Mandelli et al. 1975](#); [Shannon et al. 1972](#)). For example, fetal concentrations of diazepam at delivery are typically higher than maternal concentrations ([Erkkola et al. 1974](#)). Because benzodiazepine metabolism is slower in the fetus than in the mother, it is understandable that an agent like diazepam (which has multiple active metabolites) might accumulate in the fetus. In addition, high concentrations of diazepam are sequestered in lipophilic fetal tissues, such as the brain, lungs, and heart ([Mandelli et al. 1975](#)). In contrast, fetal-to-maternal ratios of lorazepam (which has no active metabolites) are typically less than 1.0 ([Whitelaw et al. 1981](#)). Yet neonatal clearance of lorazepam is slow, with detectable levels evident 8 days after delivery ([Whitelaw et al. 1981](#)), and the clearance of chlordiazepoxide appears to be even slower ([Athinarayanan et al. 1976](#)).

Studies evaluating the neurobehavioral effects of prenatal benzodiazepine exposure are needed. A benzodiazepine exposure syndrome—consisting of growth retardation, dysmorphism, and mental and psychomotor retardation in infants ([Laegreid et al. 1987](#))—has been reported, although some investigators have disputed this finding ([Gerhardsson and Alfredsson 1987](#); [Winter 1987](#)). One group found no differences in the incidence of behavioral abnormalities at age 8 months or in IQ scores at age 4 years among children exposed to chlordiazepoxide during gestation ([Hartz et al. 1975](#)), and another group found no correlation between antenatal exposure and language competence at age 3 years ([Odsbu et al. 2015](#)). Nevertheless, a series of laboratory animal studies raised concerns that prenatal

benzodiazepine exposure may produce deficits in memory and learning ability ([Frieder et al. 1984](#); [Hassmannova and Myslivecek 1994](#); [Jaiswal and Bhattacharya 1993](#); [Myslivecek et al. 1991](#)).

[Buist et al. \(1990\)](#) concluded that benzodiazepines at low dosages present no contraindication to nursing. A recent retrospective cohort study found a sedation rate of 1.6% in infants exposed to benzodiazepines while breast feeding, but there was no association with maternal dosage ([Kelly et al. 2012](#)). Infants with impaired metabolic capacity may show sedation and poor feeding even with low maternal dosages ([Wesson et al. 1985](#)). Overall, benzodiazepines are associated with lower milk-to-plasma ratios than are other classes of psychotropics. For example, [Wretlind \(1987\)](#) found a milk-to-plasma ratio of 0.1–0.3 for oxazepam and calculated that the infant daily dosage via lactation is 1/1,000th of the maternal dosage. The percentage of the maternal dosage of lorazepam to which a nursing infant is exposed has been estimated to be 2.2% ([Summerfield and Nielsen 1985](#)).

In summary, benzodiazepines do not appear to carry a significant risk of somatic teratogenesis, but neurobehavioral sequelae remain obscure. Because benzodiazepines are associated with neonatal risks, they should be used judiciously and tapered before delivery if possible. Benzodiazepines should not be abruptly withdrawn during pregnancy. Because lorazepam and oxazepam are less dependent on hepatic metabolism, they theoretically have less potential for fetal accumulation during pregnancy. Finally, benzodiazepines can be safely administered, in judicious doses, during lactation. However, breast feeding should be discontinued if an infant

experiences sedation or other signs of benzodiazepine toxicity.

## Buspirone

Buspirone has garnered a unique, and arguably illogical, position within the psychotropic armamentarium. Although buspirone is labeled FDA Category B, published data are extremely limited. The only report of prenatal administration of buspirone identified 1 infant born with a major malformation among 14 infants with first-trimester buspirone exposure ([Wilton et al. 1998](#)). No published reports exist regarding buspirone's safety during lactation.

---

## Future Directions and General Recommendations

---

The development of prenatal and postnatal treatment guidelines is hampered by the haphazard accrual of clinical research data with inconsistent methodologies. Whereas clinical data have confirmed the teratogenic potential for only a few psychotropic agents, animal studies, which commonly use maternal concentrations exponentially higher than those seen in clinical care, show clear somatic and neurobehavioral teratogenicity ([Elia et al. 1987](#)). Such inconsistencies between clinical and preclinical data further confound efforts to construct reliable treatment recommendations. Similarly, advances in statistical methods and the accrual of data from a variety of sources have identified statistical findings that may have limited

relevance to clinical decision making ([Ranganathan et al. 2015](#)). Because pregnant and nursing women are generally excluded from clinical trials of pharmacological agents, definitive clarification with proper control groups is unlikely to be forthcoming in the near future. Consequently, clinical treatment decisions are made on the basis of incomplete or uncertain information.

## Informed Consent

Obtaining informed consent in the clinical decision cannot be overemphasized. Informed consent should include the following:

- Agreement on the primary treatment objective, which typically is to minimize potential harm to the fetus (Acceptance of and adherence to this objective will help reduce the potential for subsequent maternal self-recrimination.)
- Discussion of the availability, affordability, accessibility, and potential efficacy of nonpharmacological treatments
- Consideration of the likelihood and severity of illness without continued pharmacotherapy
- Review of the potential risks of untreated mental illness to the fetus and mother
- Review of the potential risks of fetal psychotropic exposure
- Acknowledgment that no risk-free alternative is available other than deciding not to conceive
- Acknowledgment that the understanding of risks remains incomplete (Ultimately, it is impossible to provide an exhaustive list of all risks for any given psychotropic

agent, but the evidence—or lack of evidence—for adverse effects should be reviewed.)

## Nonpsychotropic Treatment Strategies to Reduce In Utero Exposures

Nonpsychotropic treatments should focus on maximizing maternal health during pregnancy, such as prenatal vitamins; adequate hydration; daily exercise; and avoidance of alcohol, tobacco, caffeine, and illicit substances. Good evidence indicates that concomitant exposures, such as to tobacco, increase both obstetrical and neonatal risk. Nonpsychotropic treatment strategies also include psychotherapy alternatives appropriate during pregnancy and the postpartum period.

## Medication Selection

Medication selection requires several steps. Initial treatment planning for reproductive-age women with mental illness should include the potential pregnancy and future family planning. Notably, more than 45% of the pregnancies in the United States are unplanned, and knowledge of conception is often well into the organogenesis ([Finer and Zolna 2016](#); [Kost 2015](#)). Choosing initial pharmacotherapy with this in mind supports “new and improved=limited data.”

Psychotropic therapy is administered after knowledge of conception only when the clinician and patient agree that the risks to the fetus of untreated mental illness likely

exceed the risks of fetal psychotropic exposure. Consequently, both the safety and the efficacy of the psychotropic regimen are important considerations. A psychotropic agent is preferred if 1) it has previously been effective for the patient; 2) it has previously been well tolerated by the patient; 3) the fetus has already been exposed to it (i.e., the patient was taking the agent at knowledge of conception); and 4) it has a favorable reproductive safety profile. It is important to emphasize the potential hazards of switching agents during pregnancy or lactation. Changing medications generally should be avoided (unless well-defined risks are associated with the current regimen), because medication changes increase the number of medications to which the infant has been exposed, limit the clinician's ability to apply available safety information (e.g., virtually no data exist on concomitant or tandem multiple medication exposures), and may heighten the mother's vulnerability to illness.

## Dosage Management

Maintaining maternal emotional well-being is the goal of psychotropic treatment in the antepartum and postpartum periods. Partial or subtherapeutic treatment heightens risk by continuing to expose the mother and infant to both illness and medications. The minimum effective dosage should be maintained throughout treatment, and the clinician should remain mindful that dosage requirements may change during pregnancy. Similarly, clinicians and patients should be aware that dosage adjustment may not significantly alter fetal exposure during pregnancy (i.e., the fetus is exposed to the maternal plasma concentration, not

the maternal dosage). To minimize the potential for neonatal withdrawal and maternal toxicity after delivery, careful monitoring of side effects and serum concentrations may be indicated.

## Monitoring of Nursing Infants

Because clinical laboratory assays typically lack the sensitivity to detect the serum concentrations of nursing infants, infant plasma monitoring for psychotropic medications is not routinely indicated. If there is an index of suspicion that a child is experiencing an adverse effect from nursing exposure to a psychotropic medication, breast feeding should be discontinued. However, routine laboratory monitoring (e.g., blood counts, electrolytes, hepatic profiles) is required when nursing mothers are taking medications (e.g., lithium, valproate, carbamazepine) with low therapeutic indices or known systemic toxicities.

---

## Resources

---

For clinicians involved in the care of numerous women in their reproductive years, a valuable resource that includes an interactive e-book is *Drugs in Pregnancy and Lactation* by G.G. Briggs and R.K. Freeman.

Additional online resources include the following:

Centers for Disease Control and Prevention—

[www.cdc.gov/pregnancy/meds/treatingfortwo](http://www.cdc.gov/pregnancy/meds/treatingfortwo)

InfantRisk Center—[www.infantrisk.com](http://www.infantrisk.com)

LactMed—

<https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>



Organization of Teratology Information Specialists:  
MotherToBaby—[www.mothertobaby.org](http://www.mothertobaby.org)  
Reprotox—[www.reprotox.com](http://www.reprotox.com)

---

## References

---

- Aarskog D: Letter: Association between maternal intake of diazepam and oral clefts. *Lancet* 2(7941):921, 1975 53396
- Adab N, Jacoby A, Smith D, et al: Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 70(1):15-21, 2001 11118242
- Agatonovic-Kustrin S, Ling LH, Tham SY, et al: Molecular descriptors that influence the amount of drugs transfer into human breast milk. *J Pharm Biomed Anal* 29(1-2):103-119, 2002 12062670
- Aichhorn W, Whitworth AB, Weiss U, et al: Mirtazapine and breast-feeding. *Am J Psychiatry* 161(12):2325, 2004 15569912
- Alexander FW: Sodium valproate and pregnancy. *Arch Dis Child* 54(3):240, 1979 373647
- Allen S: A quantitative analysis of the process, mediating variables, and impact of traumatic childbirth. *Journal of Reproductive and Infant Psychology* 16:107-131, 1998
- Altshuler LL, Burt VK, McMullen M, et al: Breastfeeding and sertraline: a 24-hour analysis. *J Clin Psychiatry* 56(6):243-245, 1995 7775366
- Altshuler LL, Cohen L, Szuba MP, et al: Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 153(5):592-606, 1996 8615404
- Alwan S, Reefhuis J, Rasmussen SA, et al; National Birth Defects Prevention Study: Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth

- defects. *N Engl J Med* 356(26):2684-2692, 2007 17596602
- Ambresin G, Berney P, Schulz P, et al: Olanzapine excretion into breast milk: a case report. *J Clin Psychopharmacol* 24(1):93-95, 2004 14709955
- American Academy of Pediatrics Committee on Drugs: Transfer of drugs and other chemicals into human milk. *Pediatrics* 108(3):776-789, 2001 11533352
- Andrade SE, McPhillips H, Loren D, et al: Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf* 18(3):246-252, 2009 19148882
- Ardinger HH, Atkin JF, Blackston RD, et al: Verification of the fetal valproate syndrome phenotype. *Am J Med Genet* 29(1): 171-185, 1988 3125743
- Assencio-Ferreira VJ, Abraham R, Veiga JC, et al: [Metopic suture craniosynostosis: sodium valproate teratogenic effect: case report] (Portuguese). *Arq Neuropsiquiatr* 59(2-B):417-420, 2001 11460190
- Athinarayanan P, Pierog SH, Nigam SK, et al: Chlordiazepoxide withdrawal in the neonate. *Am J Obstet Gynecol* 124(2):212-213, 1976 1247060
- Audus KL: Controlling drug delivery across the placenta. *Eur J Pharm Sci* 8(3):161-165, 1999 10379038
- Ayad M, Costantine MM: Epidemiology of medications use in pregnancy. *Semin Perinatol* 39(7):508-511, 2015 26358804
- Aydin B, Nayir T, Sahin S, et al: Olanzapine and quetiapine use during breastfeeding: excretion into breast milk and safe breastfeeding strategy. *J Clin Psychopharmacol* 35(2):206-208, 2015 25679127
- Backes CR, Cordero L: Withdrawal symptoms in the neonate from presumptive intrauterine exposure to diazepam: report of case. *J Am Osteopath Assoc* 79(9):584-585, 1980 7380678

- Baker GA, Bromley RL, Briggs M, et al; Liverpool and Manchester Neurodevelopment Group: IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. *Neurology* 84(4):382-390, 2015 25540307
- Ban L, West J, Gibson JE, et al: First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. *PLoS One* 9(6): e100996, 2014 24963627
- Bardy AH, Granström ML, Hiilesmaa VK: Valproic acid and breast feeding, in *Epilepsy, Pregnancy, and the Child*. Edited by Janz D, Dam M, Richens A. New York, Raven, 1982a, pp 359-360
- Bardy AH, Teramo K, Hiilesmaa VK: Apparent plasma clearances of phenytoin, phenobarbitone, primidone, and carbamazepine during pregnancy: results of the prospective Helsinki study, in *Epilepsy, Pregnancy, and the Child*. Edited by Janz D, Dam M, Richens A, et al. New York, Raven, 1982b, pp 141-145
- Barnas C, Bergant A, Hummer M, et al: Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk (abstract). *Am J Psychiatry* 151(6):945, 1994 8185013
- Barry WS, St Clair SM: Exposure to benzodiazepines in utero. *Lancet* 1(8547):1436-1437, 1987 2884529
- Barson AJ: Malformed infant (letter). *BMJ* 2(5804):45, 1972 5015974
- Battino D, Avanzini G, Bossi L, et al: Monitoring of antiepileptic drug plasma levels during pregnancy and puerperium, in *Epilepsy, Pregnancy, and the Child*. Edited by Janz D, Dam M, Richens A, et al. New York, Raven, 1982, pp 147-154
- Bellantuono C, Marini A, Lucarelli C: Infant health and neurodevelopmental outcomes following prenatal

- exposure to duloxetine. Clin Drug Investig 33(9):685-688, 2013 23873363
- Bellet F, Beyens MN, Bernard N, et al: Exposure to aripiprazole during embryogenesis: a prospective multicenter cohort study. Pharmacoepidemiol Drug Saf 24(4):368-380, 2015 25683615
- Bennedsen BE, Mortensen PB, Olesen AV, et al: Obstetric complications in women with schizophrenia. Schizophr Res 47(2-3):167-175, 2001 11278134
- Bérard A, Ramos E, Rey E, et al: First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol 80(1):18-27, 2007 17187388
- Bergman U, Rosa FW, Baum C, et al: Effects of exposure to benzodiazepine during fetal life. Lancet 340(8821):694-696, 1992 1355799
- Bertossi M, Virgintino D, Errede M, et al: Immunohistochemical and ultrastructural characterization of cortical plate microvasculature in the human fetus telencephalon. Microvasc Res 58(1):49-61, 1999 10388603
- Bescoby-Chambers N, Forster P, Bates G: Foetal valproate syndrome and autism: additional evidence of an association. Dev Med Child Neurol 43(12):847, 2001 11769274
- Birnbaum CS, Cohen LS, Bailey JW, et al: Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. Pediatrics 104(1):e11, 1999 10390297
- Bitnun S: Possible effect of chlordiazepoxide on the fetus. Can Med Assoc J 100(7):351, 1969 PMC1945650
- Bjerkedal T, Czeizel A, Goujard J, et al: Valproic acid and spina bifida. Lancet 2(8307):1096, 1982 6127554
- Black MM, Matula K: Essentials of Bayley Scales of Infant Development, II: Assessment. New York, Wiley, 2000

- Bogen DL, Sit D, Genovese A, et al: Three cases of lithium exposure and exclusive breastfeeding. *Arch Women Ment Health* 15(1):69-72, 2012 22277970
- Bologa M, Tang B, Klein J, et al: Pregnancy-induced changes in drug metabolism in epileptic women. *J Pharmacol Exp Ther* 257(2):735-740, 1991 2033516
- Boobis AR, Lewis PJ: Pharmacokinetics in pregnancy, in *Clinical Pharmacology in Obstetrics*. Edited by Lewis P. Boston, MA, Wright-PSG, 1983, pp 6-54
- Boshier A, Wilton LV, Shakir SA: Evaluation of the safety of bupropion (Zyban) for smoking cessation from experience gained in general practice use in England in 2000. *Eur J Clin Pharmacol* 59(10):767-773, 2003 14615857
- Boukhris T, Sheehy O, Mottron L, et al: Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. *JAMA Pediatr* 170(2):117-124, 2016 26660917
- Boyce PM, Hackett LP, Ilett KF: Duloxetine transfer across the placenta during pregnancy and into milk during lactation. *Arch Women Ment Health* 14(2):169-172, 2011 21359876
- Brent NB, Wisner KL: Fluoxetine and carbamazepine concentrations in a nursing mother/infant pair. *Clin Pediatr (Phila)* 37(1):41-44, 1998 9475699
- Briggs GG, Samson JH, Ambrose PJ, et al: Excretion of bupropion in breast milk. *Ann Pharmacother* 27(4):431-433, 1993 8477117
- Briggs GG, Freeman RK, Yaffe SJ: *Drugs in Pregnancy and Lactation*, 7th Edition. Philadelphia, PA, Lippincott Williams & Wilkins, 2005
- Brockington IF, Winokur G, Dean C: Puerperal psychosis, in *Motherhood and Mental Illness*. Edited by Brockington IF, Kumar R. London, Academic Press, 1982, pp 37-69
- Brunner E, Falk DM, Jones M, et al: Olanzapine in pregnancy and breastfeeding: a review of data from

- global safety surveillance. *BMC Pharmacol Toxicol* 14:38, 2013 23902726
- Buesching DP, Glasser ML, Frate DA: Progression of depression in the prenatal and postpartum periods. *Women Health* 11(2):61-78, 1986 3751082
- Buist A, Norman TR, Dennerstein L: Breastfeeding and the use of psychotropic medication: a review. *J Affect Disord* 19(3): 197-206, 1990 2145340
- Burch KJ, Wells BG: Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics* 89(4 pt 1):676-677, 1992 1557252
- Campbell E, Kennedy F, Russell A, et al: Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry* 85(9):1029-1034, 2014 24444855
- Canger R, Battino D, Canevini MP, et al: Malformations in offspring of women with epilepsy: a prospective study. *Epilepsia* 40(9):1231-1236, 1999 10487185
- Capello CF, Bourke CH, Ritchie JC, et al: Serotonin transporter occupancy in rats exposed to serotonin reuptake inhibitors in utero or via breast milk. *J Pharmacol Exp Ther* 339(1):275-285, 2011 21775476
- Casper RC, Fleisher BE, Lee-Ancas JC, et al: Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 142(4):402-408, 2003 12712058
- Castro VM, Kong SW, Clements CC, et al: Absence of evidence for increase in risk for autism or attention-deficit hyperactivity disorder following antidepressant exposure during pregnancy: a replication study. *Transl Psychiatry* 6:e708, 2016 26731445
- Centers for Disease Control (CDC): Spina bifida incidence at birth—United States, 1983-1990. *MMWR Morb Mortal Wkly Rep* 41(27):497-500, 1992 1614388

- Chambers CD, Johnson KA, Dick LM, et al: Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 335(14): 1010-1015, 1996 8793924
- Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al: Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 354(6):579-587, 2006 16467545
- Christensen J, Grønberg TK, Sørensen MJ, et al: Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 309(16):1696-1703, 2013 23613074
- Chun-Fai-Chan B, Koren G, Fayeze I, et al: Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol* 192(3):932-936, 2005 15746694
- Clark CT, Klein AM, Perel JM, et al: Lamotrigine dosing for pregnant patients with bipolar disorder. *Am J Psychiatry* 170(11): 1240-1247, 2013 24185239
- Cleary MF: Fluphenazine decanoate during pregnancy. *Am J Psychiatry* 134(7):815-816, 1977 869065
- Clements CC, Castro VM, Blumenthal SR, et al: Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. *Mol Psychiatry* 20(6):727-734, 2015 25155880
- Cohen LS, Friedman JM, Jefferson JW, et al: A reevaluation of risk of in utero exposure to lithium. *JAMA* 271(2):146-150, 1994 8031346
- Cohen LS, Altshuler LL, Harlow BL, et al: Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA* 295(5):499-507, 2006 16449615
- Cohen LS, Viguera AC, McInerney KA, et al: Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital National

- Pregnancy Registry for Atypical Antipsychotics. *Am J Psychiatry* 173(3):263-270, 2015 26441156
- Cohen MJ, Meador KJ, Browning N, et al; NEAD study group: Fetal antiepileptic drug exposure: adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy Behav* 29(2):308-315, 2013 24012508
- Cole JA, Ephross SA, Cosmatos IS, et al: Paroxetine in the first trimester and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 16(10):1075-1085, 2007 17729379
- Coppola D, Russo LJ, Kwartar RF Jr, et al: Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. *Drug Saf* 30(3):247-264, 2007 17343431
- Costei AM, Kozer E, Ho T, et al: Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 156(11):1129-1132, 2002 12413342
- Croen LA, Grether JK, Yoshida CK, et al: Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry* 68(11):1104-1112, 2011 21727247
- Croke S, Buist A, Hackett LP, et al: Olanzapine excretion in human breast milk: estimation of infant exposure. *Int J Neuropsychopharmacol* 5(3):243-247, 2002 12366877
- Cunnington MC, Weil JG, Messenheimer JA, et al: Final results from 18 years of the International Lamotrigine Pregnancy Registry. *Neurology* 76(21):1817-1823, 2011 21606453
- Cutrona CE: Causal attributions and perinatal depression. *J Abnorm Psychol* 92(2):161-172, 1983 6863731
- Dalens B, Raynaud EJ, Gaulme J: Teratogenicity of valproic acid. *J Pediatr* 97(2):332-333, 1980 6772753
- Dallemagne G, Weiss B: Altered adult behavior of mice following postnatal treatment with haloperidol. *Pharmacol Biochem Behav* 16(5):761-767, 1982 7089034



- Dam M, Christiansen J, Munck O, et al: Antiepileptic drugs: metabolism in pregnancy. *Clin Pharmacokinet* 4(1):53-62, 1979 421411
- Dean JC, Moore SJ, Osborne A, et al: Fetal anticonvulsant syndrome and mutation in the maternal MTHFR gene. *Clin Genet* 56(3):216-220, 1999 10563481
- de Haan GJ, Edelbroek P, Segers J, et al: Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 63(3):571-573, 2004 15304599
- Dev V, Krupp P: Adverse event profile and safety of clozapine. *Reviews in Contemporary Pharmacotherapy* 6(4):197-208, 1995
- Diav-Citrin O, Shechtman S, Tahover E, et al: Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. *Am J Psychiatry* 171(7):785-794, 2014 24781368
- DiLiberti JH, Farndon PA, Dennis NR, et al: The fetal valproate syndrome. *Am J Med Genet* 19(3):473-481, 1984 6439041
- Di Michele V, Ramenghi L, Sabatino G: Clozapine and lorazepam administration in pregnancy. *Eur Psychiatry* 11(4):214, 1996 19698455
- Dickinson RG, Harland RC, Lynn RK, et al: Transmission of valproic acid (Depakene) across the placenta: half-life of the drug in mother and baby. *J Pediatr* 94(5):832-835, 1979 376803
- Dickson RA, Hogg L: Pregnancy of a patient treated with clozapine. *Psychiatr Serv* 49(8):1081-1083, 1998 9712217
- Djulus J, Koren G, Einarson TR, et al: Exposure to mirtazapine during pregnancy: a prospective, comparative study of birth outcomes. *J Clin Psychiatry* 67(8):1280-1284, 2006 16965209
- Dodd S, Stocky A, Buist A, et al: Sertraline in paired blood plasma and breast-milk samples from nursing mothers.

- Hum Psychopharmacol 15(4):161-264, 2000 12404316
- Dolk H, Jentink J, Loane M, et al; EUROCAT Antiepileptic Drug Working Group: Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology 71(10):714-722, 2008 18650491
- Dominguez-Salgado M, Morales A, Santiago Gomez R, et al: Gestational lamotrigine monotherapy: congenital malformations and psychomotor development (abstract). Epilepsia 45 (suppl 7):229-230, 2004
- Downey G, Coyne JC: Children of depressed parents: an integrative review. Psychol Bull 108(1):50-76, 1990 2200073
- Duffy CL: Postpartum depression: identifying women at risk. Genesis 11:21, 1983
- Dursun A, Karadağ N, Karagöl B, et al: Carbamazepine use in pregnancy and coincidental thalidomide-like phocomelia in a newborn. J Obstet Gynaecol 32(5):488-489, 2012 22663328
- Ebbesen F, Joergensen A, Hoseth E, et al: Neonatal hypoglycaemia and withdrawal symptoms after exposure in utero to valproate. Arch Dis Child Fetal Neonatal Ed 83(2):F124-F129, 2000 10952707
- Edlund MJ, Craig TJ: Antipsychotic drug use and birth defects: an epidemiologic reassessment. Compr Psychiatry 25(1):32-37, 1984 6141893
- Eggermont E: Withdrawal symptoms in neonates associated with maternal imipramine therapy. Lancet 2(7830):680, 1973 4125653
- Einarson A, Fatoye B, Sarkar M, et al: Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. Am J Psychiatry 158(10):1728-1730, 2001 11579012
- Einarson A, Bonari L, Voyer-Lavigne S, et al: A multicentre prospective controlled study to determine the safety of

- trazodone and nefazodone use during pregnancy. *Can J Psychiatry* 48(2):106-110, 2003 12655908
- Einarson A, Smart K, Vial T, et al: Rates of major malformations in infants following exposure to duloxetine during pregnancy: a preliminary report. *J Clin Psychiatry* 73(11):1471, 2012 23218163
- Einarson TR, Einarson A: Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. *Pharmacoepidemiol Drug Saf* 14(12):823-827, 2005 15742359
- Elia J, Katz IR, Simpson GM: Teratogenicity of psychotherapeutic medications. *Psychopharmacol Bull* 23(4):531-586, 1987 2893424
- El Marroun H, White TJH, van der Knaap NJF, et al: Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children. *Br J Psychiatry* 205(2):95-102, 2014 25252317
- Engelhard IM, van den Hout MA, Arntz A: Posttraumatic stress disorder after pregnancy loss. *Gen Hosp Psychiatry* 23(2): 62-66, 2001 11313072
- Ennis ZN, Damkier P: Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations: a systematic review. *Basic Clin Pharmacol Toxicol* 116(4):315-320, 2015 25536446
- Entman SS, Vaughn WK: Lack of relation of oral clefts to diazepam use in pregnancy. *N Engl J Med* 310(17):1121-1122, 1984 6708998
- Epperson CN, Anderson GM, McDougale CJ: Sertraline and breast-feeding. *N Engl J Med* 336(16):1189-1190, 1997 9102576
- Epperson N, Czarkowski KA, Ward-O'Brien D, et al: Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. *Am J Psychiatry* 158(10):1631-1637, 2001 11578995

- Erkkola R, Kanto J, Sellman R: Diazepam in early human pregnancy. *Acta Obstet Gynecol Scand* 53(2):135-138, 1974 4822345
- Erkkola R, Kero P, Kanto J, et al: Severe abuse of psychotropic drugs during pregnancy with good perinatal outcome. *Ann Clin Res* 15(2):88-91, 1983 6881907
- Eros E, Czeizel AE, Rockenbauer M, et al: A population-based case-control teratologic study of nitrazepam, medazepam, tofisopam, alprazolam and clonazepam treatment during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 101(2):147-154, 2002 11858890
- Falterman CG, Richardson CJ: Small left colon syndrome associated with maternal ingestion of psychotropic drugs. *J Pediatr* 97(2):308-310, 1980 7400907
- Finer LB, Zolna MR: Declines in unintended pregnancy in the United States, 2008-2011. *N Engl J Med* 374(9):843-852, 2016 26962904
- Fisher JB, Edgren BE, Mammel MC, et al: Neonatal apnea associated with maternal clonazepam therapy: a case report. *Obstet Gynecol* 66 (3 suppl):34S-35S, 1985 4022513
- Fones C: Posttraumatic stress disorder occurring after painful childbirth. *J Nerv Ment Dis* 184(3):195-196, 1996 8600227
- Fotopoulou C, Kretz R, Bauer S, et al: Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. *Epilepsy Res* 85(1):60-64, 2009 19272754
- Franco V, Mazzucchelli I, Gatti G, et al: Changes in lamotrigine pharmacokinetics during pregnancy and the puerperium. *Ther Drug Monit* 30(4):544-547, 2008 18641557
- Frederiksen MC: Physiologic changes in pregnancy and their effect on drug disposition. *Semin Perinatol*

25(3):120-123, 2001 11453606

Freeman MP, Nolan PE Jr, Davis MF, et al: Pharmacokinetics of sertraline across pregnancy and postpartum. *J Clin Psychopharmacol* 28(6):646-653, 2008 19011433

Frey B, Schubiger G, Musy JP: Transient cholestatic hepatitis in a neonate associated with carbamazepine exposure during pregnancy and breast-feeding. *Eur J Pediatr* 150(2):136-138, 1990 2279511

Frey B, Braegger CP, Ghelfi D: Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 36(4):644-647, 2002 11918515

Frieder B, Epstein S, Grimm VE: The effects of exposure to diazepam during various stages of gestation or during lactation on the development and behavior of rat pups. *Psychopharmacology (Berl)* 83(1): 51-55, 1984 6429700

Friedman JM, Polifka JE: *Teratogenic Effects of Drugs: A Resource for Clinicians (TERIS)*, 2nd Edition. Baltimore, MD, Johns Hopkins University Press, 2000, pp ix-x

Friedman SH, Rosenthal MB: Treatment of perinatal delusional disorder: a case report. *Int J Psychiatry Med* 33(4):391-394, 2003 15152788

Fries H: Lithium in pregnancy. *Lancet* 1(7658):1233, 1970 4192416

Froescher W, Eichelbaum M, Nieson M, et al: Antiepileptic therapy with carbamazepine and valproic acid during pregnancy and the lactation period, in *Advances in Epileptology: The 12th Epilepsy International Symposium*. Edited by Dam M, Gram L, Penry JK. New York, Raven, 1981, pp 581-588

Froescher W, Eichelbaum M, Niesen M, et al: Carbamazepine levels in breast milk. *Ther Drug Monit* 6(3):266-271, 1984a 6390794

Froescher W, Gugler R, Niesen M, Hoffmann F: Protein binding of valproic acid in maternal and umbilical cord serum. *Epilepsia* 25(2):244-249, 1984b 6423379

- Gaily E, Kantola-Sorsa E, Granström ML: Specific cognitive dysfunction in children with epileptic mothers. *Dev Med Child Neurol* 32(5):403-414, 1990 2113015
- Galler JR, Harrison RH, Ramsey F, et al: Maternal depressive symptoms affect infant cognitive development in Barbados. *J Child Psychol Psychiatry* 41(6):747-757, 2000 11039687
- Gardiner SJ, Kristensen JH, Begg EJ, et al: Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. *Am J Psychiatry* 160(8):1428-1431, 2003 12900304
- Gentile S, Tofani S, Bellantuono C: Aripiprazole and pregnancy: a case report and literature review. *J Clin Psychopharmacol* 31(4):531-532, 2011 21720228
- Gerhardsson M, Alfredsson L: In-utero exposure to benzodiazepines. *Lancet* 1(8533): 628, 1987 2881162
- Gidaya NB, Lee BK, Burstyn I, et al: In utero exposure to selective serotonin reuptake inhibitors and risk for autism spectrum disorder. *J Autism Dev Disord* 44(10): 2558-2567, 2014 24803368
- Gilad O, Merlob P, Stahl B, Klinger G: Outcome of infants exposed to olanzapine during breastfeeding. *Breastfeed Med* 6(2):55-58, 2011 21034242
- GlaxoSmithKline: Epidemiology study: Updated preliminary report on bupropion and other antidepressants, including paroxetine in pregnancy and the occurrence of cardiovascular and major congenital malformations (study EPIP083). 2005. Available at: <http://www.gsk-clinicalstudyregister.com/files2/3493.pdf>. Accessed June 7, 2016.
- GlaxoSmithKline: International Pregnancy Registry: Interim Report (1 September 1992 through 31 March 2007). Wilmington, NC, Inveresk, 2007
- Glaze R, Chapman G, Murray D: Recurrence of puerperal psychosis during late pregnancy. *Br J Psychiatry* 159:567-569, 1991 1751870

- Goldberg HL, DiMascio A: Psychotropic drugs in pregnancy, in *Psychopharmacology: A Generation of Progress*. Edited by Lipton HL, DiMascio A, Killam KF. New York, Raven, 1978, pp 1047-1055
- Goldstein DJ, Sundell KL, Corbin LA: Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 336(12):872-873, author reply 873, 1997 9072683
- Goldstein DJ, Corbin LA, Fung MC: Olanzapine-exposed pregnancies and lactation: early experience. *J Clin Psychopharmacol* 20(4):399-403, 2000 10917399
- Grigoriadis S, VonderPorten EH, Mamisashvili L, et al: Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. *J Clin Psychiatry* 74(4): e293-e308, 2013 23656855
- Grover S, Madan R: Successful use of quetiapine in two successive pregnancies. *J Neuropsychiatry Clin Neurosci* 24(1):E38, 2012 22450643
- Guglielmi V, Vulink NC, Denys D, et al: Obsessive-compulsive disorder and female reproductive cycle events: results from the OCD and reproduction collaborative study. *Depress Anxiety* 31(12):979-987, 2014 24421066
- Haram K: "Floppy infant syndrome" and maternal diazepam. *Lancet* 2(8038):612-613, 1977 71430
- Harrington RA, Lee LC, Crum RM, et al: Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics* 133(5):e1241-e1248, 2014 24733881
- Hartz SC, Heinonen OP, Shapiro S, et al: Antenatal exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. *N Engl J Med* 292(14): 726-728, 1975 1113782

- Hassmannova J, Myslivecek J: Inhibitory and excitatory adult learning after prenatal diazepam application. *Studia Psychologica (Bratislava)* 36(5):323-326, 1994
- Hedegaard M, Henriksen TB, Sabroe S, et al: The relationship between psychological distress during pregnancy and birth weight for gestational age. *Acta Obstet Gynecol Scand* 75(1):32-39, 1996 8560994
- Heikkinen T, Ekblad U, Kero P, et al: Citalopram in pregnancy and lactation. *Clin Pharmacol Ther* 72(2):184-191, 2002 12189365
- Hendrick V, Fukuchi A, Altshuler L, et al: Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br J Psychiatry* 179:163-166, 2001a 11483479
- Hendrick V, Stowe ZN, Altshuler LL, et al: Fluoxetine in nursing infants and breast milk. *Biol Psychiatry* 50:775-782, 2001b 11720696
- Hendrick V, Stowe ZN, Altshuler LL, et al: Placental passage of antidepressant medications. *Am J Psychiatry* 160(5):993-996, 2003 12727706
- Hernández-Díaz S, Werler MM, Walker AM, et al: Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 153(10):961-968, 2001 11384952
- Hertzberg T, Wahlbeck K: The impact of pregnancy and puerperium on panic disorder: a review. *J Psychosom Obstet Gynaecol* 20(2):59-64, 1999 10422037
- Hill RC, McIvor RJ, Wojnar-Horton RE, et al: Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. *J Clin Psychopharmacol* 20(2): 285-286, 2000 10770482
- Hill RM, Stern L: Drugs in pregnancy: effects on the fetus and newborn. *Drugs* 17(3):182-197, 1979 88321
- Hill RM, Desmond MM, Kay JL: Extrapyrarnidal dysfunction in an infant of a schizophrenic mother. *J Pediatr* 69(4):589-595, 1966 5921334



- Hirsch MS, Swartz MN: Drug therapy: antiviral agents (first of two parts). *N Engl J Med* 302(16):903-907, 1980 6987519
- Hoffeld DR, McNew J, Webster RL: Effect of tranquilizing drugs during pregnancy on activity of offspring. *Nature* 218(5139): 357-358, 1968 5649675
- Holmes LB, Wyszynski DF, Baldwin EJ, et al: Increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy (abstract). *Birth Defects Res A Clin Mol Teratol* 76(5):318, 2006
- Hostetter A, Stowe ZN, Strader JR Jr, et al: Dose of selective serotonin uptake inhibitors across pregnancy: clinical implications. *Depress Anxiety* 11(2):51-57, 2000 10812529
- House SJ, Tripathi SP, Knight BT, et al: Obsessive-compulsive disorder in pregnancy and the postpartum period: course of illness and obstetrical outcome. *Arch Women Ment Health* 19(1):3-10, 2016 26173597
- Huang H, Coleman S, Bridge JA, et al: A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. *Gen Hosp Psychiatry* 36(1):13-18, 2014 24094568
- Huybrechts KF, Palmsten K, Avorn J, et al: Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med* 370(25):2397-2407, 2014a 24941178
- Huybrechts KF, Sanghani RS, Avorn J, Urato AC: Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. *PLoS One* 9(3):e92778, 2014b 24671232
- Huybrechts KF, Bateman BT, Palmsten K, et al: Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA* 313(21):2142-2151, 2015 26034955
- Hviid A, Melbye M, Pasternak B: Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism.

- N Engl J Med 369(25):2406-2415, 2013 24350950
- Ilett KF, Hackett LP, Dusci LJ, et al: Distribution and excretion of venlafaxine and O-desmethylenlafaxine in human milk. Br J Clin Pharmacol 45(5):459-462, 1998 9643618
- Ilett KF, Hackett LP, Kristensen JH, et al: Transfer of risperidone and 9-hydroxyrisperidone into human milk. Ann Pharmacother 38(2):273-276, 2004 14742766
- Jacobson SJ, Jones K, Johnson K, et al: Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 339(8792):530-533, 1992 1346886
- Jäger-Roman E, Deichl A, Jakob S, et al: Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. J Pediatr 108(6):997-1004, 1986 3086531
- Jaiswal AK, Bhattacharya SK: Effects of gestational undernutrition, stress and diazepam treatment on spatial discrimination learning and retention in young rats. Indian J Exp Biol 31(4):353-359, 1993 8359834
- James ME: Neuroleptic malignant syndrome in pregnancy. Psychosomatics 29(1):119-122, 1988 3340699
- Jameson PB, Gelfand DM, Kulcsar E, et al: Mother-toddler interaction patterns associated with maternal depression. Dev Psychopathol 9(3):537-550, 1997 9327238
- Jenike MA, Hyman S, Baer L, et al: A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory. Am J Psychiatry 147(9):1209-1215, 1990 2143637
- Jensen PN, Olesen OV, Bertelsen A, et al: Citalopram and desmethylenitalopram concentrations in breast milk and in serum of mother and infant. Ther Drug Monit 19(2):236-239, 1997 9108657
- Jentink J, Dolk H, Loane MA, et al; EUROCAT Antiepileptic Study Working Group: Intrauterine exposure to

carbamazepine and specific congenital malformations: systematic review and case-control study. *BMJ* 341:c6581, 2010 21127116

Johnson EL, Stowe ZN, Ritchie JC, et al: Carbamazepine clearance and seizure stability during pregnancy. *Epilepsy Behav* 33:49-53, 2014 24632353

Jones KL, Lacro RV, Johnson KA, et al: Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med* 320(25): 1661-1666, 1989 2725616

Källén B: Neonate characteristics after maternal use of antidepressants in late pregnancy. *Arch Pediatr Adolesc Med* 158(4): 312-316, 2004 15066868

Källén B, Olausson PO: Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf* 17(8):801-806, 2008 18314924

Källén B, Reis M: Neonatal complications after maternal concomitant use of SSRI and other central nervous system active drugs during the second or third trimester of pregnancy. *J Clin Psychopharmacol* 32(5):608-614, 2012 22926593

Källén B, Tandberg A: Lithium and pregnancy: a cohort study on manic-depressive women. *Acta Psychiatr Scand* 68(2):134-139, 1983 6624510

Kaneko S, Suzuki K, Sato T, et al: The problems of antiepileptic medication in the neonatal period: is breast-feeding advisable? in *Epilepsy, Pregnancy and the Child*. Edited by Janz D, Dam M, Richens A. New York, Raven, 1982, pp 343-348

Kaneko S, Battino D, Andermann E, et al: Congenital malformations due to antiepileptic drugs. *Epilepsy Res* 33(2-3):145-158, 1999 10094426

Karlsson K, Lindstedt G, Lundberg PA, et al: Letter: Transplacental lithium poisoning: reversible inhibition of fetal thyroid. *Lancet* 1(7919):1295, 1975 48921

- Kelly LE, Poon S, Madadi P, et al: Neonatal benzodiazepines exposure during breastfeeding. *J Pediatr* 161(3):448-451, 2012 22504099
- Kendell RE, Chalmers JC, Platz C: Epidemiology of puerperal psychoses. *Br J Psychiatry* 150:662-673, 1987 3651704
- Kendler KS, Kessler RC, Neale MC, et al: The prediction of major depression in women: toward an integrated etiologic model. *Am J Psychiatry* 150(8):1139-1148, 1993 8328557
- Kennedy D, Koren G: Valproic acid use in psychiatry: issues in treating women of reproductive age. *J Psychiatry Neurosci* 23(4):223-228, 1998 9785701
- Kirchheiner J, Berghöfer A, Bolk-Weischedel D: Healthy outcome under olanzapine treatment in a pregnant woman. *Pharmacopsychiatry* 33(2):78-80, 2000 10761825
- Kirksey A, Groziak SM: Maternal drug use: evaluation of risks to breast-fed infants. *World Rev Nutr Diet* 43:60-79, 1984 6147939
- Klier CM, Mossaheb N, Lee A, et al: Mirtazapine and breastfeeding: maternal and infant plasma levels. *Am J Psychiatry* 164(2):348-349, 2007 17267804
- Koch S, Jäger-Roman E, Rating D, Helge H: Possible teratogenic effect of valproate during pregnancy. *J Pediatr* 103(6):1007-1008, 1983 6417292
- Kok TH, Taitz LS, Bennett MJ, Holt DW: Drowsiness due to clemastine transmitted in breast milk. *Lancet* 1(8277):914-915, 1982 6122135
- Korebrits C, Ramirez MM, Watson L, et al: Maternal corticotropin-releasing hormone is increased with impending preterm birth. *J Clin Endocrinol Metab* 83(5):1585-1591, 1998 9589660
- Kornhuber J, Weller M: Postpartum psychosis and mastitis: a new indication for clozapine? *Am J Psychiatry* 148(12):1751-1752, 1991 1796996

- Kost K: Unintended pregnancy rates at the state level: estimates for 2010 and trends since 2002. Guttmacher Institute, 2015. Available at: <http://www.guttmacher.org/pubs/StateUP10.pdf>. Accessed June 7, 2016.
- Kozma C: Valproic acid embryopathy: report of two siblings with further expansion of the phenotypic abnormalities and a review of the literature. *Am J Med Genet* 98(2):168-175, 2001 11223853
- Kriel RL, Cloyd J: Clonazepam and pregnancy. *Ann Neurol* 11(5):544, 1982 7103432
- Kris EB: Children of mothers maintained on pharmacotherapy during pregnancy and postpartum. *Curr Ther Res Clin Exp* 7(12):785-789, 1965 4954450
- Kris EB, Carmichael DM: Chlorpromazine maintenance therapy during pregnancy and confinement. *Psychiatr Q* 31(4):690-695, 1957 13518422
- Kristensen JH, Ilett KF, Dusci LJ, et al: Distribution and excretion of sertraline and N-desmethylertraline in human milk. *Br J Clin Pharmacol* 45(5):453-457, 1998 9643617
- Kristensen JH, Ilett KF, Hackett LP, et al: Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br J Clin Pharmacol* 48(4):521-527, 1999 10583022
- Kristensen JH, Ilett KF, Rampono J, et al: Transfer of the antidepressant mirtazapine into breast milk. *Br J Clin Pharmacol* 63(3):322-327, 2007 16970569
- Kuhn W, Jäger-Roman E, Rating D, et al: Carbamazepine and carbamazepine-10,11-epoxide during pregnancy and postnatal period in epileptic mother and their nursed infants: pharmacokinetics and clinical effects. *Pediatr Pharmacol (New York)* 3(3-4):199-208, 1983 6677873
- Kulin NA, Pastuszak A, Sage SR, et al: Pregnancy outcome following maternal use of the new selective serotonin

- reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 279(8):609-610, 1998 9486756
- Kumar R, Robson KM: A prospective study of emotional disorders in childbearing women. *Br J Psychiatry* 144:35-47, 1984 6692075
- Laegreid L, Olegård R, Wahlström J, et al: Abnormalities in children exposed to benzodiazepines in utero. *Lancet* 1(8524):108-109, 1987 2879165
- Laine K, Heikkinen T, Ekblad U, et al: Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry* 60(7):720-726, 2003 12860776
- Lajeunie E, Le Merrer M, Marchac D, et al: Syndromal and nonsyndromal primary trigonocephaly: analysis of a series of 237 patients. *Am J Med Genet* 75(2):211-215, 1998 9450889
- Lajeunie E, Barcik U, Thorne JA, et al: Craniosynostosis and fetal exposure to sodium valproate. *J Neurosurg* 95(5):778-782, 2001 11702867
- Lander CM, Livingstone I, Tyrer JH, et al: The clearance of anticonvulsant drugs in pregnancy. *Clin Exp Neurol* 17:71-78, 1981 7346203
- Lee A, Giesbrecht E, Dunn E, et al: Excretion of quetiapine in breast milk. *Am J Psychiatry* 161(9):1715-1716, 2004 15337669
- Lester BM, Cucca J, Andreozzi L, et al: Possible association between fluoxetine hydrochloride and colic in an infant. *J Am Acad Child Adolesc Psychiatry* 32(6):1253-1255, 1993 8282672
- Lindhout D, Schmidt D: In-utero exposure to valproate and neural tube defects. *Lancet* 1(8494):1392-1393, 1986 2872511
- Liporace J, Kao A, D'Abreu A: Concerns regarding lamotrigine and breast-feeding. *Epilepsy Behav* 5(1):102-105, 2004 14751214

- Little BB: Pharmacokinetics during pregnancy: evidence-based maternal dose formulation. *Obstet Gynecol* 93(5 Pt 2):858–868, 1999 10912434
- Liu C, Cnattingius S, Bergström M, et al: Prenatal parental depression and preterm birth: a national cohort study. *BJOG* 123(12):1973–1982, 2016 26786413
- Llewellyn A, Stowe ZN, Strader JR Jr: The use of lithium and management of women with bipolar disorder during pregnancy and lactation. *J Clin Psychiatry* 59 (suppl 6):57–64, discussion 65, 1998 9674938
- Lobo ED, Loghin C, Knadler MP, et al: Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. *Clin Pharmacokinet* 47(2):103–109, 2008 18193916
- Louik C, Lin AE, Werler MM, et al: First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 356(26):2675–2683, 2007 17596601
- Luoma I, Tamminen T, Kaukonen P, et al: Longitudinal study of maternal depressive symptoms and child well-being. *J Am Acad Child Adolesc Psychiatry* 40(12):1367–1374, 2001 11765281
- Luoma I, Kaukonen P, Mäntymaa M, et al: A longitudinal study of maternal depressive symptoms, negative expectations and perceptions of child problems. *Child Psychiatry Hum Dev* 35(1):37–53, 2004 15626324
- Lupattelli A, Spigset O, Björnsdóttir I, et al: Patterns and factors associated with low adherence to psychotropic medications during pregnancy—a cross-sectional, multinational Web-based study. *Depress Anxiety* 32(6):426–436, 2015 25703355
- Lutz UC, Hiemke C, Wiater G, et al: Aripiprazole in pregnancy and lactation: a case report. *J Clin Psychopharmacol* 30(2):204–205, 2010 20520299
- Lyons-Ruth K, Wolfe R, Lyubchik A: Depression and the parenting of young children: making the case for early

- preventive mental health services. *Harv Rev Psychiatry* 8(3):148-153, 2000 10973939
- Mammen OK, Perel JM, Rudolph G, et al: Sertraline and norsertraline levels in three breastfed infants. *J Clin Psychiatry* 58(3):100-103, 1997 9108810
- Mandelli M, Morselli PL, Nordio S, et al: Placental transfer to diazepam and its disposition in the newborn. *Clin Pharmacol Ther* 17(5):564-572, 1975 1126114
- Manly PC, McMahon RJ, Bradley CF, et al: Depressive attributional style and depression following childbirth. *J Abnorm Psychol* 91(4):245-254, 1982 7130519
- Marcus SM, Flynn HA, Blow FC, et al: Depressive symptoms among pregnant women screened in obstetrics settings. *J Womens Health (Larchmt)* 12(4):373-380, 2003 12804344
- Martinez A, Malphurs J, Field T, et al: Depressed mothers' and their infants' interactions with nondepressed partners. *Infant Mental Health Journal* 17(1):74-80, 1996
- Martínez-Frías ML: Clinical manifestation of prenatal exposure to valproic acid using case reports and epidemiologic information. *Am J Med Genet* 37(2):277-282, 1990 2248297
- Martins C, Gaffan EA: Effects of early maternal depression on patterns of infant-mother attachment: a meta-analytic investigation. *J Child Psychol Psychiatry* 41(6):737-746, 2000 11039686
- Maschi S, Clavenna A, Campi R, et al: Neonatal outcome following pregnancy exposure to antidepressants: a prospective controlled cohort study. *BJOG* 115(2):283-289, 2008 17903222
- Matalon S, Schechtman S, Goldzweig G, et al: The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. *Reprod Toxicol* 16(1):9-17, 2002 11934528



- Matheson I, Skjaeraasen J: Milk concentrations of flupenthixol, nortriptyline and zuclopenthixol and between-breast differences in two patients. *Eur J Clin Pharmacol* 35(2):217-220, 1988 3191943
- Matheson I, Pande H, Alertsen AR: Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet* 2(8464): 1124, 1985 2865592
- Mazzi E: Possible neonatal diazepam withdrawal: a case report. *Am J Obstet Gynecol* 129(5):586-587, 1977 910847
- McAuley DM, O'Neill MP, Moore J, et al: Lorazepam premedication for labour. *Br J Obstet Gynaecol* 89(2):149-154, 1982 6121581
- McBride WG: Limb deformities associated with iminodibenzyl hydrochloride. *Med J Aust* 1(10):492, 1972 5024423
- McDonagh M, Matthews A, Phillipi C, et al: Antidepressant treatment of depression during pregnancy and the postpartum period. Evidence Report/Technology Assessment No 216 (AHRQ Publ No 14-E003-EF). 2014. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm). Accessed June 7, 2016.
- McElhatton PR, Garbis HM, Eléfant E, et al: The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants. A collaborative study of the European Network of Teratology Information Services (ENTIS). *Reprod Toxicol* 10(4):285-294, 1996 8829251
- McEvoy JP, Hatcher A, Appelbaum PS, et al: Chronic schizophrenic women's attitudes toward sex, pregnancy, birth control, and childrearing. *Hosp Community Psychiatry* 34(6):536-539, 1983 6862399
- McKenna K, Koren G, Tetelbaum M, et al: Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 66(4):444-449, quiz 546, 2005 15816786

- McMahon CL, Braddock SR: Septo-optic dysplasia as a manifestation of valproic acid embryopathy. *Teratology* 64(2):83-86, 2001 11460259
- McNeil TF, Kaij L, Malmquist-Larsson A: Women with nonorganic psychosis: mental disturbance during pregnancy. *Acta Psychiatr Scand* 70(2):127-139, 1984a 6485846
- McNeil TF, Kaij L, Malmquist-Larsson A: Women with nonorganic psychosis: pregnancy's effect on mental health during pregnancy. *Acta Psychiatr Scand* 70(2): 140-148, 1984b 6485847
- McVearry KM, Gaillard WD, VanMeter J, et al: A prospective study of cognitive fluency and originality in children exposed in utero to carbamazepine, lamotrigine, or valproate monotherapy. *Epilepsy Behav* 16(4):609-616, 2009 19892603
- Meador KJ, Baker GA, Finnell RH, et al; NEAD Study Group: In utero antiepileptic drug exposure: fetal death and malformations. *Neurology* 67(3):407-412, 2006 16894099
- Meador KJ, Baker GA, Browning N, et al; NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 360(16):1597-1605, 2009 19369666
- Meador KJ, Baker GA, Browning N, et al; NEAD Study Group: Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain* 134(pt 2):396-404, 2011 21224309
- Meador KJ, Baker GA, Browning N, et al; NEAD Study Group: Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 12(3):244-252, 2013 23352199
- Meador KJ, Baker GA, Browning N, et al; Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group: Breastfeeding in children of

women taking antiepileptic drugs: cognitive outcomes at age 6 years. *JAMA Pediatr* 168(8):729-736, 2014 24934501

Meijer A: Child psychiatric sequelae of maternal war stress. *Acta Psychiatr Scand* 72(6):505-511, 1985 2417452

Merlob P, Mor N, Litwin A: Transient hepatic dysfunction in an infant of an epileptic mother treated with carbamazepine during pregnancy and breastfeeding. *Ann Pharmacother* 26(12):1563-1565, 1992 1362364

Milkovich L, van den Berg BJ: An evaluation of the teratogenicity of certain antinauseant drugs. *Am J Obstet Gynecol* 125(2):244-248, 1976 773181

Miller ES, Chu C, Gollan J, et al: Obsessive-compulsive symptoms during the postpartum period: a prospective cohort. *J Reprod Med* 58(3-4):115-122, 2013 23539879

Miller LJ: Clinical strategies for the use of psychotropic drugs during pregnancy. *Psychiatr Med* 9(2):275-298, 1991 1677481

Miller LJ, Finnerty M: Sexuality, pregnancy, and childrearing among women with schizophrenia-spectrum disorders. *Psychiatr Serv* 47(5):502-506, 1996 8740491

Misri S, Sivertz K: Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psychiatry Med* 21(2):157-171, 1991 1894455

Misri S, Oberlander TF, Fairbrother N, et al: Relation between prenatal maternal mood and anxiety and neonatal health. *Can J Psychiatry* 49(10):684-689, 2004 15560315

Mitchell AA, Gilboa SM, Werler MM, et al; National Birth Defects Prevention Study: Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol* 205(1): 51.e1-51.e8, 2011 21514558

Mizrahi EM, Hobbs JF, Goldsmith DI: Nephrogenic diabetes insipidus in transplacental lithium intoxication. *J Pediatr* 94(3):493-495, 1979 423043

- Mølgaard-Nielsen D, Hviid A: Newer-generation antiepileptic drugs and the risk of major birth defects. *JAMA* 305(19):1996–2002, 2011 21586715
- Moore SJ, Turnpenny P, Quinn A, et al: A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet* 37(7):489–497, 2000 10882750
- Moore WM, Hellegers AE, Battaglia FC: In vitro permeability of different layers of the human placenta to carbohydrates and urea. *Am J Obstet Gynecol* 96(7):951–955, 1966 4959176
- Moreno-Bruna MD, de Montgolfier I, Chaubaud M, et al: [Case report: Neonatal delayed peristalsis after in-utero exposure to clozapine] [Article in French]. *Arch Pediatr* 19:913–916, 2012 22884999
- Morgan DJ: Drug disposition in mother and foetus. *Clin Exp Pharmacol Physiol* 24(11):869–873, 1997 9363372
- Moriarty AJ, Nance MR: Trifluoperazine and Pregnancy. *Can Med Assoc J* 88(7):375–376, 1963 20327411
- Morrison CM: A case report of the use of vilazodone in pregnancy. *Prim Care Companion CNS Disord* 16(2):pii:PCC. 13l01612, 2014 25133058
- Morrow J, Russell A, Guthrie E, et al: Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 77(2):193–198, 2006 16157661
- Moses-Kolko EL, Bogen D, Perel J, et al: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 293(19):2372–2383, 2005 15900008
- Mountain KR, Hirsh J, Gallus AS: Neonatal coagulation defect due to anticonvulsant drug treatment in pregnancy. *Lancet* 1(7641):265–268, 1970 4189292
- Myllynen PK, Pienimäki PK, Vähäkangas KH: Transplacental passage of lamotrigine in a human placental perfusion system in vitro and in maternal and cord blood in vivo. *Eur J Clin Pharmacol* 58(10):677–682, 2003 12610744

- Myslivecek J, Hassmannová J, Josífko M: Impact of prenatal low-dose diazepam or chlorpromazine on reflex and motor development and inhibitory-learning. *Homeost Health Dis* 33(1-2):77-88, 1991 1817694
- Nadebaum C, Anderson V, Vajda F, et al: The Australian brain and cognition and antiepileptic drugs study: IQ in school-aged children exposed to sodium valproate and polytherapy. *J Int Neuropsychol Soc* 17(1):133-142, 2011a 21092354
- Nadebaum C, Anderson VA, Vajda F, et al: Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology* 76(8):719-726, 2011b 21339499
- Nau H, Rating D, Koch S, et al: Valproic acid and its metabolites: placental transfer, neonatal pharmacokinetics, transfer via mother's milk and clinical status in neonates of epileptic mothers. *J Pharmacol Exp Ther* 219(3):768-777, 1981 6795343
- Nau H, Kuhn W, Egger HJ, et al: Anticonvulsants during pregnancy and lactation: transplacental, maternal and neonatal pharmacokinetics. *Clin Pharmacokinet* 7(6):508-543, 1982a 6819105
- Nau H, Wittfoht W, Rating D, et al: Pharmacokinetics of valproic acid and its metabolites in a pregnant patient: stable isotope methodology, in *Epilepsy, Pregnancy, and the Child*. Edited by Janz D, Bossi L, Dam M, et al. New York, Raven, 1982b, pp 131-139
- Newport DJ, Stowe ZN, Nemeroff CB: Parental depression: animal models of an adverse life event. *Am J Psychiatry* 159(8):1265-1283, 2002 12153816
- Newport DJ, Viguera AC, Beach AJ, et al: Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. *Am J Psychiatry* 162(11):2162-2170, 2005 16263858
- Newport DJ, Calamaras MR, DeVane CL, et al: Atypical antipsychotic administration during late pregnancy:

- placental passage and obstetrical outcomes. *Am J Psychiatry* 164(8):1214-1220, 2007a 17671284
- Newport DJ, Levey LC, Pennell PB, et al: Suicidal ideation in pregnancy: assessment and clinical implications. *Arch Women Ment Health* 10(5):181-187, 2007b 17726640
- Newport DJ, Brennan PA, Green P, et al: Maternal depression and medication exposure during pregnancy: comparison of maternal retrospective recall to prospective documentation. *BJOG* 115(6):681-688, 2008a 18410650
- Newport DJ, Pennell PB, Calamaras MR, et al: Lamotrigine in breast milk and nursing infants: determination of exposure. *Pediatrics* 122(1):e223-e231, 2008b 18591203
- Newport DJ, Stowe ZN, Viguera AC, et al: Lamotrigine in bipolar disorder: efficacy during pregnancy. *Bipolar Disord* 10(3): 432-436, 2008c 18402631
- Newport DJ, Ritchie JC, Knight BT, et al: Venlafaxine in human breast milk and nursing infant plasma: determination of exposure. *J Clin Psychiatry* 70(9):1304-1310, 2009 19607765
- Newport DJ, Ji S, Long Q, et al: Maternal depression and anxiety differentially impact fetal exposures during pregnancy. *J Clin Psychiatry* 73(2):247-251, 2012 22152400
- Newport DJ, Hostetter AL, Juul SH, et al: Prenatal psychostimulant and antidepressant exposure and risk of hypertensive disorders of pregnancy. *J Clin Psychiatry* 77(11):1538-1545, 2016 28076672
- Niebyl JR, Blake DA, Freeman JM, et al: Carbamazepine levels in pregnancy and lactation. *Obstet Gynecol* 53(1):139-140, 1979 760015
- Nora JJ, Nora AH, Toews WH: Letter: Lithium, Ebstein's anomaly, and other congenital heart defects. *Lancet* 2(7880):594-595, 1974 4140306

- Nordmo E, Aronsen L, Wasland K, et al: Severe apnea in an infant exposed to lamotrigine in breast milk. *Ann Pharmacother* 43(11):1893-1897, 2009 19826099
- Nulman I, Rovet J, Stewart DE, et al: Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 336(4):258-262, 1997a 8995088
- Nulman I, Scolnik D, Chitayat D, et al: Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. *Am J Med Genet* 68(1):18-24, 1997b 8986270
- Nulman I, Rovet J, Stewart DE, et al: Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 159(11):1889-1895, 2002 12411224
- Nulman I, Koren G, Rovet J, et al: Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. *Am J Psychiatry* 169(11): 1165-1174, 2012 23128923
- Nurnberg HG, Prudic J: Guidelines for treatment of psychosis during pregnancy. *Hosp Community Psychiatry* 35(1):67-71, 1984 6141137
- Oberlander TF, Misri S, Fitzgerald CE, et al: Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. *J Clin Psychiatry* 65(2):230-237, 2004 15003078
- Oberlander TF, Warburton W, Misri S, et al: Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry* 63(8): 898-906, 2006 16894066
- Oberlander TF, Reebye P, Misri S, et al: Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor

- antidepressant during pregnancy. *Arch Pediatr Adolesc Med* 161(1):22-29, 2007 17199063
- O'Connor M, Johnson GH, James DI: Intrauterine effect of phenothiazines. *Med J Aust* 1(8):416-417, 1981 7254089
- O'Connor TG, Heron J, Golding J, et al; ALSPAC Study Team: Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry* 44(7):1025-1036, 2003 14531585
- Odsbu I, Skurtveit S, Selmer R, et al: Prenatal exposure to anxiolytics and hypnotics and language competence at 3 years of age. *Eur J Clin Pharmacol* 71(3):283-291, 2015 25547568
- Oesterheld JR: A review of developmental aspects of cytochrome P450. *J Child Adolesc Psychopharmacol* 8(3):161-174, 1998 9853690
- O'Hara MW, Rehm LP, Campbell SB: Predicting depressive symptomatology: cognitive-behavioral models and postpartum depression. *J Abnorm Psychol* 91(6):457-461, 1982 7153419
- Ohman I, Vitols S, Tomson T: Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 41(6):709-713, 2000 10840403
- Ohman R, Hägg S, Carleborg L, et al: Excretion of paroxetine into breast milk. *J Clin Psychiatry* 60(8):519-523, 1999 10485633
- Omtzigt JG, Nau H, Los FJ, et al: The disposition of valproate and its metabolites in the late first trimester and early second trimester of pregnancy in maternal serum, urine, and amniotic fluid: effect of dose, co-medication, and the presence of spina bifida. *Eur J Clin Pharmacol* 43(4):381-388, 1992 1451717
- Omtzigt JG, Los FJ, Meijer JW, et al: The 10,11-epoxide-10,11-diol pathway of carbamazepine in early pregnancy in maternal serum, urine, and amniotic fluid: effect of



- dose, comedication, and relation to outcome of pregnancy. *Ther Drug Monit* 15(1):1-10, 1993 8451773
- Ordy JM, Samorajski T, Collins RL, et al: Prenatal chlorpromazine effects on liver, survival and behavior of mice offspring. *J Pharmacol Exp Ther* 151(1):110-125, 1966 5902168
- Ornoy A, Cohen E: Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 75(6):517-520, 1996 9014606
- Orr ST, Miller CA: Maternal depressive symptoms and the risk of poor pregnancy outcome: review of the literature and preliminary findings. *Epidemiol Rev* 17(1):165-171, 1995 8521934
- Orr ST, James SA, Blackmore Prince C: Maternal prenatal depressive symptoms and spontaneous preterm births among African-American women in Baltimore, Maryland. *Am J Epidemiol* 156(9):797-802, 2002 12396996
- Otani K: Risk factors for the increased seizure frequency during pregnancy and puerperium. *Folia Psychiatr Neurol Jpn* 39(1):33-41, 1985 4054760
- Özdemir AK, Pak SC, Canan F, et al: Paliperidone palmitate use in pregnancy in a woman with schizophrenia. *Arch Women Ment Health* 18(5):739-740, 2015 25599999
- Pacifici GM, Nottoli R: Placental transfer of drugs administered to the mother. *Clin Pharmacokinet* 28(3):235-269, 1995 7758253
- Page-Sharp M, Kristensen JH, Hackett LP, et al: Transfer of lamotrigine into breast milk. *Ann Pharmacother* 40(7-8):1470-1471, 2006 16868219
- Parkin DE: Probable Benadryl withdrawal manifestations in a newborn infant. *J Pediatr* 85(4):580, 1974 4443870
- Pastuszek A, Schick-Boschetto B, Zuber C, et al: Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 269(17):2246-2248, 1993 8474204
- Paulson GW, Paulson RB: Teratogenic effects of anticonvulsants. *Arch Neurol* 38(3): 140-143, 1981

6781455

- Paulzen M, Lammertz SE, Veselinovic T, et al: Lamotrigine in pregnancy—therapeutic drug monitoring in maternal blood, amniotic fluid, and cord blood. *Int Clin Psychopharmacol* 30(5):249–254, 2015 26086711
- Peng M, Gao K, Ding Y, et al: Effects of prenatal exposure to atypical antipsychotics on postnatal development and growth of infants: a case-controlled, prospective study. *Psychopharmacology (Berl)* 228(4):577–584, 2013 23559219
- Pennell PB, Newport DJ, Stowe ZN, et al: The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 62(2):292–295, 2004 14745072
- Pennell PB, Peng L, Newport DJ, et al: Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* 70(22 pt 2):2130–2136, 2008 18046009
- Perkin MR, Bland JM, Peacock JL, et al: The effect of anxiety and depression during pregnancy on obstetric complications. *Br J Obstet Gynaecol* 100(7):629–634, 1993 8369244
- Petersen I, Gilbert RE, Evans SJ, et al: Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from The Health Improvement Network. *J Clin Psychiatry* 72(7):979–985, 2011 21457681
- Petrenaite V, Sabers A, Hansen-Schwartz J: Individual changes in lamotrigine plasma concentrations during pregnancy. *Epilepsy Res* 65(3):185–188, 2005 16084694
- Philbert A, Pedersen B, Dam M: Concentration of valproate during pregnancy, in the newborn and in breast milk. *Acta Neurol Scand* 72(5):460–463, 1985 3936331
- Physicians' Desk Reference (PDR), 61st Edition. Montvale, NJ, Thomson Healthcare, 2007
- Piontek CM, Baab S, Peindl KS, et al: Serum valproate levels in 6 breastfeeding mother-infant pairs. *J Clin Psychiatry* 61(3):170–172, 2000 10817100

- Piontek CM, Wisner KL, Perel JM, et al: Serum fluvoxamine levels in breastfed infants. *J Clin Psychiatry* 62(2):111-113, 2001 11247095
- Polen KND, Rasmussen SA, Riehle-Colarusso T, et al; National Birth Defects Prevention Study: Association between reported venlafaxine use in early pregnancy and birth defects, national birth defects prevention study, 1997-2007 (Part A). *Birth Defects Res A Clin Mol Teratol* 97(1):28-35, 2013 23281074
- Polepally AR, Pennell PB, Brundage RC, et al: Model-based lamotrigine clearance changes during pregnancy: clinical implication. *Ann Clin Transl Neurol* 1(2):99-106, 2014 24883336
- Pynnönen S, Sillanpää M: Letter: Carbamazepine and mother's milk. *Lancet* 2(7934): 563, 1975 51396
- Pynnönen S, Kanto J, Sillanpää M, et al: Carbamazepine: placental transport, tissue concentrations in foetus and newborn, and level in milk. *Acta Pharmacol Toxicol (Copenh)* 41(3):244-253, 1977 578653
- Rai D, Lee BK, Dalman C, et al: Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ* 346:f2059, 2013 23604083
- Rambeck B, Kurlemann G, Stodieck SR, et al: Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. *Eur J Clin Pharmacol* 51(6):481-484, 1997 9112063
- Rampono J, Hackett LP, Kristensen JH, et al: Transfer of escitalopram and its metabolite demethylescitalopram into breastmilk. *Br J Clin Pharmacol* 62(3):316-322, 2006 16934048
- Rampono J, Simmer K, Ilett KF, et al: Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry* 42(3):95-100, 2009 19452377

- Rampono J, Teoh S, Hackett LP, et al: Estimation of desvenlafaxine transfer into milk and infant exposure during its use in lactating women with postnatal depression. *Arch Women Ment Health* 14(1):49–53, 2011 20960017
- Ranganathan P, Pramesh CS, Buyse M: Common pitfalls in statistical analysis: clinical versus statistical significance. *Perspect Clin Res* 6(3):169–170, 2015 26229754
- Rawlings WJ, Ferguson R, Maddison TG: Phenmetrazine and trifluoperazine. *Med J Aust* 1:370, 1963
- Reefhuis J, Devine O, Friedman JM, et al; National Birth Defects Prevention Study: Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. *BMJ* 351:h3190, 2015 26156519
- Reisinger TL, Newman M, Loring DW, et al: Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. *Epilepsy Behav* 29(1):13–18, 2013 23911354
- Rieder RO, Rosenthal D, Wender P, et al: The offspring of schizophrenics: fetal and neonatal deaths. *Arch Gen Psychiatry* 32(2):200–211, 1975 234727
- Riordan D, Appleby L, Faragher B: Mother-infant interaction in post-partum women with schizophrenia and affective disorders. *Psychol Med* 29(4):991–995, 1999 10473327
- Robertson RT, Majka JA, Peter CP, et al: Effects of prenatal exposure to chlorpromazine on postnatal development and behavior of rats. *Toxicol Appl Pharmacol* 53(3):541–549, 1980 7385249
- Rodríguez-Pinilla E, Arroyo I, Fondevilla J, et al: Prenatal exposure to valproic acid during pregnancy and limb deficiencies: a case-control study. *Am J Med Genet* 90(5):376–381, 2000 10706358
- Rosa FW: Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med*

324(10):674-677, 1991 1994251

Rosenberg L, Mitchell AA, Parsells JL, et al: Lack of relation of oral clefts to diazepam use during pregnancy. *N Engl J Med* 309(21):1282-1285, 1983 6633586

Ross LE, Grigoriadis S, Mamisashvili L, et al: Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry* 70(4): 436-443, 2013 23446732

Rumeau-Rouquette C, Goujard J, Huel G: Possible teratogenic effect of phenothiazines in human beings. *Teratology* 15(1):57-64, 1977 841482

Sabers A, Dam M, A-Rogvi-Hansen B, et al: Epilepsy and pregnancy: lamotrigine as main drug used. *Acta Neurol Scand* 109(1):9-13, 2004 14653845

Samrén EB, van Duijn CM, Koch S, et al: Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 38(9):981-990, 1997 9579936

Samrén EB, van Duijn CM, Christiaens GC, et al: Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Ann Neurol* 46(5):739-746, 1999 10553991

Sanchis A, Rosique D, Catala J: Adverse effects of maternal lorazepam on neonates. *DICP* 25(10):1137-1138, 1991 1803810

Sathanandar S, Blesi K, Tran T, et al: Lamotrigine clearance increases markedly during pregnancy. *Epilepsia* 41:246, 2000

Saxén I: Letter: Cleft palate and maternal diphenhydramine intake. *Lancet* 1(7854): 407-408, 1974 4131054

Saxén I: Associations between oral clefts and drugs taken during pregnancy. *Int J Epidemiol* 4(1):37-44, 1975 1116890

- Saxén I, Saxén L: Letter: Association between maternal intake of diazepam and oral clefts. *Lancet* 2(7933):498, 1975 51304
- Schell LM: Environmental noise and human prenatal growth. *Am J Phys Anthropol* 56(1):63-70, 1981 7337145
- Schick-Boschetto B, Zuber C: Alprazolam exposure during early human pregnancy. *Teratology* 45:460, 1992
- Schlotterbeck P, Leube D, Kircher T, et al: Aripiprazole in human milk. *Int J Neuropsychopharmacol* 10(3):433, 2007 17291382
- Schlotterbeck P, Saur R, Hiemke C, et al: Low concentration of ziprasidone in human milk: a case report. *Int J Neuropsychopharmacol* 12(3):437-438, 2009 19203410
- Schmidt K, Olesen OV, Jensen PN: Citalopram and breastfeeding: serum concentration and side effects in the infant. *Biol Psychiatry* 47(2):164-165, 2000 10664835
- Schou M: What happened later to the lithium babies? A follow-up study of children born without malformations. *Acta Psychiatr Scand* 54(3):193-197, 1976 970196
- Schou M, Amdisen A: Lithium and pregnancy. 3. Lithium ingestion by children breast-fed by women on lithium treatment. *BMJ* 2(5859):138, 1973 4699592
- Scokel PW3rd, Jones WN: Infant jaundice after phenothiazine drugs for labor: an enigma. *Obstet Gynecol* 20:124-127, 1962 13909880
- Scolnik D, Nulman I, Rovet J, et al: Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA* 271(10):767-770, 1994 7509419
- Shallcross R, Bromley RL, Irwin B, et al; Liverpool Manchester Neurodevelopment Group; UK Epilepsy and Pregnancy Register: Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 76(4):383-389, 2011 21263139

- Shannon RW, Fraser GP, Aitken RG, et al: Diazepam in preeclamptic toxemia with special reference to its effect on the newborn infant. *Br J Clin Pract* 26(6):271-275, 1972 5044095
- Shao P, Ou J, Peng M, et al: Effects of clozapine and other atypical antipsychotics on infants development who were exposed to as fetus: a post hoc analysis. *PLoS One* 10(4):e0123373, 2015 25909513
- Shiono PH, Mills JL: Oral clefts and diazepam use during pregnancy. *N Engl J Med* 311(14):919-920, 1984 6472406
- Simon GE, Cunningham ML, Davis RL: Outcomes of prenatal antidepressant exposure. *Am J Psychiatry* 159(12):2055-2061, 2002 12450956
- Sit DK, Perel JM, Helsel JC, Wisner KL: Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. *J Clin Psychiatry* 69(4):652-658, 2008 18426260
- Sivojelezova A, Shuhaiber S, Sarkissian L, et al: Citalopram use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. *Am J Obstet Gynecol* 193(6):2004-2009, 2005 16325604
- Skausig OB, Schou M: [Breast feeding during lithium therapy] (Danish). *Ugeskr Laeger* 139(7):400-401, 1977 841726
- Slone D, Siskind V, Heinonen OP, et al: Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 128(5):486-488, 1977 879206
- Smit M, Wennink H, Heres M, et al: Mirtazapine in pregnancy and lactation: data from a case series. *J Clin Psychopharmacol* 35(2):163-167, 2015 25689290
- Smith MV, Poschman K, Cavaleri MA, et al: Symptoms of posttraumatic stress disorder in a community sample of

- low-income pregnant women. *Am J Psychiatry* 163(5):881-884, 2006 16648330
- Sodhi P, Poddar B, Parmar V: Fatal cardiac malformation in fetal valproate syndrome. *Indian J Pediatr* 68(10):989-990, 2001 11758141
- Søndergaard C, Olsen J, Friis-Haschè E, et al: Psychosocial distress during pregnancy and the risk of infantile colic: a follow-up study. *Acta Paediatr* 92(7):811-816, 2003 12892160
- Sørensen MJ, Grønberg TK, Christensen J, et al: Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin Epidemiol* 5:449-459, 2013 24255601
- Speight AN: Floppy-infant syndrome and maternal diazepam and/or nitrazepam. *Lancet* 2(8043):878, 1977 72227
- Spigset O, Carleborg L, Norström A, et al: Paroxetine level in breast milk. *J Clin Psychiatry* 57(1):39, 1996 8543546
- Spigset O, Carieborg L, Ohman R, et al: Excretion of citalopram in breast milk. *Br J Clin Pharmacol* 44(3):295-298, 1997 9296327
- St Clair SM, Schirmer RG: First-trimester exposure to alprazolam. *Obstet Gynecol* 80(5):843-846, 1992 1407925
- Stahl MM, Neiderud J, Vinge E: Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was treated with valproic acid. *J Pediatr* 130(6):1001-1003, 1997 9202628
- Steer RA, Scholl TO, Hediger ML, et al: Self-reported depression and negative pregnancy outcomes. *J Clin Epidemiol* 45(10): 1093-1099, 1992 1474405
- Stewart RB, Karas B, Springer PK: Haloperidol excretion in human milk. *Am J Psychiatry* 137(7):849-850, 1980 7386670
- Stiegler A, Schaletzky R, Walter G, et al: Olanzapine treatment during pregnancy and breastfeeding: a



- chance for women with psychotic illness? Psychopharmacology (Berl) 231(15):3067-3069, 2014 24938920
- Stirrat GM, Edington PT, Berry DJ: Letter: Transplacental passage of chlordiazepoxide. BMJ 2(5921):729, 1974 4859397
- Stoner SC, Sommi RW Jr, Marken PA, et al: Clozapine use in two full-term pregnancies. J Clin Psychiatry 58(8):364-365, 1997 9515978
- Stott DH: Follow-up study from birth of the effects of prenatal stresses. Dev Med Child Neurol 15(6):770-787, 1973 4129091
- Stowe ZN, Nemeroff CB: Women at risk for postpartum-onset major depression. Am J Obstet Gynecol 173(2):639-645, 1995 7645646
- Stowe ZN, Owens MJ, Landry JC, et al: Sertraline and desmethylsertraline in human breast milk and nursing infants. Am J Psychiatry 154(9):1255-1260, 1997 9286185
- Stowe ZN, Cohen LS, Hostetter A, et al: Paroxetine in human breast milk and nursing infants. Am J Psychiatry 157(2):185-189, 2000 10671385
- Stowe ZN, Hostetter AL, Owens MJ, et al: The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. J Clin Psychiatry 64(1):73-80, 2003 12590627
- Stowe ZN, Hostetter AL, Newport DJ: The onset of postpartum depression: implications for clinical screening in obstetrical and primary care. Am J Obstet Gynecol 192(2):522-526, 2005 15695997
- Summerfield RJ, Nielsen MS: Excretion of lorazepam into breast milk. Br J Anaesth 57(10):1042-1043, 1985 4041315
- Suri R, Stowe ZN, Hendrick V, et al: Estimates of nursing infant daily dose of fluoxetine through breast milk. Biol

- Psychiatry 52(5):446–451, 2002 12242061
- Sykes PA, Quarrie J, Alexander FW: Lithium carbonate and breast-feeding. *BMJ* 2(6047):1299, 1976 1000200
- Taddio A, Ito S, Koren G: Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *J Clin Pharmacol* 36(1):42–47, 1996 8932542
- Targum SD, Davenport YB, Webster MJ: Postpartum mania in bipolar manic-depressive patients withdrawn from lithium carbonate. *J Nerv Ment Dis* 167(9):572–574, 1979 479871
- Taylor CL, Stewart R, Ogden J, et al: The characteristics and health needs of pregnant women with schizophrenia compared with bipolar disorder and affective psychoses. *BMC Psychiatry* 15:88, 2015 25886140
- Tenyi T, Tixler M: Clozapine in the treatment of pregnant schizophrenic women. *Psychiatria Danubina* 10:15–18, 1998
- ter Horst PGJ, van der Linde S, Smit JP, et al: Clomipramine concentration and withdrawal symptoms in 10 neonates. *Br J Clin Pharmacol* 73(2):295–302, 2012 21801198
- Thisted E, Ebbesen F: Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child* 69(3 Spec No):288–291, 1993 8215567
- Tomson T, Lindbom U, Ekqvist B, et al: Disposition of carbamazepine and phenytoin in pregnancy. *Epilepsia* 35(1):131–135, 1994 8112235
- Tomson T, Ohman I, Vitols S: Lamotrigine in pregnancy and lactation: a case report. *Epilepsia* 38(9):1039–1041, 1997 9579945
- Tomson T, Battino D, Bonizzoni E, et al; EURAP study group: Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 10(7):609–617, 2011 21652013

- Tomson T, Battino D, Bonizzoni E, et al; EURAP Study Group: Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. *Neurology* 85(10):866-872, 2015 26085607
- Tonn P, Reuter SC, Hiemke C, et al: High mirtazapine plasma levels in infant after breast feeding: case report and review of the literature. *J Clin Psychopharmacol* 29(2):191-192, 2009 19512989
- Tran TA, Leppik IE, Blesi K, et al: Lamotrigine clearance during pregnancy. *Neurology* 59(2):251-255, 2002 12136066
- Troutman BR, Cutrona CE: Nonpsychotic postpartum depression among adolescent mothers. *J Abnorm Psychol* 99(1):69-78, 1990 2307769
- Tsuru N, Maeda T, Tsuruoka M: Three cases of delivery under sodium valproate—placental transfer, milk transfer and probable teratogenicity of sodium valproate. *Jpn J Psychiatry Neurol* 42(1):89-96, 1988 3135429
- Tunnessen WWJr, Hertz CG: Toxic effects of lithium in newborn infants: a commentary. *J Pediatr* 81(4):804-807, 1972 5074360
- Turton P, Hughes P, Evans CD, et al: Incidence, correlates and predictors of post-traumatic stress disorder in the pregnancy after stillbirth. *Br J Psychiatry* 178: 556-560, 2001 11388974
- Uguz F, Sahingoz M, Sonmez EO, et al: The effects of maternal major depression, generalized anxiety disorder, and panic disorder on birth weight and gestational age: a comparative study. *J Psychosom Res* 75(1):87-89, 2013 23751245
- Vajda FJ, O'Brien TJ, Hitchcock A, et al: The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. *J Clin Neurosci* 10(5):543-549, 2003 12948456

- Vajda FJ, O'Brien TJ, Graham J, et al: Associations between particular types of fetal malformation and antiepileptic drug exposure in utero. *Acta Neurol Scand* 128(4):228-234, 2013 23461556
- Van Boekholt AA, Hartong EGTM, Huntjens-Fleuren H, et al: Quetiapine concentrations during exclusive breastfeeding and maternal quetiapine use. *Ann Pharmacother* 49(6):743-744, 2015 25975996
- Van den Bergh BR, Marcoen A: High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Dev* 75(4):1085-1097, 2004 15260866
- van der Lugt NM, van de Maat JS, van Kamp IL, et al: Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies. *Early Hum Dev* 88(6):375-378, 2012 22000820
- van der Pol MC, Hadders-Algra M, Huisjes HJ, et al: Antiepileptic medication in pregnancy: late effects on the children's central nervous system development. *Am J Obstet Gynecol* 164(1 pt 1):121-128, 1991 1986598
- Van Waes A, Van de Velde EJ: Safety evaluation of haloperidol in the treatment of hyperemesis gravidarum. *J Clin Pharmacol* 9(4):224-227, 1969
- Vasilakis-Scaramozza C, Aschengrau A, Cabral H, et al: Antidepressant use during early pregnancy and the risk of congenital anomalies. *Pharmacotherapy* 33(7):693-700, 2013 23744675
- Veiby G, Daltveit AK, Schjølberg S, et al: Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia* 54(8):1462-1472, 2013 23865818
- Veiby G, Daltveit AK, Engelsen BA, et al: Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 261(3):579-588, 2014 24449062

- Venkatesh KK, Riley L, Castro VM, et al: Association of antenatal depression symptoms and antidepressant treatment with preterm birth. *Obstet Gynecol* 127(5):926-933, 2016 27054941
- Viguera AC, Newport DJ, Ritchie J, et al: Lithium in breast milk and nursing infants: clinical implications. *Am J Psychiatry* 164(2):342-345, 2007a 17267800
- Viguera AC, Whitfield T, Baldessarini RJ, et al: Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry* 164(12):1817-1824, quiz 1923, 2007b 18056236
- von Unruh GE, Froescher W, Hoffmann F, et al: Valproic acid in breast milk: how much is really there? *Ther Drug Monit* 6(3):272-276, 1984 6438834
- Waldman MD, Safferman AZ: Pregnancy and clozapine. *Am J Psychiatry* 150(1):168-169, 1993 8018113
- Wang JS, Newport DJ, Stowe ZN, et al: The emerging importance of transporter proteins in the psychopharmacological treatment of the pregnant patient. *Drug Metab Rev* 39(4):723-746, 2007 18058331
- Warner A: Drug use in the neonate: interrelationships of pharmacokinetics, toxicity, and biochemical maturity. *Clin Chem* 32(5):721-727, 1986 2421942
- Watanabe N, Kasahara M, Sugibayashi R, et al: Perinatal use of aripiprazole: a case report. *J Clin Psychopharmacol* 31(3):377-379, 2011 21532364
- Watson JP, Elliott SA, Rugg AJ, et al: Psychiatric disorder in pregnancy and the first postnatal year. *Br J Psychiatry* 144:453-462, 1984 6733369
- Weggelaar NM, Keijer WJ, Janssen PKC: A case report of risperidone distribution and excretion into human milk: how to give good advice if you have not enough data available. *J Clin Psychopharmacol* 31(1):129-131, 2011 21192160

- Weinstein MR, Goldfield M: Lithium carbonate treatment during pregnancy; report of a case. *Dis Nerv Syst* 30(12):828-832, 1969 5369134
- Weinstein MR, Goldfield M: Cardiovascular malformations with lithium use during pregnancy. *Am J Psychiatry* 132(5):529-531, 1975 1119612
- Weissman MM, Prusoff BA, Gammon GD, et al: Psychopathology in the children (ages 6-18) of depressed and normal parents. *J Am Acad Child Psychiatry* 23(1):78-84, 1984 6693680
- Welch RM, Findlay JW: Excretion of drugs in human breast milk. *Drug Metab Rev* 12(2):261-277, 1981 7040016
- Wesson DR, Camber S, Harkey M, et al: Diazepam and desmethyldiazepam in breast milk. *J Psychoactive Drugs* 17(1):55-56, 1985 3920372
- Whalley LJ, Blain PG, Prime JK: Haloperidol secreted in breast milk. *Br Med J (Clin Res Ed)* 282(6278):1746-1747, 1981 6786603
- Whitelaw AG, Cummings AJ, McFadyen IR: Effect of maternal lorazepam on the neonate. *Br Med J (Clin Res Ed)* 282(6270): 1106-1108, 1981 6113019
- Whitworth A, Stuppaeck C, Yazdi K, et al: Olanzapine and breast-feeding: changes of plasma concentrations of olanzapine in a breast-fed infant over a period of 5 months. *J Psychopharmacol* 24(1):121-123, 2010 18801835
- Wide K, Winbladh B, Tomson T, et al: Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. *Dev Med Child Neurol* 42(2):87-92, 2000 10698324
- Williams G, King J, Cunningham M, et al: Fetal valproate syndrome and autism: additional evidence of an association. *Dev Med Child Neurol* 43(3):202-206, 2001 11263692

- Williams KE, Koran LM: Obsessive-compulsive disorder in pregnancy, the puerperium, and the premenstruum. *J Clin Psychiatry* 58(7):330-334, quiz 335-336, 1997 9269260
- Williams PG, Hersh JH: A male with fetal valproate syndrome and autism. *Dev Med Child Neurol* 39(9):632-634, 1997 9344057
- Wilson KL, Zelig CM, Harvey JP, et al: Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. *Am J Perinatol* 28(1):19-24, 2011 20607643
- Wilson JT, Brown RD, Cherek DR, et al: Drug excretion in human breast milk: principles, pharmacokinetics and projected consequences. *Clin Pharmacokinet* 5(1): 1-66, 1980 6988135
- Wilson N, Forfar JD, Godman MJ: Atrial flutter in the newborn resulting from maternal lithium ingestion. *Arch Dis Child* 58(7):538-539, 1983 6870336
- Wilton LV, Pearce GL, Martin RM, et al: The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *Br J Obstet Gynaecol* 105(8):882-889, 1998 9746382
- Windhager E, Kim SW, Saria A, et al: Perinatal use of aripiprazole: plasma levels, placental transfer, and child outcome in 3 new cases. *J Clin Psychopharmacol* 34(5):637-641, 2014 24949701
- Winter RM: In-utero exposure to benzodiazepines. *Lancet* 1(8533):627-628, 1987 2881161
- Winter RM, Donnai D, Burn J, et al: Fetal valproate syndrome: is there a recognisable phenotype? *J Med Genet* 24(11):692-695, 1987 3123693
- Winterfeld U, Klinger G, Panchaud A, et al: Pregnancy outcomes following maternal exposure to mirtazapine: a multicenter, prospective study. *J Clin Psychopharmacol* 35(3):250-259, 2015 25830592

- Wisner KL, Perel JM: Psychopharmacologic agents and electroconvulsive therapy during pregnancy and the puerperium, in *Psychiatric Consultation in Childbirth Settings: Parent- and Child-Oriented Approaches*. Edited by Cohen RL. New York, Plenum, 1988, pp 165-206
- Wisner KL, Perel JM: Serum levels of valproate and carbamazepine in breastfeeding mother-infant pairs. *J Clin Psychopharmacol* 18(2):167-169, 1998 9555601
- Wisner KL, Perel JM, Wheeler SB: Tricyclic dose requirements across pregnancy. *Am J Psychiatry* 150(10):1541-1542, 1993 8379562
- Wisner KL, Peindl KS, Hanusa BH: Effects of childbearing on the natural history of panic disorder with comorbid mood disorder. *J Affect Disord* 41(3):173-180, 1996a 8988449
- Wisner KL, Perel JM, Findling RL: Antidepressant treatment during breast-feeding. *Am J Psychiatry* 153(9):1132-1137, 1996b 8780414
- Wisner KL, Perel JM, Blumer J: Serum sertraline and N-desmethylsertraline levels in breast-feeding mother-infant pairs. *Am J Psychiatry* 155(5):690-692, 1998 9585724
- Wood AG, Nadebaum C, Anderson V, et al: Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy. *Epilepsia* 56(7):1047-1055, 2015 25963613
- Woods DL, Malan AF: Side-effects of maternal diazepam on the newborn infant. *S Afr Med J* 54(16):636, 1978 741269
- Woody JN, London WL, Wilbanks GD Jr: Lithium toxicity in a newborn. *Pediatrics* 47(1):94-96, 1971 5545409
- Wretling M: Excretion of oxazepam in breast milk. *Eur J Clin Pharmacol* 33(2):209-210, 1987 3691611
- Wright S, Dawling S, Ashford JJ: Excretion of fluvoxamine in breast milk. *Br J Clin Pharmacol* 31(2):209, 1991 1904751



- Wyska E, Jusko WJ: Approaches to pharmacokinetic/pharmacodynamic modeling during pregnancy. *Semin Perinatol* 25(3): 124-132, 2001 11453607
- Yerby MS, Friel PN, Miller DQ: Carbamazepine protein binding and disposition in pregnancy. *Ther Drug Monit* 7(3):269-273, 1985 4049462
- Yerby MS, Friel PN, McCormick K, et al: Pharmacokinetics of anticonvulsants in pregnancy: alterations in plasma protein binding. *Epilepsy Res* 5(3):223-228, 1990 2384078
- Yerby MS, Friel PN, McCormick K: Antiepileptic drug disposition during pregnancy. *Neurology* 42 (4 suppl 5):12-16, 1992 1574166
- Yonkers KA, Gotman N, Smith MV, et al: Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? *Epidemiology* 22(6):848-854, 2011 21900825
- Yonkers KA, Blackwell KA, Glover J, et al: Antidepressant use in pregnant and postpartum women. *Annu Rev Clin Psychol* 10:369-392, 2014 24313569
- Yoshida K, Smith B, Craggs M, et al: Fluoxetine in breast-milk and developmental outcome of breast-fed infants. *Br J Psychiatry* 172:175-178, 1998a 9519072
- Yoshida K, Smith B, Craggs M, et al: Neuroleptic drugs in breast-milk: a study of pharmacokinetics and of possible adverse effects in breast-fed infants. *Psychol Med* 28(1):81-91, 1998b 9483685
- Zambaldi CF, Cantilino A, Montenegro AC, et al: Postpartum obsessive-compulsive disorder: prevalence and clinical characteristics. *Compr Psychiatry* 50(6):503-509, 2009 19840587
- Zeskind PS, Stephens LE: Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics* 113(2):368-375, 2004 14754951

Zuckerman B, Amaro H, Bauchner H, et al: Depressive symptoms during pregnancy: relationship to poor health behaviors. *Am J Obstet Gynecol* 160(5 pt 1):1107-1111, 1989 2729387

## CHAPTER 58

# Treatment of Psychiatric Emergencies

Steven J. Garlow, M.D., Ph.D.

Margaret B. Weigel, M.D.

Barbara D'Orio, M.D., M.P.A.

**Psychiatric emergencies** occur in many different situations and settings. While often managed in specialized crisis stabilization units, psychiatric emergencies occur in other locations, such as general medical/surgical units, outpatient clinics, general emergency departments, and other, nonclinical areas. The effective practice of emergency psychiatry requires a broad range of knowledge and clinical skills, including general and psychosomatic medicine, behavioral neurology, psychopharmacology, individual and family psychotherapy, and addiction medicine. In addition, a basic knowledge of forensic and legal issues is essential. With recent large-scale changes in mental health care delivery, including deinstitutionalization

and downsizing of inpatient mental health facilities, the role of an emergency psychiatrist has expanded dramatically. These changes impact not only psychiatric facilities but also general emergency medicine departments, with at least 6.3% of all emergency room visits being for psychiatric issues ([Larkin et al. 2005](#)). There were on average 420,000 emergency room visits per year for attempted suicide and self-injurious behaviors between 1993 and 2008. Ominously, the annual number of ED visits for suicide-related behaviors more than doubled from 1993–1996 (244,000/year) to 2005–2008 (538,000/year) ([Ting et al. 2012](#)). This trend continues unabated; the [Centers for Disease Control and Prevention \(2015\)](#) reports that there were 836,000 emergency department visits for self-inflicted injury in 2011.

Patients with emergent behavioral and psychiatric syndromes are often unable or unwilling to provide accurate historical details; therefore, the clinician must rely on collateral sources of information, including friends, family, and previous treatment providers. One consequence of this process of data collection is that absolute patient confidentiality, the standard of care in other clinical settings, is more tenuous. The Health Insurance Portability and Accountability Act (HIPAA) regulates all disclosures of Protected Health Information (PHI) by health care providers. In [2014, the U.S. Department of Health and Human Services](#) issued guidance on the implementation of HIPAA in the setting of psychiatric emergencies. In the context of a psychiatric emergency, the need to acquire critical information supersedes the individual's absolute right to privacy. The guiding principal is the determination of the clinician, based on professional judgment, that disclosure of certain PHI would be in the best interests of

the patient in that particular emergent situation. Disclosures to family, friends, and other care providers can be made if the patient does not object when informed of the proposed disclosure, or if (in the professional judgment of the clinician) the patient does not have capacity based on his or her mental status (examples being psychosis, substance intoxication, or unresponsive states). In emergent situations, resources such as medical records, friends, and relatives may provide critical data for diagnosis and treatment. There is no prohibition in HIPAA for a clinician to listen to information provided by family, friends, and other care providers or to read outside clinical records. This is one situation in which it is appropriate to stretch the boundaries of confidentiality in order to provide the best clinical care. The focus is on obtaining components of history and developing a treatment plan while not needlessly disclosing protected information, and only those disclosures absolutely necessary for the well-being of the patient should be made. There are other circumstances in which there is a mandated breach of confidentiality, which include a patient's risk of harm to self or others and the knowledge of child or elder abuse. HIPAA does not prevent these mandatory disclosures to protect the safety of the patient or others. Specific disclosure and third-party contact requirements vary by jurisdiction.

Another consequence of the need to make diagnostic and treatment decisions with limited information is that these decisions should be conservative. A 1-year study of diagnostic stability suggested that 38.7% of psychiatric emergency room patients received a different discharge diagnosis from the emergency room than they received from the inpatient service ([Woo et al. 2006](#)). Following the principles of Hippocrates, the emphasis is to make

treatment decisions in the best interests of the patient while balancing the need to prevent further harm. The ultimate goals are to provide adequate treatment of the underlying pathology based on a careful but succinct evaluation of the patient and to provide this treatment in the least restrictive environment while maintaining the safety of the patient, the clinician, and the staff.

As the numbers of psychiatric emergency cases continue to increase and flood general emergency rooms, new and novel methods of providing psychiatric consultation need to be explored. One method of expanding access to psychiatric services in emergency settings that has been underutilized in emergency psychiatry compared with other disciplines of medicine is telemedicine systems ([Hilty et al. 2013](#)). An essential requirement for developing these systems is a set of empirically derived and validated guidelines for implementation ([Shore et al. 2007](#)). There are qualitative data indicating that telemedicine systems might be useful in the diagnosis and management of psychiatric emergencies in emergency rooms without ready access to in-person psychiatric consultation ([Yellowlees et al. 2008](#)). These systems appear to be accepted by providers, staff, and patients ([Trondsen et al. 2014](#)).

Clearly, development of a well-trained work force of clinicians to deal with this rising tide of psychiatric emergencies is an urgent national imperative. The Accreditation Council for Graduate Medical Education (ACGME) does specify training requirements for emergency psychiatry for all psychiatric residents, which include a supervised experience in a 24-hour psychiatric emergency service, with direct clinical supervision from experienced attending physicians, and with no more than 50% of the experience allocated to off-hours call responsibilities. The

American Association of Emergency Psychiatry (AAEP) has proposed a curriculum and recommended training experience in response to the ACGME guidelines ([Brasch et al. 2004](#)). Disturbingly, a recent analysis of psychiatry training programs suggests that one-third do not adhere to the ACGME training guidelines for emergency psychiatry ([Bennett et al. 2011](#)). Efforts should be made through the American Association of Directors of Psychiatric Residency Training (AADPRT) and other organizations to ensure that all psychiatry residents receive adequate, high-quality training in psychiatric emergencies. But given that a large proportion of psychiatric emergency cases present to general emergency rooms, the case could be made that training in diagnosing and managing psychiatric emergencies should be provided to professionals other than psychiatrists, from physicians in emergency medicine residencies through nurses and other practitioners.

---

## Nonpharmacological Psychiatric Emergencies

---

Situations that require emergent psychiatric intervention but not psychopharmacological treatment include evaluation of need for hospitalization, assessment of suicide or homicide risk, determination of ability to care for self, and requirements to notify third parties to ensure safety of the patient or others ([Table 58-1](#)). Emergency psychiatrists are in a unique position of having to make predictions about patients' future behavior (e.g., suicide, homicide) and take appropriate preemptive action to prevent these outcomes. All states have civil commitment laws that allow for the

involuntary hospitalization of persons who by virtue of a mental illness may be considered an imminent risk to themselves or others. Typically, these laws allow for commitments of 48–72 hours in secure receiving facilities. Involuntary hospitalization beyond this holding period for observation and stabilization generally involves judicial review.

---

**TABLE 58-1. Psychiatric emergencies that do not require pharmacological intervention**

---

<b>Emergency</b>	<b>Intervention</b>
Suicidal state	Risk assessment Decision to admit
Homicidal state	Establish or rule out presence of psychiatric disorder Risk assessment Decision to admit <i>Tarasoff</i> notification
Grave disability, unable to care for self	Patient identification (if wandered from caregivers) Medical evaluation Decision to admit
Child, elder, spouse abuse	Notify/report to law enforcement and other agencies Referral to safe shelters

---



# Need for Hospitalization

The decision to hospitalize a psychiatric patient is dependent on several factors, but the welfare of the patient is of the greatest importance. There should be clear, definable treatment objectives for hospitalization, and the facility in which the patient is to be admitted should be capable of meeting those needs. Other factors that can contribute to the decision to hospitalize a patient include availability of psychiatric hospital beds and admission authorization by third-party payers ([Simon 1998](#)). Thus, the clinician must balance the availability of resources with the needs of individual patients.

Once the decision is made to hospitalize a patient, every effort should be made to have this occur on a voluntary basis. This is the first step in establishing therapeutic rapport with patients. The indiscriminate use of involuntary commitment can set up the perception of an adversarial relationship between patients and treatment providers ([Olofsson and Jacobsson 2001](#)). Avoiding experiences that elicit the perception of being “locked up” is one way of facilitating the long-term care engagement of the mentally ill patient.

## Suicidal State

Suicide is the tenth leading cause of death in the United States, with 41,149 suicide deaths in 2013, which translates into a population rate of around 13 deaths per 100,000 per year ([Centers for Disease Control and Prevention 2015](#)). One of the truly vexing problems in psychiatry is the lack of impact of specific psychiatric treatments on the suicide

rate. Several studies have failed to find any association between the availability of psychiatric treatment resources and the suicide rate ([Garlow et al. 2002](#); [Lewis et al. 1994](#)).

Predicting imminent suicide in any individual patient is difficult and can provoke significant anxiety in the clinician ([Pokorny 1983, 1993](#)). Suicide is a rare event, but it has profound effects on the surviving family members and friends of the patient and the physician and treatment staff ([Gitlin 1999](#); [Hendin et al. 2000](#)). There are also potential legal ramifications of a patient's suicide if he or she has been in recent contact with mental health providers ([Simon 2000](#)).

The relationship between suicidal ideation, attempted suicide, and completed suicide is complex ([Mościcki 1997](#)). No direct relation exists between any one of these states and the others. In one population-based study of completed suicides, 56% of the individuals died from the first attempt ([Isometsä and Lönnqvist 1998](#)). In another study of suicides, 75% of the individuals had no contact with mental health providers in the year prior to death ([Appleby et al. 1999](#)). One ominous finding was that 16% of the suicides occurred while the individuals were inpatients in psychiatric wards, and 24% occurred within 3 months after discharge from psychiatric facilities. In a 10-year follow-up study of patients admitted to the hospital for a medically serious suicide attempt, 25% made a second attempt, and 12% eventually died by suicide, with the majority of those deaths occurring in the 2 years following the index admission ([Isometsä and Lönnqvist 1998](#)).

Suicide risk is estimated by assessing both acute and chronic risk factors ([Table 58-2](#)), which include patient characteristics, nature of suicidal behavior, availability of a high-lethality means, and level of and access to psychosocial

support systems (e.g., family, friends, community) ([Hall et al. 1999](#); [Simon and Gutheil 2002](#)). This is an example of a psychiatric emergency in which acquiring reliable and accurate past and collateral history is essential, which may lead to some breach of patient confidentiality. Acute risk factors are most predictive of emergent suicidality and should carry the most weight in the decision to hospitalize a patient ([Busch et al. 2003](#)).

---

**TABLE 58-2. Acute and chronic risk factors for suicide**

---

<b>Acute</b>	<b>Chronic</b>
Increasing anxiety/frank panic attacks	Gender (male:female=4:1)
Psychic turmoil	Age (18-24 years; >65 years)
Global insomnia	Chronic illness
Mood-congruent nihilistic delusions	Race (white:nonwhite=2:1)
Profound hopelessness	Presence of a mental illness
Recent discharge from a psychiatric hospital	Substance abuse/dependence
Substance intoxication	Access to high-lethality means
Access to high-lethality means	Previous suicide attempts
Previous suicide attempts	Family history of suicide

---

Generating a comprehensive suicide risk assessment involves organizing and balancing risk with protective

factors. Clear documentation of these risk/protective factors, steps taken toward intervention, and associated clinical reasoning are essential. A basic statement describing competency should also be included. In the case of a chronically suicidal patient, clearly documenting this pattern and obtaining a second opinion to corroborate the treatment plan and objectives may be beneficial.

## **Acute Risk Factors**

Acute risk factors include increasing anxiety and frank panic attacks, psychic turmoil, global insomnia, mood-congruent nihilistic delusions, profound hopelessness, and recent discharge from a psychiatric hospital ([Busch et al. 2003](#); [Deisenhammer et al. 2007](#); [Fawcett 1992](#); [Fawcett et al. 1990](#)). Patients who are experiencing the first three of these symptoms should be viewed as being at particularly high risk regardless of whether they verbalize suicidal ideation.

Current intoxication is another acute risk factor. Recent alcohol consumption plays a role in 25%–50% of all suicides, and the consumption of both alcohol and cocaine may be particularly dangerous ([Cornelius et al. 1998](#)). Alcohol intoxication is related to higher rates of completed suicide, while cocaine intoxication is related to higher rates of suicidal ideation ([Garlow et al. 2002](#); [Garlow et al. 2003](#)). In this comprehensive series of individuals who died by suicide, 40% had alcohol or cocaine detected at the time of autopsy ([Garlow 2002](#)). Fully 21% of these individuals had blood alcohol levels above the legal limit for intoxication (0.08 µg/mL). Cocaine intoxication doubles the risk of suicide in white teenagers compared with African American teenagers ([Garlow et al. 2007](#)).

Previous suicide attempts are known precursors for completed suicide; thus, nonlethal suicide attempts are acute risk factors ([Deisenhammer et al. 2007](#); [Isometsä and Lönnqvist 1998](#); [Tejedor et al. 1999](#)). Consideration should be given to the actual lethality of the attempt; the patient's perception of that lethality; efforts made to conceal the attempt; calls for help; contacts with friends or family during the attempt; and use of a firearm. Access to firearms must always be determined in a suicide attempt and in someone who appears to be at high risk ([Conwell et al. 1996, 2002](#); [Miller et al. 2002](#); [Romero and Wintemute 2002](#)).

## **Chronic Risk Factors**

Chronic risk factors for suicide set the background on which acute risk is evaluated. They are derived from population-based analyses of suicides and often are not modifiable by any therapeutic intervention ([Kessler et al. 1999](#); [Mościcki 1997](#)). Males complete suicide four times more often than females, but females attempt suicide three times more often than males. Males tend to choose more lethal and violent means of suicide than females. Among males, firearms are the most commonly used (57.6%) method of suicide ([National Center for Injury Prevention and Control 2005](#)). Individuals age 65 years and older constitute 13% of the population but account for 19% of the suicides. The suicide rate for white men older than 85 years is 65 deaths per 100,000 population. A coincident risk factor is chronic illness, especially if diagnosed in the previous year. Another at-risk group is teenagers and young adults between the ages of 18 and 24 years, in whom suicide is the third leading cause of death.

Whites complete suicide two times more often than nonwhites, with white males accounting for 73% of the suicides in 1998 ([National Center for Injury Prevention and Control 2002](#)). The suicide rates for Native Americans are 1.5 times the national average. Suicide rates for specific ethnic groups change with the age and gender of the individual. In one study, African American males constituted the largest group, numerically and statistically, of teenage suicide victims but accounted for only 26% of victims from all age groups. In this same data set, African American females accounted for only 3% of all suicides, with only one occurring in an individual older than 45 years ([Garlow et al. 2005](#)).

Approximately 90%–95% of suicide victims have a major psychiatric illness, of which approximately half have a mood disorder ([Angst et al. 2002](#); [Fawcett 1992](#); [Harris and Barraclough 1997](#)). Male bipolar patients are at higher risk, especially those at an earlier phase of the illness, those who are currently in a depressed state, and those with comorbid substance abuse ([Simpson and Jamison 1999](#)). Patients with alcohol and other substance use disorders have higher rates of completed suicide than the national average, with alcoholic patients having a suicide rate twice the national average ([Fowler et al. 1986](#)). For alcoholic patients, comorbid depression and recent interpersonal loss increase risk ([Murphy and Wetzel 1990](#); [Murphy et al. 1992](#)). A family history of suicide increases suicide risk independent of a family history of mental illness ([Qin et al. 2002, 2003](#)).

Patients with borderline personality disorders often express ongoing suicidal ideation; as a result, suicidality becomes embedded in their sense of self ([Soloff et al. 1994](#)). This can manifest as repeated acts of self-injurious behavior, such as cutting and sublethal overdoses. These

patients can be very difficult to manage and can put a great deal of strain on the emergency medical and mental health delivery system. A consistently applied treatment plan, restrained responses on the part of clinical staff (minimizing countertransference behaviors), and use of secure 24-hour observation areas can be particularly useful in managing these patients. The goal is to allow patients to deescalate so that they can be discharged back into their ongoing outpatient treatment regimens ([Maltsberger and Buie 1974](#)).

## **Protective Factors**

In formulating a suicide risk assessment, it is important to note protective factors in addition to the presence or absence of acute and chronic risk factors. Protective factors against suicide include an expression of responsibility toward family, fear of social disapproval, moral objections to suicide, greater coping skills, and greater fear of suicide ([Malone et al. 2000](#)). Social connectivity also serves a protective role for depressed patients, as first described by Emile [Durkheim \(1951\)](#). Having close familial relationships, living with another person (family or friend), and having dependent children are all protective factors. Belonging to certain cultural groups, such as a community of faith, and having moral objections to suicide are associated with lower rates of suicide ([Dervic et al. 2004, 2006](#)).

## **Management of Suicidal Patients**

Ensuring safety is the first and most important step in managing a potentially suicidal patient. This can best be accomplished through admission to a secure patient observation area. If no such facility is available, close

observation by a trained staff member is another option. Staff assigned to monitor patients should be given specific instructions regarding their role and responsibilities.

The decision to hospitalize a potentially suicidal patient should take into account both acute and chronic risk factors; specific treatment needs of the patient; availability of other treatment options, including partial hospitalization, day treatment, and crisis group home settings; and social support network for the patient. Patients who are intoxicated and expressing suicidal ideation should be allowed to sober up before receiving a more definitive assessment. No-harm contracts between patients and clinicians are not useful in making treatment decisions with suicidal patients ([Kroll 2000](#); [Simon 1999](#)). Focusing on the acute behavioral state of the patient (anxiety, agitation, and insomnia), the presence of chronic risk factors, and access to high-lethality means (firearms) is much more relevant to making the decision to hospitalize the patient.

Patients who are not hospitalized require close follow-up, including a detailed treatment plan, an identified treatment provider, and instructions for the patient and family members on what to do in case of symptom worsening. Recommendations for management of acutely suicidal outpatients have been operationalized into an approach called Safety Planning Intervention (SPI). SPI is specifically designed to be deployed in emergency room settings for patients with suicidal ideation who are not hospitalized. A trained staff member assists the patient in developing a written document that includes warning signs, coping mechanisms, and sources of support and other treatment resources ([Stanley and Brown 2012](#)). Individuals with access to high-lethality means should be advised to remove these items from the home. Firearms and medications



lethal in overdose should be neither in the home nor readily accessible. Family members and friends may be consulted to assist with the removal of these items from the patient's possession ([Mann et al. 2005](#)).

Another approach being investigated for the management of suicide risk in patients is the use of cognitive-behavioral therapy (CBT) ([Brown and Jager-Hyman 2014](#)). In one seminal report on the use of CBT with suicidal patients initially assessed in a general emergency room, patients who received a 10-session CBT intervention were much less likely to make a second suicide attempt within the 18-month follow-up period compared with those who did not receive this intervention ([Brown et al. 2005](#)). The patients who received CBT also had improvements in depression symptom severity and lower levels of hopelessness than those in the control group.

Although management of emergent suicide risk has historically not been considered to warrant acute pharmacological interventions, recent evidence suggests that the dissociative anesthetic agent ketamine may have specific therapeutic benefit in suicidal patients ([Price and Mathew 2015](#)). Single and repeated infusions of subanesthetic dosages of ketamine (0.5 mg/kg body weight) have been shown to rapidly relieve symptoms of depression and suicidal ideation ([DiazGranados et al. 2010](#); [Price et al. 2009](#)). The antisuicide response appears to occur regardless of the impact on severity of mood symptoms, suggesting a specific antisuicide action of ketamine ([Ballard et al. 2014](#)). Pilot investigations of ketamine infusions in acutely suicidal patients in emergency room settings provide tantalizing preliminary evidence that this intervention may offer a novel method of managing acute suicide risk ([Larkin and Beautrais 2011](#)). Clearly, additional

research is needed to fully determine the utility, if any, of this intervention in general clinical practice.

## Homicidal State

Establishment of a psychiatric diagnosis is the first step in developing a management plan for a patient expressing homicidal ideation. Whereas suicide most often occurs in the context of a mental illness, homicide and homicidal behaviors do not. There is a relation between sadness and other negative affective states and suicide, but there is no correlation between these mood states and homicidal or violent acts ([Apter et al. 1991](#)). Nonetheless, a patient may develop homicidal ideation in the context of a psychotic disorder, particularly disorders that include firmly held paranoid, persecutory, or erotomanic delusions. If such delusional beliefs are driving the expression of homicidal ideation, involuntary hospitalization would be the appropriate course of action.

Expressions of anger, hostility, rage, and violent intent occur in many interpersonal situations and conflicts in which the perpetrator does not have a psychiatric disorder. In these cases, once a determination has been made that the individual is not psychotic or delusional or expressing homicidal ideation on the basis of some other psychiatric disorder, appropriate interventions are in the domain of law enforcement, not psychiatry.

If a patient who is expressing homicidal ideation is not admitted to a psychiatric facility, the clinician must give very careful consideration to the need to notify the intended victim and law enforcement agencies based on the principles set forth in *Tarasoff v. Regents of the University*

of California ([Tarasoff 1976](#); [Simon 1998](#); [Walcott et al. 2001](#)). This case established a precedent for mental health workers to breach confidentiality to notify an intended victim and law enforcement agencies if they are aware of a patient's plan to harm that victim. Adoption of the principles set forth in the *Tarasoff* ruling varies by state.

Predicting which individuals may act on homicidal ideation is very difficult ([Resnick and Scott 2000](#)). Factors that contribute to this assessment are the specificity of the plan, identity of the victim, access to high-lethality means (firearms), capacity of the patient to persist in the plan, and proximity of the perpetrator to the intended victim ([Borum and Reddy 2001](#)). Even with a careful history, assessment, and appropriate intervention, preventing an adverse outcome may not be possible. In the *Tarasoff* case, the police determined that the perpetrator was not a threat when they interviewed him, but he eventually carried out the lethal act 3 months later.

## Grave Disability and Inability to Care for Self

Another condition for which involuntary commitment laws exist is when patients by virtue of a mental illness are unable to care for themselves; some states also include "as a result of substance abuse disorders" under this heading (K.T. [Hall and Appelbaum 2002](#)). The consideration is whether the patient cannot provide adequately for basic needs, shelter, food, and medical attention because of a mental illness. A common example of this situation is a patient with a psychotic disorder who is living on the streets, without regular or adequate nutrition, and

neglecting his or her ongoing medical conditions. This situation is not the same as that in which a person is homeless because of some other occurrence or circumstance, because homelessness does not in itself constitute grave disability. Another common situation that falls under this heading is a patient with dementia or other profound cognitive impairments who has wandered away from his or her caregivers. In this case, effort should be focused on establishing the identity of the individual and returning him or her to the appropriate facility.

## Notification of Third Parties

The principles set forth by the *Tarasoff* ruling in California encourage clinicians to act in the best interests of the intended victim, with notification of the intended victim and law enforcement agencies in the case of expressed homicidal ideation. This places a unique burden on psychiatrists—to predict future behavior of a patient and to assume responsibility for the welfare of another person with whom the psychiatrist does not have a therapeutic relationship.

Another circumstance that requires breach of patient confidentiality is notification of authorities in cases of suspected child abuse and neglect. All states have statutes that require clinicians of all disciplines to notify the appropriate agency in the case of suspected child abuse. Many states also have laws for reporting elder abuse and abuse of other vulnerable individuals.

---

# Psychiatric Emergencies Requiring Minimal or Adjunctive Pharmacological Intervention

---

Psychiatric emergencies requiring minimal or adjunctive pharmacological intervention occur in many different situations, although many share a common thread of developing in response to some discrete, identifiable stressor (Table 58-3). The practice of crisis intervention psychiatry involves identifying the root cause or stressor of the presenting syndrome and developing a focused treatment plan. The principal therapeutic goals are to alleviate short-term distress, rapidly return the patient to his or her previous level of functioning, and prevent the development of a more serious long-term syndrome. The judicious use of psychopharmacological agents, in concert with psychotherapeutic, psychosocial, and family system interventions, can be particularly effective in these emergencies.

---

**TABLE 58-3. Psychiatric emergencies requiring minimal or adjunctive pharmacological intervention**

---

Emergency	Intervention
-----------	--------------

---

**Emergency****Intervention**

---

Adjustment disorder or  
acute grief

Diagnostic/psychosocial  
assessment  
Psychotherapy  
Social and family system  
intervention  
Short course of sedative-  
hypnotic  
Short course of  
benzodiazepine  
Selective serotonin  
reuptake inhibitor

Rape, assault, or trauma

Medical evaluation and  
treatment  
Law enforcement  
notification  
Psychotherapy  
Short course of sedative-  
hypnotic  
Short course of  
benzodiazepine  
Insult-specific  
psychotherapy  
Rape counseling  
Spousal abuse counseling  
Violence victim  
counseling

<b>Emergency</b>	<b>Intervention</b>
Borderline personality disorder	Controlled environment/de-escalation Structured psychotherapies Low-dose antipsychotics
Panic disorder	Medical evaluation Short course of benzodiazepine Treatment referral

## Adjustment Disorders

Adjustment disorders are defined as the maladaptive response to an identifiable psychosocial stressor within 3 months of onset of the stressor, with the symptoms having persisted for no more than 6 months after termination of the stressor ([American Psychiatric Association 2013](#)). The common clinical manifestations of adjustment disorders encountered in psychiatric emergency settings involve a mixture of anxiety, depressive, and neurovegetative symptoms in response to some external stressor or crisis. The potential stressors are myriad, including death of a family member or friend, job loss, diagnosis of a serious medical condition, divorce and other disturbances of family function, financial hardship, and many other circumstances.

The principal interventions for adjustment disorders are psychotherapeutic, educational, and psychosocial. Most crises have a natural time course and resolution. Feelings of distress in response to many of these insults are innate and expected. Psychoeducational interventions are aimed at

helping the patient realize that the syndrome is self-limited and expectable in response to the stressor. Often, these patients have a sleep disturbance, so the short-term use of a soporific (diphenhydramine 25–50 mg, hydroxyzine 25 mg, trazodone 50–100 mg, mirtazapine 7.5–15.0 mg) or a sedative-hypnotic (zolpidem 5–10 mg, zaleplon 5–10 mg, eszopiclone 2–3 mg, ramelteon 8 mg) could be considered to assist in reestablishing a normal sleep-wake cycle. In general, benzodiazepine use should be avoided, because there is no evidence that the early use of these agents prevents the eventual development of more serious disorders such as posttraumatic stress disorder (PTSD) ([Gelpin et al. 1996](#)).

## Acute Trauma

Patients who have been exposed to a catastrophic stressor or an acute psychological trauma are at risk for developing acute stress disorder (ASD) or PTSD ([Foa et al. 1989](#)). The definition of a traumatic event includes direct personal experience of an event that involves actual or threatened death, injury, or threat to one's physical integrity or witnessing such an event or learning about such an event happening to a family member or close associate. Most people who experience such traumas do not go on to develop any psychiatric disorder, but a significant minority, up to 30%, will develop PTSD.

Psychological debriefing has become one of the standard interventions after traumatic events ([Mitchell 1983](#)). A trained moderator conducts the debriefing with the goal of encouraging the expression of thoughts and feelings about an event shortly after it has occurred. This type of



intervention is commonly offered to both the victims of a trauma and the care providers (e.g., police officers, firefighters, emergency medical technicians) that were involved. Evidence shows that the timing of the debriefing is critical and that this might not be the ideal posttraumatic intervention in all situations ([Campfield and Hills 2001](#); [Greenberg 2001](#)). An evolving approach to immediate trauma intervention is to assess the risk of a patient developing PTSD and educate the patient about normal reactions to trauma and potential symptoms of PTSD. Other studies have evaluated the use of brief CBT for patients with acute traumatic exposures. One such study indicated accelerated rates of recovery in patients who received this intervention ([Sijbrandij et al. 2007](#)).

Behavioral indicators of risk of developing PTSD include heightened levels of arousal and coping via disengagement after a traumatic event ([Mellman et al. 2001](#)). Personalization of the traumatic event, especially thoughts that one might die, is another risk factor. The typical time course for posttraumatic reactions to resolve is on the order of 4 weeks. During this time, it is extremely common for all trauma victims to experience some of the symptoms of PTSD. One of the main early therapeutic goals should be to educate patients about this time course and to encourage them to return to treatment if these symptoms persist past 4 weeks or become particularly debilitating. Referral to trauma-specific psychotherapies (rape crisis, violent crime, survivor groups) can be helpful to victims of these specific insults.

The use of benzodiazepines is controversial in the context of acute trauma. While these medications may be useful in decreasing overall levels of anxiety, there is no clinical evidence supporting their use as prophylaxis against the

development of PTSD. The Consensus Statement on PTSD from the International Consensus Group on Depression and Anxiety discouraged the use of benzodiazepines secondary to limited efficacy, concern for tolerance and withdrawal, and the possibility of “impairment of learning” ([Ballenger et al. 2000, 2004](#)). If the decision is made to use these medications, long-half-life agents, such as clonazepam and diazepam, minimize the risk of withdrawal or rebound anxiety ([Davidson 2004](#)).

## Conditions That Require Medical Evaluation

With any acute change in mental status or sudden-onset change in behavior in a previously well individual, organic causes must be considered first, before it is assumed that the symptoms are a manifestation of a previously undiagnosed psychiatric disorder ([Frame and Kercher 1991](#); [Hall et al. 1978, 1981](#)). This is especially true when the syndrome occurs outside of the usual age-based window of vulnerability. For example, new-onset psychotic symptoms in a patient older than 40 years or mania in a patient older than 50 years should be considered to be due to a medical condition until proven otherwise.

### **Panic Disorder**

A patient presenting for the very first time with dyspnea, tachycardia, diaphoresis, chest pain, and light-headedness should receive a thorough medical evaluation before being assigned a diagnosis of panic disorder. Many different conditions can present with some or all of these symptoms,

including unstable angina and myocardial infarction, hypoglycemia, anemia, pulmonary embolism, asthma, obstructive pulmonary disease, gastroesophageal reflux disease, irritable bowel disease, hyperparathyroidism, hyperthyroidism, pheochromocytoma, Huntington's disease, Parkinson's disease, seizure disorder, and auto-immune disorders, such as systemic lupus erythematosus ([Roy-Byrne et al. 2006](#)). Only after these medical conditions have been ruled out should a diagnosis of panic disorder be entertained. Current U.S. Food and Drug Administration (FDA)-approved medications for panic disorder include alprazolam (a benzodiazepine), sertraline and paroxetine (selective serotonin reuptake inhibitors [SSRIs]), and venlafaxine (a serotonin-norepinephrine reuptake inhibitor). SSRIs tend to be utilized first line because of their general tolerability, lack of potential for dependence/misuse, and good safety profile ([Katon 2006](#)).

## **Dissociative Episodes**

Amnestic and acute confusional states should always be considered to be due to a medical or neurological condition until proven otherwise. Amnestic symptoms are common after head injury, during cerebrovascular accidents and transient ischemic accidents, in postictal states, with brain tumors, in intentional and unintentional intoxications, and in many other medical conditions. Another important diagnostic consideration is of a delirium, which could have any number of medical or metabolic causes. Establishing the correct diagnosis in this type of patient is facilitated by extended observation, with repeated assessments. This allows for detection of the fluctuating levels of consciousness and awareness common in delirium and of the temporal evolution of the amnestic symptoms.

Unobtrusive observation of these patients also allows for assessment of purposeful, deliberate, and organized behaviors, which are observed in patients with psychogenic or factitious amnestic conditions but often are not seen in those with an organic condition.

## **Catatonia**

Catatonia is a syndrome characterized by the presence of at least three of the following symptoms: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation, grimacing, echolalia, and echopraxia ([Fink and Taylor 2006](#); [Taylor and Fink 2003](#)). Catatonia can occur in psychiatric and nonpsychiatric conditions and can be diagnosed in 7%–15% of psychiatric patients in acute inpatient services and emergency room settings ([Fink and Taylor 2006](#)). If a patient has not had previous documented episodes of catatonia in conjunction with a known psychiatric disorder, a medical cause should be sought vigorously. Episodes of catatonic behavior can occur in a variety of neurological and medical conditions, including metabolic encephalopathies, viral encephalitis, cerebrovascular accidents, epileptic episodes, hypercalcemia, and adverse medication (e.g., antipsychotic) or drug (e.g., phencyclidine [PCP]) side effects. These conditions should be ruled out before a psychiatric diagnosis is made. Although no established standard of care exists for the treatment of catatonia, acceptable treatment options include intravenous barbiturates (e.g., amobarbital) and benzodiazepines (e.g., lorazepam), as well as electroconvulsive therapy (ECT) ([Fink 2001](#); [Rosebush et al. 1990](#)).

## **Mania or Psychosis**

New-onset mania or psychosis should always be approached as being potentially caused by a medical condition. The clinical context will guide the urgency of the medical evaluation. New-onset psychotic symptoms in a 40-year-old and new-onset mania in a 50-year-old should prompt an urgent medical evaluation. Such symptoms appearing in an adolescent or a young adult should still be evaluated medically, although not with the same urgency as in the older adult. These symptoms can be caused by brain tumors, cerebrovascular accidents, autoimmune disorders, multiple sclerosis, and hyperthyroidism. Many medications, including exogenously administered steroids and stimulants, as well as illicit drugs can provoke manic and psychotic symptoms. Therefore, a thorough physical examination and a urine drug screen are essential components of the diagnostic workup.

## **Conversion Disorder (Functional Neurological Symptom Disorder)**

Conversion disorder is a diagnosis of exclusion. Accordingly, new-onset neurological symptoms, including non-epileptic seizures, non-anatomical movement disorders, paresthesias, paresis, and amnestic syndromes, should be thoroughly evaluated before being attributed to a psychogenic cause. Management of conversion symptoms includes a complete medical assessment and reassurance that the symptoms will resolve with time. Long-term management involves both physical rehabilitation and treatment of the underlying psychological conflict or distress. Family therapy can be a useful tool, given that family dynamics are often an essential part of the psychosomatic response to stress ([Hurwitz 2004](#)).

---

# Psychiatric Emergencies That Usually Require Pharmacological Intervention

---

Management of severe behavioral emergencies usually requires psychopharmacological intervention prior to definitive diagnosis (Table 58-4). Many psychiatric patients will have episodes of disorganized, disinhibited, agitated, aggressive, or violent behavior. These behavioral states can occur in patients who are psychotic, manic, or intoxicated as well as in those who have organic syndromes such as traumatic brain injury, dementia, or delirium. Patients who are experiencing severe medication side effects also require pharmacological intervention, as do patients with substance use disorders in withdrawal states.

---

**TABLE 58-4. Psychiatric emergencies that usually require pharmacological intervention**

---

Emergency	Intervention
<b>Assaultive, aggressive, or violent behavior</b>	Calm, controlled staff Adequate staff/“show of force” Seclusion/stimulus minimization Physical restraint

## Emergency

## Intervention

Primary psychotic or mood disorder

Medication:

Lorazepam

Haloperidol

Atypical (second generation) antipsychotics

Definitive diagnosis and treatment plan

Delirium

Diagnose delirium vs. other disorder

Definitive medical diagnosis

Treat underlying cause

Intravenous (IV) or intramuscular (IM) haloperidol

Ethanol or sedative-hypnotic withdrawal

Benzodiazepine to stabilize withdrawal symptoms

Controlled taper under supervision

Referral to chemical dependency treatment

Alcohol withdrawal delirium

Medical intensive care

Supportive measures

Benzodiazepine taper

## Medication side effects

Emergency	Intervention
Antipsychotic-induced dystonia	Acute: Diphenhydramine 25–50 mg IV Maintenance: Diphenhydramine 25–100 mg once daily (QD), or Benztropine 0.5–4.0 mg QD, or Trihexyphenidyl 2–10 mg QD
Antipsychotic-induced akathisia	Reduce antipsychotic dose Propranolol 10 mg two to three times daily Benzodiazepine
Neuroleptic malignant syndrome	Discontinue offending agent Medical intensive care/support: Cooling Hydration Anticoagulation Dantrolene Benzodiazepine Electroconvulsive therapy
Anticholinergic delirium	Discontinue offending agent(s) Supportive measures



<b>Emergency</b>		<b>Intervention</b>
Hypertensive crisis		Management of blood pressure
Serotonin syndrome		Supportive measures Discontinue offending agent Medical supportive measures/intensive care Benzodiazepine
Priapism		Discontinue offending agent Medical supportive measures Urology evaluation if condition does not resolve
Selective reuptake discontinuation syndrome	serotonin inhibitor	Reassurance; restart medications

## Assaultive, Aggressive, or Violent Behavior

Assaultive, aggressive, and violent behaviors can have many different etiologies, including psychotic or delusional ideation secondary to a primary psychotic or mood disorder, intoxication, acute confusional states associated with dementia and delirium, rage attacks in patients with

personality disorders, and deliberate, volitional acts by antisocial individuals. The most important chronic risk factor for predicting violent behavior is a history of such behavior. Acute risk factors include over- or undercontrolled behavior. The former refers to a patient with decreased psychomotor activity, tension, anger, and paranoia, whereas the latter refers to a patient who is agitated, intrusive, and verbally provocative. Intoxication is an independent acute risk factor that can potentiate violent behaviors in patients with many different diagnoses.

A well-trained staff of an adequate number in an appropriately designed facility is the best strategy for preventing violent episodes. Staff members who are trained to respond in a calm, deliberate, and nonthreatening manner help to establish an atmosphere of order and control. Preventing a violent act from occurring is preferable to responding to a violent act after it has occurred. It is better to have a patient take a medication voluntarily and orally before his or her behavior has escalated than to be required to involuntarily medicate the patient after a crisis has occurred. Research has suggested that clinicians may overutilize intramuscular injections because they are easy to administer ([Damsa et al. 2006](#)).

There are several pharmacological options in the acute management of the agitated patient. Orally available agents include benzodiazepines and antipsychotics. Lorazepam in 2-mg doses given every 45–60 minutes will sedate most patients by the second dose. Other alternatives are 15–20 mg of olanzapine, 4–6 mg of risperidone, or 5 mg of haloperidol in a single oral dose. If a patient with a known diagnosis of schizophrenia or bipolar disorder is experiencing a psychotic or manic decompensation, a second-generation (atypical) antipsychotic should be used.

If the diagnosis is not known or is unclear, then lorazepam is a better choice, especially in view of the fact that acute intoxication with some agents—for example, anticholinergics such as diphenhydramine—may be worsened by the addition of second-generation antipsychotics.

New alternatives to the established pill or tablet formulations of second-generation antipsychotics are available and have demonstrated positive results in comparative trials. Risperidone M-Tab, Zyprexa Zydis, and Abilify Discmelt are rapidly dissolving forms of their parent agents. Risperidone is also available in an oral concentrate solution. These formulations exhibit benefit over the traditional pill formulation for patients who “cheek” medications (i.e., store the administered pill in their cheeks and subsequently dispose of it rather than swallowing it) ([Allen et al. 2001, 2005](#)). The FDA recently approved an inhaled form (marketed under the name Adasuve) of loxapine, a first-generation antipsychotic with second-generation properties ([Alexza Pharmaceuticals, Inc. 2016](#)). This route of administration may have a more rapid onset of action than other formulations; however, the overall clinical utility and safety of this agent have yet to be determined.

Involuntary administration of psychotropic medications is permitted in behavioral emergencies, although rather wide variations exist in the legal definitions and rules regarding the practice of administering involuntary medication. Clinicians should be well informed about the local definitions and regulations regarding involuntary administration of psychotropic medication. Accurate and timely documentation of the need for restraint and involuntary medication administration is essential.

Currently, six medications are suitable for intravenous or intramuscular administration in behavioral emergencies: the benzodiazepines lorazepam and diazepam; the first-generation antipsychotic haloperidol; and the second-generation antipsychotics olanzapine, ziprasidone, and aripiprazole. Lorazepam is the most useful and should be the mainstay for controlling behavioral emergencies ([Battaglia et al. 1997](#); [Foster et al. 1997](#); [Salzman et al. 1991](#)). Lorazepam is rapidly absorbed from intramuscular injections, has a rapid onset of action and a short half-life, and is anxiolytic as well as sedating. Patients who are being combative generally are experiencing high levels of fear or anxiety, so the anxiolytic properties of lorazepam are an additional advantage. Absorption of intramuscular diazepam can be erratic; therefore, this medication is not particularly useful. Haloperidol should be reserved for patients who are clearly psychotic, with the expectation that they will be receiving long-term treatment with an antipsychotic agent.

In a behavioral emergency, a sufficiently large dose should be given with the first injection to ensure rapid onset of sedation and to minimize the need for a second or third injection. Lorazepam should be administered in 2-mg doses that can be repeated at 45 minutes if the initial dose is not sufficient. Very rarely will any additional injections be required after a second 2-mg dose of lorazepam. The initial haloperidol injection should be 2.5–5.0 mg and should not be repeated for at least 2 hours. Sufficient time must be given for the medication to be absorbed and for maximal sedation to occur. Under no circumstances should a patient receive more than 5 mg of haloperidol in a single injection or more than two injections (10 mg) in 24 hours, which can provoke a severe dystonic reaction. To prevent dystonia, 1

mg of benztropine should be included with intramuscular haloperidol. Alternatively, 25 mg of diphenhydramine may be added to prevent dystonia while providing additional sedation. The combination of lorazepam and haloperidol in a ratio of 2 mg of lorazepam to 5 mg of haloperidol is often used to provide adequate sedation and anxiolysis while treating the underlying psychosis.

The injectable second-generation antipsychotics should be reserved for patients who will be given an oral second-generation agent after the immediate emergency has resolved. Intramuscular ziprasidone has been studied in patients with schizophrenia who were psychotic and agitated and is currently indicated for the treatment of these conditions ([Daniel et al. 2001](#); [Lesem et al. 2001](#)). In these clinical trials, patients received an initial injection of 10 mg, followed by injections of 5–20 mg every 4–6 hours, for a maximum dose of 80 mg in 24 hours. The package insert for intramuscular ziprasidone ([Pfizer, Inc. 2015](#)) recommends doses of 10–20 mg, with 10-mg doses repeatable at 2-hour intervals or 20-mg doses at 4-hour intervals. The maximum recommended intramuscular dose in 24 hours is 40 mg. Intramuscular ziprasidone appears to have a low incidence of extrapyramidal side effects compared with intramuscular haloperidol ([Brook et al. 2000](#)). Results from one naturalistic study suggest that the use of intramuscular ziprasidone may reduce time in restraints for agitated patients compared with treatment with a first-generation agent ([Preval et al. 2005](#)).

Injectable olanzapine has been studied for use in agitated patients with schizophrenia, bipolar mania, or dementia ([Breier et al. 2002](#); [Meehan et al. 2001, 2002](#); [Wright et al. 2001](#)). In the schizophrenia trials, patients received up to three individual injections of 2.5–10.0 mg in 24 hours, with

the higher doses producing more significant and sustained reduction of agitation. In the bipolar trials, patients received up to three injections of 5 or 10 mg of olanzapine in 24 hours, with significant reduction in agitated behaviors. In the dementia trial, agitated patients received up to three olanzapine injections of 2.5 or 5 mg in 24 hours, with significant reduction in agitation. A review of the literature by [Tulloch and Zed \(2004\)](#) concluded that injectable olanzapine was superior to placebo in all study populations and to intramuscular lorazepam in patients with bipolar disorder. However, this review further concluded that injectable olanzapine did not differ significantly from intramuscular haloperidol or lorazepam in the management of agitation associated with schizophrenia/schizoaffective disorder or dementia. It is relevant to note that olanzapine is FDA approved for the treatment of schizophrenia and bipolar mania, but not for management of agitation associated with dementia.

Injectable aripiprazole is approved for the treatment of agitation in patients with schizophrenia and bipolar mania. Efficacy studies found that injectable aripiprazole at a dose of 9.75 mg was superior to placebo and comparable to injectable olanzapine. Injectable aripiprazole demonstrated tolerability and symptom reduction without oversedation ([Tran-Johnson et al. 2007](#)).

## Schizophrenia

Atypical (second-generation) antipsychotics represent the current standard of care for the treatment of acute agitation in patients with schizophrenia ([American Psychiatric Association 2004](#)). With proven efficacy and improved tolerability in comparison with haloperidol, these agents represent the first-line treatment in the agitated

psychotic patient ([Aleman and Kahn 2001](#); [Currier and Trenton 2002](#); [Yildiz et al. 2003](#)). The optimal intervention in a patient with schizophrenia who is experiencing an acute exacerbation is to rapidly initiate treatment with a second-generation antipsychotic. In this regard, risperidone and olanzapine are the most useful agents, because both can be initiated at a high therapeutic dose (15–20 mg for olanzapine; 4–6 mg for risperidone) and can be given in multiple oral doses (two or three doses) over a period of 24 hours.

In a patient who is too disorganized or combative to take medication orally, intramuscular administration is the only viable route. Currently, chlorpromazine, haloperidol, ziprasidone, olanzapine, and aripiprazole are available in injectable preparations. In a patient who is psychotic and agitated, coadministration of a benzodiazepine during the first few days of treatment can be particularly effective in controlling behavior while the antipsychotic response develops. Studies suggest that this combination may reduce the total antipsychotic dosage required and potentially result in fewer adverse antipsychotic effects ([Salzman et al. 1991](#); [Yildiz et al. 2003](#)). One caveat to this choice of treatment is the increased risk of sedation and cardiorespiratory depression associated with the combined use of intramuscular olanzapine and intramuscular lorazepam, which led to a black box warning in the prescribing information provided by Eli Lilly, the manufacturer of olanzapine ([Lilly USA 2017](#)).

## **Bipolar Disorder**

The goal of managing acutely manic patients is to rapidly establish a long-term definitive treatment regimen, which means initiating a mood-stabilizing agent such as lithium

(10–20 mg/kg) or valproic acid (20–30 mg/kg) as soon as possible. Prior to initiating either of these two agents, a serum pregnancy test should be obtained and documented as negative, since both agents are teratogenic. Both lithium and valproic acid require time to reach a therapeutic blood level and may take up to 14 days to become fully effective. Until steady state is established, behavioral control can be achieved with oral or intramuscular lorazepam on an as-needed basis or with a second-generation antipsychotic such as olanzapine, risperidone, ziprasidone, quetiapine, or aripiprazole, all of which are FDA approved for the treatment of acute bipolar mania. Olanzapine, risperidone, and quetiapine have the advantage of being sedating, which can be useful in an emergency room setting. A review of the literature indicated that intramuscular olanzapine was superior to lorazepam monotherapy in the treatment of agitated manic patients ([Tulloch and Zed 2004](#)). If the long-term plans do not include an antipsychotic, lorazepam or another benzodiazepine should be used for short-term behavioral control. If, however, the plan is to use both a mood stabilizer and an antipsychotic for long-term management, an antipsychotic should be substituted for the benzodiazepine.

## **Substance Intoxication**

Violent and combative behavior by intoxicated patients is a very common occurrence in psychiatric and medical emergency departments. Alcohol, cocaine, PCP, methamphetamines,  $\gamma$ -hydroxybutyrate (GHB), and hallucinogens and “designer” drugs (modified cathinones such as bath salts and Flakka) can lead to violent behavior. Recent research in a large urban psychiatric emergency room suggests that use of designer drugs may be a larger



problem than was previously appreciated. In this analysis, standard urine drug screening systems missed a significant number of cases of drug ingestion. Use of a more sensitive enzyme-linked immunosorbent assay (ELISA) and gas chromatography-mass spectrometry (GC-MS) system identified patients who had ingested opiates and amphetamines that were not detected by the standard screening test. This more sensitive detection system also identified a number of patients who had used designer drugs such as cathinone derivatives and tryptamines, which are not detectable with standard screening systems ([Reidy et al. 2014](#)).

Ethanol intoxication is a very common cause of violent behavior. The appropriate interventions are physical restraint and sedation with a benzodiazepine or haloperidol if the agitation is significant, to allow the patient to become sober. Once a patient's blood alcohol level is below the legal limit for intoxication, a more definitive evaluation can be carried out, focusing on presence of an underlying psychiatric diagnosis or other treatment needs.

Prolonged cocaine use can lead to development of both mood and psychotic syndromes. Transient paranoid states are very common in cocaine users, as are frank delusions and hallucinations. Agitated, paranoid states accompanying cocaine intoxication can lead to significant violent behavior. Interventions include seclusion and restraint, use of intramuscular lorazepam, and use of an antipsychotic if the patient is frankly psychotic. When the patient is no longer intoxicated, the presence of underlying psychopathology can be assessed.

PCP intoxication can be particularly provocative of agitated, combative, and violent behavior. Fortunately (or unfortunately), PCP use tends to occur in localized

geographical regions. In areas where PCP use is common, intoxicated persons are common in emergency facilities. PCP intoxication can present with frank psychotic symptoms, agitation, disorientation, and disorganized behavior. Violent outbursts can be sudden, unprovoked, and unexpected. Patients in the throes of PCP intoxication can be very insensitive to pain, so they are prone to continue to fight even if seriously injured. Adequate numbers of well-trained staff are essential when dealing with patients who have been using PCP. Restraint rooms should be dark and quiet so as to minimize stimulation. Intramuscular lorazepam should be used to sedate the patient. The half-life of PCP is 20 hours, so these behavioral states can persist for several days before fully resolving.

Methamphetamine; designer drugs such as bath salts and Flakka, which are amphetamine-like; and GHB can cause agitated, disorganized, and violent behavior. Methamphetamine in particular can have behavioral consequences very similar to those of cocaine. Because of the long half-life of methamphetamine compared with cocaine, this drug can be particularly provocative of frank paranoid and psychotic symptoms. There have been significant increases in cases of intoxication with designer drugs such as bath salts and Flakka in some localities. These patients can have psychotic, paranoid, agitated, and violent presentations.

Presenting symptoms of methamphetamine intoxication often include agitation, hallucinations, suicidal ideation, and chest pain ([Derlet et al. 1989](#)). Distinguishing stimulant intoxication from other clinical conditions can be challenging, given the symptom overlap. Generally, stimulant-induced psychosis tends to be distinguishable from primary psychotic disorders by the absence of a

thought disorder and a prominence of visual hallucinations ([Harris and Batki 2000](#)). However, given the potential for comorbidity, a positive drug screen does not completely discount the diagnosis of a mood or psychotic disorder. Treatment should focus on maintaining the patient's safety while awaiting the drug's metabolism and dissipation from the patient's system.

## **Delirium**

Patients with delirium can become disorganized, agitated, and combative. Delirium is defined as a state of disturbance in attention, awareness, and cognition, during which the symptoms occur rapidly and fluctuate with time. Delirium may be due to a general medical condition or to substance intoxication or withdrawal; it may also be secondary to multiple etiologies ([American Psychiatric Association 2013](#)). Delirium is a medical emergency and carries a very high burden of morbidity and mortality. The definitive treatment of delirium requires diagnosing the underlying cause and taking corrective action. Interventions aimed at controlling behavior include restraints, environmental modification including frequent reorientation of the patient, and use of intravenous haloperidol. Behavioral control is essential so that the patient does not further injure him- or herself or interfere with treatment and to protect staff and other patients. The first intravenous dose of haloperidol should be 2.5 mg. If the patient is still agitated after 2 hours, the dose should be increased to 5 mg. This dose can be repeated in another 2 hours if the patient continues to be agitated. Once the patient is stabilized, a routine antipsychotic regimen should be initiated, dividing the total dose into two or four regular doses. The antipsychotic can be decreased

and discontinued as the delirium clears. Benzodiazepines are generally contraindicated in cases of delirium.

## **Dementia**

Patients with dementia can become agitated, combative, or psychotic for many different reasons. The most common cause for these symptoms is a delirium superimposed on the dementia. Definitive diagnosis and treatment of the disorder causing the delirium are essential to achieving adequate long-term resolution. Patients with dementia who are not delirious can become agitated as a result of confusion or psychosis inherent in the neurodegenerative pathology. In these cases, the best interventions are nonpharmacological and include environmental modification, behavior modification, and supportive measures. Aggressive behavior in patients with dementia can be treated pharmacologically, in the short term with low-dose antipsychotics and in the long term with low-dose antipsychotics, the anticonvulsants carbamazepine or valproic acid, the  $\beta$ -blocker propranolol, the SSRI antidepressants, or the anxiolytic drug buspirone. As is true in all geriatric prescribing, low doses and slow titration schedules are the appropriate course. Second-generation antipsychotics are not approved for the treatment of dementia-related psychosis, and the prescribing information carries a black box warning regarding an increased risk of death from cerebrovascular events (e.g., sudden cardiac arrest) and infections (e.g., pneumonia) in elderly patients who are treated with these agents ([Schneider et al. 2005](#)).

## **Substance Withdrawal States**

## Alcohol and Sedative-Hypnotics

Alcohol or sedative-hypnotic withdrawal can result in a frank delirium that is life-threatening ([Marco and Kelen 1990](#); [Olmedo and Hoffman 2000](#)). The acute signs of early alcohol, sedative-hypnotic, and benzodiazepine withdrawal are similar and include autonomic instability, tremulousness, diaphoresis, and gastrointestinal disturbances. Autonomic signs include tachycardia, hypertension, and hyperthermia. Treatment of this withdrawal state is best accomplished with symptom-triggered (vital signs and/or Clinical Institute Withdrawal Assessment [CIWA] scores) administration of a long-half-life benzodiazepine. Use of long-half-life agents such as diazepam or chlordiazepoxide prevents peaks and troughs in blood levels. During the first 72 hours, vital signs and/or CIWA scores should be obtained at 2- to 4-hour intervals and additional benzodiazepine given if vital signs are still elevated. This approach has been shown to reduce total time and medication exposure in the detoxification phase. It is important to consider concomitant medications, given that  $\beta$ -blockers prescribed for a general medical condition may mask the autonomic signs of withdrawal.

Alcohol withdrawal delirium (delirium tremens) is a life-threatening medical condition ([Erwin et al. 1998](#)). This syndrome has a very high mortality rate—up to 35% in untreated patients and as high as 5%-15% in optimally treated patients. The delirium usually develops 48-72 hours after discontinuation of alcohol or sedative-hypnotics, peaks around day 4, and can persist for weeks. The symptoms include autonomic instability, fever, disorientation, perceptual disturbances and hallucinations, agitation, and confusion. Patients with delirium tremens should be treated

in a medical intensive care unit. These patients typically require physical restraint and vigorous supportive measures. Intravenous haloperidol can be used to control agitation and psychosis. High doses of benzodiazepines have also been used in this situation to manage agitated behavior.

Wernicke-Korsakoff syndrome is another consequence of long-term alcohol use. Wernicke encephalopathy is the symptom complex of ophthalmoplegia, ataxia, and an acute confusional state. Wernicke-Korsakoff syndrome is diagnosed if persistent learning and memory deficits are also present. Alcoholic patients should receive three daily 100-mg doses of thiamine via the intramuscular route from the day of presentation, followed by three daily oral doses to prevent development of this syndrome. Patients should receive the first intramuscular dose before oral or intravenous administration of a carbohydrate load in order to prevent rapid thiamine depletion and emergent development of Wernicke-Korsakoff syndrome. Patients should also be given folic acid and magnesium replacement supplementation.

## **Opiates**

Opiate withdrawal can be exceedingly uncomfortable for the patient but, unlike alcohol and sedative-hypnotic withdrawal, is generally not life-threatening. Accordingly, the goal of opiate withdrawal treatment is relief of pain and suffering. Symptoms of opiate withdrawal include dysphoria, anxiety, irritability, craving, mydriasis, piloerection, diaphoresis, nausea, vomiting, diarrhea, rhinorrhea, lacrimation, insomnia, fever, and hypertension. Onset of this syndrome depends on the half-life of the drug used and with heroin is usually 6–8 hours after the last use.

The syndrome can last 2–5 days, depending on the individual patient. Clonidine in doses of 0.1–0.3 mg every 3 hours, up to 0.8 mg/day, can be given to suppress signs of opiate withdrawal ([Ahmadi-Abhari et al. 2001](#); [Akhondzadeh et al. 2000](#); [Charney et al. 1981](#); [Gossop 1988](#)). A major side effect of this regimen is hypotension, so the regimen must be carried out in a medically supervised setting. Clonidine should be avoided in patients who are dependent on both opiates and alcohol or a sedative-hypnotic; clonidine may mask the autonomic signs of ethanol withdrawal without actually preventing the emergence of delirium tremens. Other agents commonly utilized for symptomatic opiate withdrawal include promethazine or ondansetron, loperamide, ibuprofen, methocarbamol, and hydroxyzine.

## Psychotropic Medication Side Effects

### Antipsychotics

Several adverse events can occur in patients taking antipsychotics. Dystonic reactions are characterized by extreme muscle contraction and rigidity in a patient with stable vital signs and a clear sensorium. These occur most frequently with high-potency first-generation antipsychotics ([Moleman et al. 1982](#); [Schillevoort et al. 2001](#)). Young males are particularly susceptible to dystonic reactions. Most dystonic reactions are extremely uncomfortable and frightening to the patient. Treatment of these reactions is typically 1–2 mg of benztropine via the oral or intramuscular route. An alternative is diphenhydramine in doses of 25–50 mg via the oral or intramuscular route. Dystonias that include the eyes, the so-called oculogyric

crises, are particularly frightening, as are dystonias that cause laryngeal spasms, which can compromise the airway. These reactions should be treated with 50 mg of intramuscular diphenhydramine, which provides rapid relief. Maintenance treatment of 1-2 mg of benztropine twice a day or 25-50 mg of diphenhydramine twice a day should be initiated after the acute reaction has resolved ([Keepers et al. 1983](#)).

Akathisia is a syndrome characterized by internal restlessness, often perceived as the need to be in motion. This leads to increased psychomotor activity, including pacing, rocking, leg tapping and bouncing, and moving frequently between sitting and standing. The patient may complain of feeling anxious or irritable, or of having the sensation that his or her “skin is crawling.” Lowering the dosage of the antipsychotic or switching to a second-generation antipsychotic are treatment options. Propranolol in doses of 10 mg two or three times a day is an effective treatment for akathisia.

Neuroleptic malignant syndrome (NMS) is a potentially fatal delirium that develops in some patients in response to antipsychotic agents ([Susman 2001](#)). The diagnosis is made on the triad of symptoms of altered level of consciousness, muscular rigidity (often described as lead-pipe rigidity), and autonomic instability. The autonomic instability includes hyperthermia, tachycardia, labile blood pressure, diaphoresis, incontinence, and occasional dysphagia and bowel obstruction. Associated findings include elevated creatine phosphokinase (CPK), elevated white blood cell count, and metabolic acidosis. Later complications include rhabdomyolysis and renal failure. The main interventions in NMS are discontinuation of the offending agent and provision of general supportive measures, including



cooling, rehydration, intensive nursing care, and anticoagulation. A few drugs have been used to treat NMS, including benzodiazepines, bromocriptine (15 mg/day), dantrolene (100–300 mg/day), and amantadine (200 mg/day). ECT also has been used to treat NMS.

The atypical antipsychotic clozapine can cause catastrophic agranulocytosis in up to 1% of patients treated. This usually occurs within 6 weeks to 6 months of initiating therapy with clozapine. A white blood cell count of less than  $3,500/\text{mm}^3$  or a granulocyte count of less than  $1,500/\text{mm}^3$  warrants discontinuation of the medication. Other signs of impending marrow failure are fever, flulike symptoms, and sore throat. Discontinuation of the clozapine, supportive measures, and treatment of specific infections if identified are the main interventions for agranulocytosis, and in life-threatening cases, growth factors (filgrastim [Neupogen]) can be used.

## **Antidepressants**

Adverse events associated with tricyclic antidepressants include anticholinergic delirium, cardiac conduction delays, and seizures. Anticholinergic delirium is more common in elderly and impaired individuals and may be potentiated by concomitant anticholinergic medications. The principal intervention is to decrease or discontinue the offending agent. Furthermore, the coadministration of an SSRI or other drug known to inhibit the cytochrome P450 2D6 enzyme with a tricyclic antidepressant can cause dramatic increases in tricyclic antidepressant blood levels and resultant delirium. These drugs also can affect cardiac conduction, can lower seizure thresholds, and are lethal in overdose.

A hypertensive crisis can occur in a patient who is taking monoamine oxidase inhibitors. This usually happens after ingestion of a large dose of tyramine (which can be found in certain food products) or after an interaction with another drug (e.g., meperidine, other antidepressants, sympathomimetic agents). Discontinuation of the monoamine oxidase inhibitor and management of the hypertension are the appropriate treatments.

Serotonin syndrome is a delirium characterized by altered level of consciousness, autonomic instability, and neuromuscular abnormalities including myoclonus, hyperreflexia, nystagmus, akathisia, and muscle rigidity ([Martin 1996](#); [Mason et al. 2000](#)). Several different drugs, usually administered in combination, can cause this adverse event. Drugs reported to provoke serotonin syndrome include SSRIs, tricyclic antidepressants, monoamine oxidase inhibitors, venlafaxine, trazodone, nefazodone, lithium, tryptophan, meperidine, sumatriptan, buspirone, duloxetine, milnacipran, and amphetamines. Discontinuation of the offending agent and general supportive measures are the principal interventions. Unlike in NMS, bromocriptine can worsen the serotonin syndrome. Other drugs useful in treating this condition are benzodiazepines, cyproheptadine, chlorpromazine, methysergide, and propranolol.

Although not a life-threatening emergency, SSRI discontinuation syndrome can be very frightening and distressing to patients. This syndrome develops after abrupt discontinuation of a short-half-life SSRI, with paroxetine and venlafaxine the two most common agents. Symptoms include dizziness, malaise, nausea, paresthesias, tremor, ataxia, confusion, myoclonus, anxiety, and vivid dreaming. Symptoms usually develop 48 hours after the last dose,

peak around day 4-5, and can last as long as 2 weeks. Interventions include reassuring the patient and restarting the medicine, followed by a very gradual taper.

Priapism is a rare but potentially serious adverse event that has been associated with psychotropic medications including trazodone. This physiological condition is usually self-limiting. However, a patient with an erection lasting for more than 4 hours warrants an evaluation and treatment by appropriate medical personnel ([Montague et al. 2003](#)). Patients should be warned of this rare but serious potential side effect.

---

## Conclusion

---

In the modern era, with changes in the mental health care delivery systems and the resultant limitations placed on the utilization of inpatient treatment resources, the emergency psychiatrist will increasingly be called upon to diagnose and initiate definitive treatment of patients with a wide range of psychiatric disorders. Emergency psychiatrists must balance the needs of individual patients with those of the larger community, the health care system, and the third-party payer system, with a focus on delivering care that is both efficacious and cost-effective. This requires a broad knowledge base, incorporating elements of all branches of psychiatry, and consideration of thorough yet expeditious evaluation, diagnosis, and treatment of patients with mental illnesses.

---

## References

---

- Ahmadi-Abhari SA, Akhondzadeh S, Assadi SM, et al: Baclofen versus clonidine in the treatment of opiates withdrawal, side-effects aspect: a double-blind randomized controlled trial. *J Clin Pharm Ther* 26(1):67-71, 2001 11286609
- Akhondzadeh S, Ahmadi-Abhari SA, Assadi SM, et al: Double-blind randomized controlled trial of baclofen vs. clonidine in the treatment of opiates withdrawal. *J Clin Pharm Ther* 25(5):347-353, 2000 11123486
- Aleman A, Kahn RS: Effects of the atypical antipsychotic risperidone on hostility and aggression in schizophrenia: a meta-analysis of controlled trials. *Eur Neuropsychopharmacol* 11(4):289-293, 2001 11532383
- Alexza Pharmaceuticals, Inc.: ADASUVE (loxapine) inhalation powder, full prescribing information. Mountain View, CA, Alexza Pharmaceuticals, Inc., 2016. Available at: <http://www.adasuve.com/PDF/AdasuvePI.pdf>. Accessed January 2017.
- Allen MH, Currier GW, Hughes DH, et al; Expert Consensus Panel for Behavioral Emergencies: The Expert Consensus Guideline Series. Treatment of behavioral emergencies. *Postgrad Med (Spec No)*:1-88, quiz 89-90, 2001 11500996
- Allen MH, Currier GW, Carpenter D, et al; Expert Consensus Panel for Behavioral Emergencies 2005: The expert consensus guideline series. Treatment of behavioral emergencies 2005. *J Psychiatr Pract* 11 (suppl 1):5-108, quiz 110-112, 2005 16319571
- American Psychiatric Association: Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 61 (2 suppl):1-56, 2004 15000267
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013

- Angst F, Stassen HH, Clayton PJ, Angst J: Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord* 68(2–3):167–181, 2002 12063145
- Appleby L, Shaw J, Amos T, et al: Suicide within 12 months of contact with mental health services: national clinical survey. *BMJ* 318(7193):1235–1239, 1999 10231250
- Apter A, Kotler M, Sevy S, et al: Correlates of risk of suicide in violent and nonviolent psychiatric patients. *Am J Psychiatry* 148(7):883–887, 1991 2053628
- Ballard ED, Ionescu DF, Vande Voort JL, et al: Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. *J Psychiatr Res* 58:161–166, 2014 25169854
- Ballenger JC, Davidson JR, Lecrubier Y, et al: Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 61 (suppl 5): 60–66, 2000 10761680
- Ballenger JC, Davidson JRT, Lecrubier Y, et al: Consensus statement update on posttraumatic stress disorder from the international consensus group on depression and anxiety. *J Clin Psychiatry* 65 (suppl 1): 55–62, 2004 14728098
- Battaglia J, Moss S, Rush J, et al: Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 15(4):335–340, 1997 9217519
- Bennett JI, Dzara K, Mazhar MN, et al: A preliminary report on resident emergency psychiatry training from a survey of psychiatry chief residents. *J Grad Med Educ* 3(1):21–25, 2011 22379518
- Borum R, Reddy M: Assessing violence risk in Tarasoff situations: a fact-based model of inquiry. *Behav Sci Law* 19(3):375–385, 2001 11443698
- Brasch J, Glick RL, Cobb TG, Richmond J: Residency training in emergency psychiatry: a model curriculum developed

by the education committee of the american association for emergency psychiatry. Acad Psychiatry 28(2):95-103, 2004 15298860

Breier A, Meehan K, Birkett M, et al: A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Arch Gen Psychiatry 59(5):441-448, 2002 11982448

Brook S, Lucey JV, Gunn KP; Ziprasidone I.M. Study Group: Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. J Clin Psychiatry 61(12):933-941, 2000 11206599

Brown GK, Jager-Hyman S: Evidence-based psychotherapies for suicide prevention: future directions. Am J Prev Med 47 (3 suppl 2):S186-S194, 2014 25145738

Brown GK, Ten Have T, Henriques GR, et al: Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. JAMA 294(5):563-570, 2005 16077050

Busch KA, Fawcett J, Jacobs DG: Clinical correlates of inpatient suicide. J Clin Psychiatry 64(1):14-19, 2003 12590618

Campfield KM, Hills AM: Effect of timing of critical incident stress debriefing (CISD) on posttraumatic symptoms. J Trauma Stress 14(2):327-340, 2001 11469160

Centers for Disease Control and Prevention: FastStats: Suicide and Self-Inflicted Injury. Updated September 30, 2015. Available at: <http://www.cdc.gov/nchs/fastats/suicide.htm>. Accessed October 23, 2015.

Charney DS, Sternberg DE, Kleber HD, et al: The clinical use of clonidine in abrupt withdrawal from methadone. Effects on blood pressure and specific signs and symptoms. Arch Gen Psychiatry 38(11): 1273-1277, 1981 7305608

- Conwell Y, Duberstein PR, Cox C, et al: Relationships of age and Axis I diagnoses in victims of completed suicide: a psychological autopsy study. *Am J Psychiatry* 153(8):1001-1008, 1996 8678167
- Conwell Y, Duberstein PR, Connor K, et al: Access to firearms and risk for suicide in middle-aged and older adults. *Am J Geriatr Psychiatry* 10(4):407-416, 2002 12095900
- Cornelius JR, Thase ME, Salloum IM, et al: Cocaine use associated with increased suicidal behavior in depressed alcoholics. *Addict Behav* 23(1):119-121, 1998 9468750
- Currier GW, Trenton A: Pharmacological treatment of psychotic agitation. *CNS Drugs* 16(4):219-228, 2002 11945106
- Damsa C, Ikelheimer D, Adam E, et al: Heisenberg in the ER: observation appears to reduce involuntary intramuscular injections in a psychiatric emergency service. *Gen Hosp Psychiatry* 28(5):431-433, 2006 16950380
- Daniel DG, Potkin SG, Reeves KR, et al: Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology (Berl)* 155(2):128-134, 2001 11401000
- Davidson JR: Use of benzodiazepines in social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. *J Clin Psychiatry* 65 (suppl 5):29-33, 2004 15078116
- Deisenhammer EA, Huber M, Kemmler G, et al: Psychiatric hospitalizations during the last 12 months before suicide. *Gen Hosp Psychiatry* 29(1):63-65, 2007 17189748
- Derlet RW, Rice P, Horowitz BZ, Lord RV: Amphetamine toxicity: experience with 127 cases. *J Emerg Med* 7(2):157-161, 1989 2661673

- Dervic K, Oquendo MA, Grunebaum MF, et al: Religious affiliation and suicide attempt. *Am J Psychiatry* 161(12):2303-2308, 2004 15569904
- Dervic K, Oquendo MA, Currier D, et al: Moral objections to suicide: Can they counteract suicidality in patients with cluster B psychopathology? *J Clin Psychiatry* 67(4):620-625, 2006 16669727
- DiazGranados N, Ibrahim LA, Brutsche NE, et al: Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 71(12):1605-1611, 2010 20673547
- Durkheim E: *Suicide*. Translated by Spaulding JA, Simpson G. New York, Free Press, 1951
- Erwin WE, Williams DB, Speir WA: Delirium tremens. *South Med J* 91(5):425-432, 1998 9598848
- Fawcett J: Suicide risk factors in depressive disorders and in panic disorder. *J Clin Psychiatry* 53 (suppl):9-13, 1992 1548256
- Fawcett J, Scheftner WA, Fogg L, et al: Time-related predictors of suicide in major affective disorder. *Am J Psychiatry* 147(9): 1189-1194, 1990 2104515
- Fink M: Catatonia: syndrome or schizophrenia subtype? Recognition and treatment. *J Neural Transm* 108(6):637-644, 2001 11478416
- Fink M, Taylor MA: Catatonia: subtype or syndrome in DSM? *Am J Psychiatry* 163(11):1875-1876, 2006 17074935
- Foa EB, Steketee G, Rothbaum BO: Behavioral/cognitive conceptualizations of post-traumatic stress disorder. *Behav Ther* 20:(2):155-176, 1989
- Foster S, Kessel J, Berman ME, Simpson GM: Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting. *Int Clin Psychopharmacol* 12(3):175-179, 1997 9248875



- Fowler RC, Rich CL, Young D: San Diego Suicide Study. II. Substance abuse in young cases. *Arch Gen Psychiatry* 43(10):962-965, 1986 3753161
- Frame DS, Kercher EE: Acute psychosis. Functional versus organic. *Emerg Med Clin North Am* 9(1):123-136, 1991 2001662
- Garlow SJ: Age, gender, and ethnicity differences in patterns of cocaine and ethanol use preceding suicide. *Am J Psychiatry* 159(4):615-619, 2002 11925300
- Garlow SJ, D'Orio B, Purselle DC: The relationship of restrictions on state hospitalization and suicides among emergency psychiatric patients. *Psychiatr Serv* 53(10):1297-1300, 2002 12364678
- Garlow SJ, Purselle D, D'Orio B: Cocaine use disorders and suicidal ideation. *Drug Alcohol Depend* 70(1):101-104, 2003 12681530
- Garlow SJ, Purselle D, Heninger M: Ethnic differences in patterns of suicide across the life cycle. *Am J Psychiatry* 162(2):319-323, 2005 15677597
- Garlow SJ, Purselle DC, Heninger M: Cocaine and alcohol use preceding suicide in African American and white adolescents. *J Psychiatr Res* 41(6):530-536, 2007 16203014
- Gelpin E, Bonne O, Peri T, et al: Treatment of recent trauma survivors with benzodiazepines: a prospective study. *J Clin Psychiatry* 57(9):390-394, 1996 9746445
- Gitlin MJ: A psychiatrist's reaction to a patient's suicide. *Am J Psychiatry* 156(10): 1630-1634, 1999 10518176
- Gossop M: Clonidine and the treatment of the opiate withdrawal syndrome. *Drug Alcohol Depend* 21(3):253-259, 1988 3048954
- Greenberg N: A critical review of psychological debriefing: the management of psychological health after traumatic experiences. *J R Nav Med Serv* 87(3):158-161, 2001 11974426

- Hall KT, Appelbaum PS: The origins of commitment for substance abuse in the United States. *J Am Acad Psychiatry Law* 30(1):33-45, discussion 46-48, 2002 11931367
- Hall RC, Popkin MK, Devaul RA, et al: Physical illness presenting as psychiatric disease. *Arch Gen Psychiatry* 35(11):1315-1320, 1978 568461
- Hall RC, Gardner ER, Popkin MK, et al: Unrecognized physical illness prompting psychiatric admission: a prospective study. *Am J Psychiatry* 138(5):629-635, 1981 7235058
- Hall RC, Platt DE, Hall RC: Suicide risk assessment: a review of risk factors for suicide in 100 patients who made severe suicide attempts. Evaluation of suicide risk in a time of managed care. *Psychosomatics* 40(1):18-27, 1999 9989117
- Harris D, Batki SL: Stimulant psychosis: symptom profile and acute clinical course. *Am J Addict* 9(1):28-37, 2000 10914291
- Harris EC, Barraclough B: Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry* 170:205-228, 1997 9229027
- Hendin H, Lipschitz A, Maltsberger JT, et al: Therapists' reactions to patients' suicides. *Am J Psychiatry* 157(12):2022-2027, 2000 11097970
- Hilty DM, Ferrer DC, Parish MB, et al: The effectiveness of telemental health: a 2013 review. *Telemed J E Health* 19(6):444-454, 2013 23697504
- Hurwitz TA: Somatization and conversion disorder. *Can J Psychiatry* 49(3):172-178, 2004 15101499
- Isometsä ET, Lönnqvist JK: Suicide attempts preceding completed suicide. *Br J Psychiatry* 173:531-535, 1998 9926085
- Katon WJ: Clinical practice. Panic disorder. *N Engl J Med* 354(22):2360-2367, 2006 16738272

- Keepers GA, Clappison VJ, Casey DE: Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. *Arch Gen Psychiatry* 40(10):1113-1117, 1983 6138011
- Kessler RC, Borges G, Walters EE: Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 56(7):617-626, 1999 10401507
- Kroll J: Use of no-suicide contracts by psychiatrists in Minnesota. *Am J Psychiatry* 157(10):1684-1686, 2000 11007726
- Larkin GL, Beautrais AL: A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol* 14(8):1127-1131, 2011 21557878
- Larkin GL, Claassen CA, Emond JA, et al: Trends in U.S. emergency department visits for mental health conditions, 1992 to 2001. *Psychiatr Serv* 56(6):671-677, 2005 15939942
- Lesem MD, Zajecka JM, Swift RH, et al: Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients (erratum appears in *J Clin Psychiatry* 62:209, 2001). *J Clin Psychiatry* 62(1):12-18, 2001 11235922
- Lewis G, Appleby L, Jarman B: Suicide and psychiatric services. *Lancet* 344(8925):822, 1994 7916100
- Lilly USA: ZYPREXA IntraMuscular (olanzapine) injection, powder, for solution for intramuscular use, full prescribing information. Literature revised January 23, 2017. Indianapolis, IN, Lilly USA, LLC. Available at: <http://pi.lilly.com/us/zyprexa-pi.pdf>. Accessed January 2017.
- Malone KM, Oquendo MA, Haas GL, et al: Protective factors against suicidal acts in major depression: reasons for

- living. Am J Psychiatry 157(7):1084-1088, 2000 10873915
- Maltsberger JT, Buie DH: Countertransference hate in the treatment of suicidal patients. Arch Gen Psychiatry 30(5):625-633, 1974 4824197
- Mann JJ, Apter A, Bertolote J, et al: Suicide prevention strategies: a systematic review. JAMA 294(16):2064-2074, 2005 16249421
- Marco CA, Kelen GD: Acute intoxication. Emerg Med Clin North Am 8(4):731-748, 1990 2171904
- Martin TG: Serotonin syndrome. Ann Emerg Med 28(5):520-526, 1996 8909274
- Mason PJ, Morris VA, Balcezak TJ: Serotonin syndrome. Presentation of 2 cases and review of the literature. Medicine (Baltimore) 79(4):201-209, 2000 10941349
- Meehan K, Zhang F, David S, et al: A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. J Clin Psychopharmacol 21(4):389-397, 2001 11476123
- Meehan KM, Wang H, David SR, et al: Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 26(4):494-504, 2002 11927174
- Mellman TA, David D, Bustamante V, et al: Predictors of post-traumatic stress disorder following severe injury. Depress Anxiety 14(4):226-231, 2001 11754130
- Miller M, Azrael D, Hemenway D: Household firearm ownership and suicide rates in the United States. Epidemiology 13(5):517-524, 2002 12192220
- Mitchell JT: When disaster strikes...the critical incident stress debriefing process. JEMS 8(1):36-39, 1983 10258348

- Moleman P, Schmitz PJ, Ladee GA: Extrapyramidal side effects and oral haloperidol: an analysis of explanatory patient and treatment characteristics. *J Clin Psychiatry* 43(12):492-496, 1982 7161250
- Montague DK, Jarow J, Broderick GA, et al; Members of the Erectile Dysfunction Guideline Update Panel; American Urological Association: American Urological Association guideline on the management of priapism. *J Urol* 170(4 Pt 1):1318-1324, 2003 14501756
- Mościcki EK: Identification of suicide risk factors using epidemiologic studies. *Psychiatr Clin North Am* 20(3):499-517, 1997 9323310
- Murphy GE, Wetzel RD: The lifetime risk of suicide in alcoholism. *Arch Gen Psychiatry* 47(4):383-392, 1990 2181963
- Murphy GE, Wetzel RD, Robins E, McEvoy L: Multiple risk factors predict suicide in alcoholism. *Arch Gen Psychiatry* 49(6):459-463, 1992 1599370
- National Center for Injury Prevention and Control: Web-Based Injury Statistics Query and Reporting System (WISQARS). Atlanta, GA, National Center for Injury Prevention and Control, 2002
- National Center for Injury Prevention and Control: Web-Based Injury and Statistics Query and Reporting System (WISCARS). Atlanta, GA, National Center for Injury Prevention and Control, 2005
- Olmedo R, Hoffman RS: Withdrawal syndromes. *Emerg Med Clin North Am* 18(2):273-288, 2000 10767884
- Olofsson B, Jacobsson L: A plea for respect: involuntarily hospitalized psychiatric patients' narratives about being subjected to coercion. *J Psychiatr Ment Health Nurs* 8(4):357-366, 2001 11882148
- Pfizer, Inc.: GEODON (ziprasidone mesylate) injection for intramuscular use, full prescribing information. Revised August 2015. New York, NY, Roerig (Division of Pfizer Inc). Available at:

<http://labeling.pfizer.com/ShowLabeling.aspx?id=584>.

Accessed January 2017.

Pokorny AD: Prediction of suicide in psychiatric patients. Report of a prospective study. Arch Gen Psychiatry 40(3):249-257, 1983 6830404

Pokorny AD: Suicide prediction revisited. Suicide Life Threat Behav 23(1):1-10, 1993 8475527

Preval H, Klotz SG, Southard R, Francis A: Rapid-acting IM ziprasidone in a psychiatric emergency service: a naturalistic study. Gen Hosp Psychiatry 27(2):140-144, 2005 15763126

Price RB, Mathew SJ: Does ketamine have anti-suicidal properties? Current status and future directions. CNS Drugs 29(3):181-188, 2015 25715884

Price RB, Nock MK, Charney DS, Mathew SJ: Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 66(5):522-526, 2009 19545857

Qin P, Agerbo E, Mortensen PB: Suicide risk in relation to family history of completed suicide and psychiatric disorders: a nested case-control study based on longitudinal registers. Lancet 360(9340):1126-1130, 2002 12387960

Qin P, Agerbo E, Mortensen PB: Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: a national register-based study of all suicides in Denmark, 1981-1997. Am J Psychiatry 160(4):765-772, 2003 12668367

Reidy LJ, Junquera P, Van Dijck K, et al: Underestimation of substance abuse in psychiatric patients by conventional hospital screening. J Psychiatr Res 59:206-212, 2014 25262418

Resnick PJ, Scott CL: The prediction of violence, in Aggression and Physical Violence: An Introductory Text. Edited by Hersen M, VanHassett V. Needham Heights, MA, Allyn & Bacon, 2000, pp 284-302

- Romero MP, Wintemute GJ: The epidemiology of firearm suicide in the United States. *J Urban Health* 79(1):39-48, 2002 11937614
- Rosebush PI, Hildebrand AM, Furlong BG, Mazurek MF: Catatonic syndrome in a general psychiatric inpatient population: frequency, clinical presentation, and response to lorazepam. *J Clin Psychiatry* 51(9):357-362, 1990 2211547
- Roy-Byrne PP, Craske MG, Stein MB: Panic disorder. *Lancet* 368(9540):1023-1032, 2006 16980119
- Salzman C, Solomon D, Miyawaki E, et al: Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. *J Clin Psychiatry* 52(4):177-180, 1991 1673123
- Schillevoort I, de Boer A, Herings RM, et al: Risk of extrapyramidal syndromes with haloperidol, risperidone, or olanzapine. *Ann Pharmacother* 35(12):1517-1522, 2001 11793611
- Schneider LS, Dagerman KS, Insel P: Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 294(15):1934-1943, 2005 16234500
- Shore JH, Hilty DM, Yellowlees P: Emergency management guidelines for telepsychiatry. *Gen Hosp Psychiatry* 29(3):199-206, 2007 17484936
- Sijbrandij M, Olff M, Reitsma JB, et al: Treatment of acute posttraumatic stress disorder with brief cognitive behavioral therapy: a randomized controlled trial. *Am J Psychiatry* 164(1):82-90, 2007 17202548
- Simon RI: Psychiatrists' duties in discharging sicker and potentially violent inpatients in the managed care era. *Psychiatr Serv* 49(1):62-67, 1998 9444682
- Simon RI: The suicide prevention contract: clinical, legal, and risk management issues. *J Am Acad Psychiatry Law* 27(3): 445-450, 1999 10509943

- Simon RI: Taking the “sue” out of suicide: a forensic psychiatrist’s perspective. *Psychiatr Ann* 30(6):399–407, 2000
- Simon RI, Gutheil TG: A recurrent pattern of suicide risk factors observed in litigated cases: lessons in risk management. *Psychiatr Ann* 32(7):384–387, 2002
- Simpson SG, Jamison KR: The risk of suicide in patients with bipolar disorders. *J Clin Psychiatry* 60 (suppl 2):53–56; discussion 75–76, 113–116, 1999 10073388
- Soloff PH, Lis JA, Kelly T, et al: Risk factors for suicidal behavior in borderline personality disorder. *Am J Psychiatry* 151(9):1316–1323, 1994 8067487
- Stanley B, Brown G: Safety planning intervention: a brief intervention to mitigate suicide risk. *Cognit Behav Pract* 19(2):256–264, 2012
- Susman VL: Clinical management of neuroleptic malignant syndrome. *Psychiatr Q* 72(4):325–336, 2001 11525080
- Tarasoff v Regents of the University of California, 551 P2d 334 (Cal. 1976)
- Taylor MA, Fink M: Catatonia in psychiatric classification: a home of its own. *Am J Psychiatry* 160(7):1233–1241, 2003 12832234
- Tejedor MC, Díaz A, Castellón JJ, Pericay JM: Attempted suicide: repetition and survival—findings of a follow-up study. *Acta Psychiatr Scand* 100(3):205–211, 1999 10493087
- Ting SA, Sullivan AF, Boudreaux ED, et al: Trends in US emergency department visits for attempted suicide and self-inflicted injury, 1993–2008. *Gen Hosp Psychiatry* 34(5):557–565, 2012 22554432
- Tran-Johnson TK, Sack DA, Marcus RN, et al: Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 68(1):111–119, 2007 17284138



- Trondsen MV, Bolle SR, Stensland GØ, Tjora A: Video-confidence: a qualitative exploration of videoconferencing for psychiatric emergencies. BMC Health Serv Res 14:544-551, 2014 25359404
- Tulloch KJ, Zed PJ: Intramuscular olanzapine in the management of acute agitation. Ann Pharmacother 38(12):2128-2135, 2004 15522977
- U.S. Department of Health and Human Services: HIPAA Privacy Rule and Sharing Information Related to Mental Health. February 20, 2014. Available at: <http://www.hhs.gov/ocr/privacy/hipaa/understanding/special/mhguidance.html>. Accessed October 23, 2015.
- Walcott DM, Cerundolo P, Beck JC: Current analysis of the Tarasoff duty: an evolution towards the limitation of the duty to protect. Behav Sci Law 19(3):325-343, 2001 11443695
- Woo BK, Sevilla CC, Obrocea GV: Factors influencing the stability of psychiatric diagnoses in the emergency setting: review of 934 consecutively inpatient admissions. Gen Hosp Psychiatry 28(5):434-436, 2006 16950381
- Wright P, Birkett M, David SR, et al: Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry 158(7):1149-1151, 2001 11431240
- Yellowlees P, Burke MM, Marks SL, et al: Emergency telepsychiatry. J Telemed Telecare 14(6):277-281, 2008 18776070
- Yildiz A, Sachs GS, Turgay A: Pharmacological management of agitation in emergency settings. Emerg Med J 20(4):339-346, 2003 12835344

## CHAPTER 59

# Treatment of Agitation and Aggression in the Elderly

Carl Salzman, M.D.

Severe behavioral agitation and aggression—including restlessness, wandering, assaultiveness, or screaming—may accompany late-life psychosis, dementia, or mood disorders, with particularly high prevalence rates in nursing homes. Severely depressed or very anxious elderly individuals can also become behaviorally disruptive, endangering themselves and others as well as decreasing the quality of their lives ([Banerjee et al. 2006](#)). Behavioral and psychiatric symptoms develop in more than half of community-dwelling patients with dementia ([Lyketsos et al. 2000](#)), and virtually all individuals with dementia will display behavioral complications at some point. In nursing homes, rates of behavioral and psychiatric symptoms are estimated to be as high as 80% in patients with dementia

([Testad et al. 2007](#); [Zuidema et al. 2007](#)); over the course of a lifetime, the risk of these symptoms is estimated at 100% ([Lyketsos et al. 2000](#)).

Serious behavioral symptoms, especially those associated with psychosis and dementia, may have devastating consequences for patients and their families. Such symptoms decrease the quality of life for the patient and family ([Matsui et al. 2006](#)) and may indicate a worse prognosis. Although various medications have been employed to treat disruptive behavior in elderly patients, no medications have been approved by the U.S. Food and Drug Administration (FDA) for this specific therapeutic indication. Antipsychotic drugs have been frequently used off-label for this purpose; however, these drugs can cause serious side effects in some patients. Other medications that have been tried, without reliable success, include antidepressants, mood stabilizers, cognitive enhancers, and even benzodiazepines.

---

## Antipsychotic Medications

---

Despite a growing awareness of the potential hazards of antipsychotic medications, these drugs are still the mainstay of pharmacological treatment given to elderly individuals with dementia who are agitated or psychotic ([Ballard et al. 2014](#)). In previous years, conventional antipsychotics (also known as first-generation antipsychotics [FGAs]) such as haloperidol were used to help control serious agitated behaviors. In recent years, the so-called atypical antipsychotics (also known as second-generation antipsychotics [SGAs]) have become the primary

psychopharmacological approach to management of this difficult clinical state. Haloperidol and other FGAs have been shown to have higher rates of side effects and possible increased rates of mortality compared with the newer SGA drugs. Unfortunately, both FGA and SGA medications produce only modest benefits and carry a potential for serious adverse effects and inappropriate use ([Jeste et al. 2005](#)). As a general prescribing guideline, antipsychotic drug dosages used for elderly adults should be considerably lower than those used for younger and middle-aged adults.

SGAs are as effective as FGAs for late-life psychotic symptoms as well as for management of agitation and aggression with or without associated psychosis ([Ballard and Waite 2006](#); [Sink et al. 2005](#)). Because of their more benign side-effect profile, the SGAs are now the preferred first-choice medications for management of behavioral symptoms in the elderly. Nonetheless, the overall efficacy of antipsychotic drugs in controlling serious behavioral and psychotic disturbance is modest; even with treatment, many older individuals with dementia continue to display behavioral and affective dyscontrol, especially when stressed, as well as in the evenings (i.e., sundowning). As a generalization, studies comparing SGAs with FGAs have reported greater efficacy for the SGAs ([Lopez et al. 2013](#)), and in all studies, the SGAs were associated with fewer extrapyramidal side effects (EPS) than the FGAs ([Chan et al. 2001](#)).

Pharmacological treatment of the aggression, agitation, and behavioral disruption commonly seen in moderate to severe dementia is difficult. Despite the obvious need for safe and effective pharmacological approaches, no drugs have been approved by the FDA for the management of persisting agitation or aggression associated with

dementia. In one large study (the Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer’s Disease [CATIE-AD]), overall response rates ranged from 48% to 65% with olanzapine treatment versus 30%–48% with placebo, showing an incremental treatment benefit of about 18% for active drug over placebo ([Schneider et al. 2006](#)), although olanzapine was associated with worsening of cognition ([Vigen et al. 2011](#)). Other SGA medications also reported to be beneficial for disruptive behavior in the context of dementia include aripiprazole ([Coley et al. 2009](#)), ziprasidone ([Greco et al. 2005](#)), olanzapine ([Street et al. 2000](#)), risperidone ([Brodaty et al. 2003](#); [Devanand et al. 2012](#)), and quetiapine ([Tariot et al. 2006](#)).

All antipsychotic medications produce side effects, and in general, elderly individuals are more susceptible and sensitive to these effects. For this reason, drugs with anticholinergic or orthostatic hypotensive properties (e.g., clozapine) should be avoided in the elderly whenever clinically possible. Because many antipsychotics are substrates of cytochrome P450-metabolizing enzymes, caution must also be exercised regarding the potential for adverse drug interactions.

In the early years of the twenty-first century, evidence pointing to increased rates of morbidity and early death in elderly individuals receiving antipsychotic drugs generated considerable concern. An initial report indicating a heightened risk of cerebrovascular adverse events (CVAEs; e.g., stroke, transient ischemic attack [TIA], death) in male nursing home residents older than 85 years who were treated with risperidone ([Wooltorton 2002](#)) prompted further investigation. Similar suggestive evidence was reported for olanzapine, and ultimately for other SGAs ([Kryzhanovskaya et al. 2006](#)). Taken together, these

observations of increased CVAEs in elderly individuals receiving SGAs stimulated an examination of all studies. The findings supported the concerns regarding a possible increased risk of CVAEs associated with use of risperidone or olanzapine in elderly patients with dementia. Data from 11 olanzapine or risperidone studies collectively suggested that 2.2% of drug-treated subjects experienced CVAEs, compared with 0.8% of placebo-treated subjects. The combined relative risk was 2.7. [Ballard and Waite \(2006\)](#) concluded that despite the modest efficacy of these drugs, the significance of the adverse events dictated that “neither risperidone nor olanzapine should be used routinely to treat dementia patients with aggression or psychosis unless there is marked risk or severe distress.”

In 2003, the FDA issued a black box warning regarding a possible increased risk of CVAEs associated with use of atypical antipsychotics in older adults with dementia. The warning was eventually extended to include aripiprazole, olanzapine, and risperidone. The death rate in clinical trials was 3.5% with SGAs versus 2.3% with placebo, leading the FDA to impose a black box warning for all antipsychotics. Studies examining large public databases ([Ballard and Waite 2006](#); [Schneider et al. 2006](#)) have found similar rates of death among elderly people receiving FGAs ([Schneeweiss et al. 2007](#); [Wang et al. 2005](#)). Causes of death vary, but most of the deaths appear to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

The FDA warning has generated considerable controversy. Some observers concur with the FDA warning suggesting that mortality is increased ([Kales et al. 2012](#)) in a dose-dependent fashion ([Ballard et al. 2014](#)). Other researchers, examining the data on which the FDA's

warning was based, have become concerned that methodological faults in many of the studies may have compromised the meta-analyses and led to an overly harsh interpretation of the data and an unwarranted concern for safety. Some studies failed to find an increase in death rate or incidence of CVAEs. For example, [Herrmann et al. \(2004\)](#), as well as [Haupt et al. \(2006\)](#), [Raivio et al. \(2007\)](#), and [Gill et al. \(2005\)](#), found no significant increase in the risk of ischemic stroke with either FGAs or SGAs or among those receiving SGAs compared with FGAs. The American College of Neuropsychopharmacology issued a White Paper ([Jeste et al. 2008](#)) concluding that further research data are needed to clarify the ongoing significance, if any, of increased development of CVAEs with SGAs. An expert consensus conference held in 2006 ([Salzman et al. 2008](#)) essentially made the same point. It is clear that not all individuals with dementia who receive antipsychotic medication for disruptive symptoms have an increased risk of premature mortality ([Devanand 2013](#)).

When confronted with elderly patients with dementia who are possibly psychotic and who are manifesting extreme agitation and/or aggression, clinicians face a difficult treatment dilemma. The essential conclusion of the CATIE-AD study, and a sensible statement about the role of antipsychotics in management of behavioral symptoms in dementia ([Jeste et al. 2008](#); [Salzman et al. 2008](#); [Sink et al. 2005](#)), was that on average, patients receive modest benefit from these agents without being harmed: these are the patients for whom continued therapy is rational. The following clinical conclusions appear to be warranted at present:

1. Recognizing that the use of antipsychotic drugs to treat agitation or aggression is “off label,” clinicians must be certain that the behavior cannot be managed nonpharmacologically and that the severity of the disruptive behavior warrants the selection of antipsychotic medications.
2. SGAs are still preferred to FGAs because of the former’s lower likelihood of EPS and tardive dyskinesia.
3. Clinicians should confer with the patient’s family or significant others regarding the use of these drugs and should attempt to obtain some type of informed consent, balancing the possible risks of using these medications against the likelihood of worsening behavior and clinical status without such treatment.
4. Clinicians should closely follow patients receiving antipsychotics for early warning signs of a CVAE.
5. Antipsychotic medications are often prescribed at dosages that are too high for elderly individuals, especially those with dementia. Clinicians should strive to use the lowest therapeutic doses. If necessary, liquid preparations can facilitate very-low-dose administration.
6. Clinicians should be mindful of an elderly individual’s medical status and medication treatment to avoid unwanted side effects of drug interactions due to polypharmacy.

The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia ([Reus et al. 2016](#)) notes that antipsychotic medication may be modestly helpful, but emphasizes that medication must be part of a comprehensive program of medical care that includes careful medication monitoring.



---

## Other Medication Classes

---

An increasing number of other medication classes are being used as second-line choices for management of agitation and aggression, but with less reliable effectiveness ([Salzman et al. 2008](#)). These include trazodone, benzodiazepines, anticonvulsants (mood stabilizers), serotonergic antidepressants, and cognitive enhancers.

### Trazodone

The antidepressant drug trazodone was reported to be effective in treating agitation and severely disruptive behavior ([Pinner and Rich 1988](#); [Seitz et al. 2011](#); [Tariot 1996](#)), although these studies did not distinguish between psychotic and nonpsychotic patients. Extensive clinical experience suggests that trazodone is effective at dosages of 50–200 mg/day, with few side effects other than sedation. The mechanism of trazodone's effect is unknown. Current clinical experience continues to suggest that trazodone is often extremely helpful as an add-on medication when antipsychotics or other drugs alone cannot control disruptive behavior. Priapism is a rare side effect of trazodone in elderly men.

### Benzodiazepines

Although benzodiazepines are quite widely used in the elderly agitated population, there have been no studies of benzodiazepine treatment of agitation or aggression in nearly a decade. Most of the older studies were not placebo

controlled, but they nonetheless suggested that on average, agitation could be reduced with short-term benzodiazepine therapy (Loy et al. 1999). For example, Coccaro et al. (1990) compared oxazepam (10–60 mg/day) with low-dose haloperidol in patients with dementia diagnoses. Five percent of patients in the benzodiazepine group improved, compared with 24% of those in the haloperidol group, a difference that was not statistically significant, perhaps because of the small sample size. Christensen and Benfield (1998) compared alprazolam (0.5 mg twice daily) with haloperidol (0.6 mg/day) in a crossover study. Adverse events were not significantly different between groups. The dosages of both agents used in this study were probably too low to expect an effect, and none was seen. Meehan et al. (2002) noted that intramuscular lorazepam 1.0 mg or 0.5 mg was superior to placebo at 2 hours but not at 24 hours.

Possible side effects of benzodiazepines in elderly individuals include ataxia, falls, confusion, anterograde amnesia, sedation, light-headedness, and tolerance and withdrawal syndromes. There is evidence that mild anterograde amnesia may occur in elderly patients who are taking therapeutic doses of a benzodiazepine, although this side effect is often reversible (Salzman et al. 1992). A recent review suggests that benzodiazepines may increase the risk of developing Alzheimer's disease (Billioti de Gage et al. 2014), although this finding is controversial (Salzman and Shader 2015). Nevertheless, the potential side effects of benzodiazepines in the context of scant evidence of efficacy suggest that their use for agitation should be time limited or on a low-dose, as-needed basis, with chronic use reserved for those patients in whom other agents have proved ineffective. Benzodiazepines with simpler

metabolisms and relatively short half-lives, such as lorazepam and oxazepam, are always preferred.

## Anticonvulsants

Although early studies reported benefit for carbamazepine in elderly patients with agitation ([Tariot et al. 1994](#)), most subsequent studies suggested that anticonvulsants are not reliably helpful for controlling agitation and aggression in elderly individuals, especially those with dementia. Small clinical observation studies have reported a modest benefit for divalproex, as well as for lamotrigine, but subsequent experience has not borne out the clinical usefulness of these agents.

## Serotonergic Antidepressants, Cognitive Enhancers, and Their Combination

Although disappointing experience has been reported for serotonergic antidepressants, the combination of a selective serotonin reuptake inhibitor (SSRI) antidepressant and a cognitive-enhancing cholinesterase inhibitor is commonly used in an effort to control agitation without resorting to use of antipsychotics. However, clinical experience suggests that this combination has inconsistent, modest efficacy ([Holmes et al. 2004](#)).

## New Approaches

A new approach to the treatment of dementia-related agitation has recently been published. In a preliminary 10-week Phase II randomized clinical trial of patients with probable Alzheimer's disease, combination dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated ([Ballard et al. 2015](#); [Cummings et al. 2015](#)).

Another recent study suggested that some patients with Alzheimer's disease accompanied by aggression or agitation may respond to citalopram 20–30 mg/day ([Peters et al. 2016](#); [Schneider et al. 2016](#)). The authors noted a significant clinical heterogeneity of agitation and aggression in this disorder that made specific symptoms or identifying patient data predict response or nonresponse. Residence in long-term care, however, was associated with a negative outcome with citalopram. Patients for whom citalopram was more effective were more likely to be outpatients, to have the least cognitive impairment, to have moderate agitation, and to be in the age range of 76–82 years.

---

## Conclusion

---

Dementia-associated agitation is common and can be difficult to treat. The usual first-choice medications are the antipsychotics, but they have only modest efficacy and may cause significant side effects. New treatment guidelines do not favor these drugs, although clinicians may find that the other choices are less effective. Trazodone is a useful second choice or an addition to the antipsychotics. Anticonvulsants have an uncertain therapeutic effect; initial

data were promising, but subsequent experience and further research has not supported their routine use. Benzodiazepines and other sedative-hypnotics are generally not recommended for the behavioral treatment of individuals with dementia or agitation. Cognitive enhancers, alone or in combination with SSRI antidepressants, are commonly used, but their therapeutic effect is unreliable and usually inadequate when behavioral disruption is severe or frequent. Most recently, the report of treatment success with a dextromethorphan-quinidine combination has raised hopes that treatment of this difficult behavioral problem associated with dementia may be making progress.

---

## References

---

- Ballard C, Waite J: The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev* (1): CD003476, 2006 16437455
- Ballard C, Corbett A, Howard R: Prescription of antipsychotics in people with dementia. *Br J Psychiatry* 205(1):4-5, 2014 24986385
- Ballard C, Sharp S, Corbett A: Dextromethorphan and quinidine for treating agitation in patients with Alzheimer disease dementia. *JAMA* 314(12):1233-1235, 2015 26393843
- Banerjee S, Smith SC, Lamping DL, et al: Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. *J Neurol Neurosurg Psychiatry* 77(2):146-148, 2006 16421113
- Billioti de Gage S, Moride Y, Ducruet T, et al: Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ* 349:g5205, 2014 25208536

- Brodaty H, Ames D, Snowdon J, et al: A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* 64(2):134-143, 2003 12633121
- Chan WC, Lam LC, Choy CN, et al: A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. *Int J Geriatr Psychiatry* 16(12):1156-1162, 2001 11748775
- Christensen DB, Benfield WR: Alprazolam as an alternative to low-dose haloperidol in older, cognitively impaired nursing facility patients. *J Am Geriatr Soc* 46(5): 620-625, 1998 9588378
- Coley KC, Scipio TM, Ruby C, et al: Aripiprazole prescribing patterns and side effects in elderly psychiatric inpatients. *J Psychiatr Pract* 15(2):150-153, 2009 19339850
- Coccaro EF, Kramer E, Zemishlany Z, et al: Pharmacologic treatment of noncognitive behavioral disturbances in elderly demented patients. *Am J Psychiatry* 147(12): 1640-1645, 1990 2244643
- Cummings JL, Lyketsos CG, Peskind ER: Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA* 314(12):1242-1254, 2015 26393847
- Devanand DP: Psychosis, agitation, and antipsychotic treatment in dementia. *Am J Psychiatry* 170(9):957-960, 2013 24030608
- Devanand DP, Mintzer J, Schultz SK, et al: Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med* 367(16):1497-1507, 2012 23075176
- Gill SS, Rochon PA, Herrmann N, et al: Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ* 330(7489):445, 2005 15668211

- Greco KE, Tune LE, Brown FW, Van Horn WA: A retrospective study of the safety of intramuscular ziprasidone in agitated elderly patients. *J Clin Psychiatry* 66(7): 928-929, 2005 16013910
- Haupt M, Cruz-Jentoft A, Jeste D: Mortality in elderly dementia patients treated with risperidone. *J Clin Psychopharmacol* 26(6):566-570, 2006 17110812
- Herrmann N, Mamdani M, Lanctôt KL: Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 161(6):1113-1115, 2004 15169702
- Holmes C, Wilkinson D, Dean C, et al: The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* 63(2):214-219, 2004 15277611
- Jeste DV, Dolder CR, Nayak GV, Salzman C: Atypical antipsychotics in elderly patients with dementia or schizophrenia: review of recent literature. *Harv Rev Psychiatry* 13(6):340-351, 2005 16373328
- Jeste DV, Blazer D, Casey D, et al: ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology* 33(5):957-970, 2008 17637610
- Kales HC, Kim HM, Zivin K, et al: Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry* 169(1):71-79, 2012 22193526
- Kryzhanovskaya LA, Jeste DV, Young CA, et al: A review of treatment-emergent adverse events during olanzapine clinical trials in elderly patients with dementia. *J Clin Psychiatry* 67(6):933-945, 2006 16848653
- Lopez OL, Becker JT, Chang Y-F, et al: The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer's disease. *Am J Psychiatry* 170(9):1051-1058, 2013 23896958
- Loy R, Tariot PN, Rosenquist K: Alzheimer's disease: behavioral management, in *Annual Review of Gerontology and Geriatrics: Focus on*

Psychopharmacologic Interventions in Late Life. Edited by Katz IR, Oslin D, Lawton MP. New York, Springer, 1999, pp 136-194

Lyketsos CG, Steinberg M, Tschanz JT, et al: Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 157(5):708-714, 2000 10784462

Matsui T, Nakaaki S, Murata Y, et al: Determinants of the quality of life in Alzheimer's disease patients as assessed by the Japanese version of the Quality of Life-Alzheimer's disease scale. *Dement Geriatr Cogn Disord* 21(3):182-191, 2006 16401890

Meehan KM, Wang H, David SR, et al: Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. *Neuropsychopharmacology* 26(4):494-504, 2002 11927174

Peters MF, Vaidya V, Drye LT, et al; CitAD Research Group: Citalopram for the treatment of agitation in Alzheimer dementia: genetic influences. *J Geriatr Psychiatry Neurol* 29(2):59-64, 2016 26303700

Pinner E, Rich CL: Effects of trazodone on aggressive behavior in seven patients with organic mental disorders. *Am J Psychiatry* 145(10):1295-1296, 1988 3048122

Raivio MM, Laurila JV, Strandberg TE, et al: Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two-year prospective study. *Am J Geriatr Psychiatry* 15(5):416-424, 2007 17463191

Reus VI, Fochtmann LJ, Eyler AE, et al: The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *Am J Psychiatry* 173(5):543-546, 2016 27133416



- Salzman C, Shader RI: Benzodiazepine use and risk for Alzheimer disease. *J Clin Psychopharmacol* 35(1):1-3, 2015 25407694
- Salzman C, Fisher J, Nobel K, et al: Cognitive improvement following benzodiazepine discontinuation in elderly nursing home residents. *Int J Geriatr Psychiatry* 7(2):89-93, 1992
- Salzman C, Jeste DV, Meyer RE, et al: Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. *J Clin Psychiatry* 69(6):889-898, 2008 18494535
- Schneeweiss S, Setoguchi S, Brookhart A, et al: Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ* 176(5):627-632, 2007 17325327
- Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 355(15):1525-1538, 2006 17035647
- Schneider LS, Frangakis C, Drye LT, et al; CitAD Research Group: Heterogeneity of treatment response to citalopram for patients with Alzheimer's disease with aggression or agitation: the CitAD randomized clinical trial. *Am J Psychiatry* 173(5):465-472, 2016 26771737
- Seitz DP, Adunuri N, Gill SS, et al: Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev* (2):CD008191, 2011 21328305
- Sink KM, Holden KF, Yaffe K: Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA* 293(5):596-608, 2005 15687315
- Street JS, Clark WS, Gannon KS, et al; The HGEU Study Group: Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized,

- placebo-controlled trial. Arch Gen Psychiatry 57(10):968-976, 2000 11015815
- Tariot PN: Treatment strategies for agitation and psychosis in dementia. J Clin Psychiatry 57 (suppl 14):21-29, 1996 9024333
- Tariot PN, Erb R, Leibovici A, et al: Carbamazepine treatment of agitation in nursing home patients with dementia: a preliminary study. J Am Geriatr Soc 42(11):1160-1166, 1994 7963202
- Tariot PN, Schneider L, Katz IR, et al: Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. Am J Geriatr Psychiatry 14(9):767-776, 2006 16905684
- Testad I, Aasland AM, Aarsland D: Prevalence and correlates of disruptive behavior in patients in Norwegian nursing homes. Int J Geriatric Psychiatry 22(9):916-921, 2007 17323402
- Vigen CL, Mack WJ, Keefe RS, et al: Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. Am J Psychiatry 168(8):831-839, 2011 21572163
- Wang PS, Schneeweiss S, Avorn J, et al: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353(22):2335-2341, 2005 16319382
- Wooltorton E: Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. CMAJ 167(11):1269-1270, 2002 12451085
- Zuidema SU, Derksen E, Verhey FR, Koopmans RT: Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. Int J Geriatric Psychiatry 22(7):632-638, 2007 17136713

# APPENDIX

## Psychiatric Medications

Robert H. Chew, Pharm.D.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
ANTIDEPRESSANTS				
Tricyclic and tetracyclic antidepressants				
Secondary tricyclics				
Desipramine (Norpramin)	MDD	100-200 mg/day (at bedtime or in divided doses)	300	Ages 10-17: 100 mg/day (at bedtime or in divided doses)

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Nortriptyline (Pamelor)	MDD	75-100 mg/day (once daily or divided tid-qid)	150	Ages 18-64: 75-100 mg/day (once daily or divided tid-qid); Ages 65-74: 75-100 mg/day (once daily or divided tid-qid); Ages 75+: 75-100 mg/day (once daily or divided tid-qid)
Protriptyline (Vivactil)	MDD	15-40 mg/day (divided tid-qid)	60	Ages 18-64: 15-40 mg/day (divided tid-qid); Ages 65-74: 15-40 mg/day (divided tid-qid); Ages 75+: 15-40 mg/day (divided tid-qid)
<b><i>Tertiary tricyclics</i></b>				
Amitriptyline (Elavil)	MDD	50-150 mg/day (at bedtime or in divided doses)	300	Ages 18-64: 50-150 mg/day (at bedtime or in divided doses); Ages 65-74: 50-150 mg/day (at bedtime or in divided doses); Ages 75+: 50-150 mg/day (at bedtime or in divided doses)
	MDD, hospitalized patients	100-200 mg/day (at bedtime or in divided doses)	300	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release. Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Clomipramine (Anafranil)	OCD	150-250 mg/day (at bedtime or in divided doses)	250	Ages 12 and older: 200 mg, bid in divided doses
Doxepin	Depression and/or anxiety			
	Mild-moderate symptoms	75-150 mg/day (at bedtime or in divided doses)	150	
	Severe symptoms	300 mg/day (at bedtime or in divided doses)	300	
Doxepin tablets (Silenor)	Insomnia	3-6 mg at bedtime	6	
Imipramine (Tofranil)	MDD	50-150 mg/day (at bedtime or in divided doses)	200	Ages 12 and older: 40 mg, bid or in divided doses
	MDD, hospitalized patients	250-300 mg/day (in divided doses)	300	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	Nocturnal enuresis			Ages 5-10 years: 50 mg/day; 10-15 years: 75 mg/day; 15 years and older: 100 mg/day
Trimipramine (Surmontil)	MDD	50-150 mg/day (at bedtime or in divided doses)	200	Ages 10-15 years: 100 mg/day; 15 years and older: 200 mg/day
	MDD, hospitalized patients	250-300 mg/day (at bedtime or in divided doses)	300	
<b>Tetracyclines</b>				
Amoxapine	MDD	200-300 mg/day (at bedtime or in divided doses)	400	
	MDD, hospitalized patients		600	
Maprotiline	MDD	75-150 mg/day (at bedtime or in divided doses)	150	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release; *Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	MDD, hospitalized patients	150-225 mg/day (at bedtime or in divided doses)	225	
<b>Selective serotonin reuptake inhibitor (SSRI) antidepressants</b>				
Citalopram (Celexa)	MDD	20-40 mg/day	40	
Escitalopram (Lexapro)	MDD	10-20 mg/day	20	Ages 18 and older
	GAD	10-20 mg/day	20	
Fluoxetine (Prozac)	MDD	20-80 mg/day in morning or divided bid; or 90 mg weekly <sup>†</sup>	80	Ages 18 and older
	OCD	20-60 mg/day in morning or divided bid	80	Ages 18 and older
	Panic disorder	20-60 mg/day	60	
	Bulimia nervosa	20-60 mg/day	60	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling RL: *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Fluoxetine (Sarafem)	PMDD	20-60 mg/day <sup>†</sup>	80	
Fluvoxamine	OCD	100-300 mg/day (divided bid)	300	Ages 18-29 years: 200 mg/day (divided bid); Ages 30-39 years: 300 mg/day (divided bid)
Fluvoxamine extended-release (Luvox CR)	OCD	100-300 mg/day at bedtime	300	
Paroxetine (Paxil)	MDD	20-50 mg/day in morning	50	
Paroxetine extended-release (Paxil CR)	MDD	ER: 25-62.5 mg/day	62.5	
	GAD	20-50 mg/day	50	
	Social anxiety disorder	20-60 mg/day	60	Ages 18-29 years: 60 mg/day
		ER: 12.5-37.5 mg/day	37.5	in morning

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; Available at: <http://eanswers.factsandcomparisons.com>.



Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	Panic disorder	40 mg/day in morning ER: 12.5-75 mg/day in morning	60-75	
	OCD	20-60 mg/day in morning	60	Ages 18-60 mg/day in morning
	PTSD	20-50 mg/day in morning	50	
	PMDD	ER: 12.5-25 mg/day in morning <sup>†</sup>	25	
Sertraline (Zoloft)	MDD	50-200 mg/day in morning	200	Ages 18-60 mg/day in morning
	Social anxiety disorder	50-200 mg/day	200	
	Panic disorder	50-200 mg/day in morning	200	
	OCD	50-200 mg/day in morning	200	Ages 18-60 mg/day in morning

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling RL: *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
				Ages 12 and older 200 mg/day
	PTSD	50-200 mg/day in morning	200	
	PMDD	50-200 mg/day in morning <sup>†</sup>	150	

### Serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants

Desvenlafaxine (Pristiq)	MDD	50 mg/day	50	
Duloxetine (Cymbalta)	MDD	40-60 mg/day (once daily or divided bid)	120	
	GAD	60 mg/day	120	Ages 18 and older
	Fibromyalgia	60 mg/day	60	
	Diabetic neuropathic pain	60 mg/day	60	
	Musculoskeletal pain	60 mg/day	60	
Levomilnacipran (Fetzima)	MDD	40-120 mg/day	120	
Milnacipran (Savella)	Fibromyalgia	100 mg/day (divided bid)	200	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; Available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Venlafaxine	MDD	75-225 mg/day	225	
Venlafaxine extended-release (Effexor ER)	MDD	75-225 mg/day	225	
	GAD	75-225 mg/day	225	
	Social anxiety disorder	75 mg/day	75	
	Panic disorder	75-225 mg/day	225	
<b>Norepinephrine-dopamine reuptake inhibitor antidepressant (putative<sup>†</sup>)</b>				
Bupropion immediate-release	MDD	300 mg/day (divided tid)	150 mg/dose; 450 mg/day	
	ADHD*	300 mg/day (divided tid)	†	Ages 6.0 mg, (div bid)
Bupropion sustained-release (Wellbutrin SR)	MDD	SR: 300 mg/day (divided bid)	400	
	ADHD*	SR: 300 mg/day (divided bid)	400	Ages 6.0 mg, (div bid)
Bupropion extended-release				

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release; \*not available; †not available; Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Bupropion XL	MDD, seasonal affective disorder	300 mg/day in morning	450	Ages 18 and older 150 mg/day in morning
	ADHD*	300 mg/day in morning	300	
Aplenzin	MDD, seasonal affective disorder	348 mg/day in morning	522	
<b>Multimodal serotonin antagonist antidepressants</b>				
Nefazodone	MDD	300-600 mg/day (divided bid)	600	
Trazodone	MDD	150-300 mg/day (divided bid-tid)	400	
	Insomnia*	25-100 mg at bedtime	200	
Trazodone extended-release (Oleptro)	MDD	150-375 mg/day at bedtime	375	
Vortioxetine (Trintellix)	MDD	20 mg/day	20†	
Vilazodone (Viibryd)	MDD	20-40 mg/day	40	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release. Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Noradrenergic-specific serotonin antidepressant (NaSSA)				
Mirtazapine (Remeron)	MDD	15–45 mg/day at bedtime	45	
Monoamine oxidase inhibitor (MAOI) antidepressants				
Isocarboxazid (Marplan)	MDD and atypical depression	40–60 mg/day (divided bid–qid)	60	
Phenelzine (Nardil)	MDD and atypical depression	40–60 mg/day in divided doses†	90	
Selegiline transdermal patch (Emsam)	MDD	6–12 mg patch per 24 hours	12	
Tranylcypromine (Parnate)	MDD and atypical depression	30 mg/day in divided doses	60	
N-methyl-D-aspartate (NMDA) receptor antagonist				
Ketamine	Relief of acute depression with suicidal ideation*	0.5 mg/kg IV — over 40 minutes		

## ANXIOLYTICS

### Benzodiazepines

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release. Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Alprazolam (Xanax)	GAD	0.25–0.5 mg tid	4	
	Panic disorder	1.5–9 mg/day (divided tid)	10	
Alprazolam extended-release (Xanax XR)	GAD	3–6 mg/day	6	
Chlordiazepoxide	GAD, mild–moderate	5–10 mg tid–qid	†	Ages 12–17: 5–10 mg tid
	GAD, severe	20–25 mg tid–qid	†	
	Acute alcohol withdrawal	50–100 mg prn	300	
Clonazepam (Klonopin)	Panic disorder	1–4 mg/day (divided bid)	4	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release. Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Clorazepate	GAD	15-30 mg/day (at bedtime or divided bid)	60	
	Acute alcohol withdrawal	Dosage titration <sup>†</sup>		
Diazepam (Valium)	GAD	2-10 mg bid-qid	40	
	Acute alcohol withdrawal	10 mg tid-qid for first 24 hours; then 5 mg tid-qid prn	—	
Lorazepam (Ativan)	GAD	2-6 mg/day (divided bid-tid)	10	
	Insomnia	2-4 mg at bedtime	4	
Lorazepam injection (Ativan Injection)	Acute agitation*	0.5-1 mg IM prn every 30-60 minutes	—	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Oxazepam	GAD	10-30 mg tid-qid	120	
	Acute alcohol withdrawal	15-30 mg tid-qid	—	
<b>Nonbenzodiazepine</b>				
Buspirone	GAD	20-30 mg/day (divided bid-tid)	60	

## AGENTS FOR TREATMENT OF INSOMNIA

### Benzodiazepines

Estazolam		1-2 mg at bedtime	2
Flurazepam (Dalmane)		15-30 mg at bedtime	30
Quazepam (Doral)		7.5-15 mg at bedtime	15
Temazepam (Restoril)		7.5-30 mg at bedtime	30
Triazolam (Halcion)		0.125-0.5 mg at bedtime	0.5; 0.25 in elderly

### Nonbenzodiazepines

Eszopiclone (Lunesta)		1-3 mg at bedtime	3
Ramelteon (Rozerem)		8 mg at bedtime	8
Suvorexant (Belsomra)		10-20 mg at bedtime	20
Tasimelteon (Hetlioz)	Non-24-hour sleep-wake disorder	20 mg at bedtime	20

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.



Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Zaleplon (Sonata)		10-20 mg at bedtime	20	
Zolpidem (Ambien)		5-10 mg at bedtime	10	
Zolpidem extended-release (Ambien CR)		6.5-12.5 mg	12.5	
Zolpidem sublingual (SL) (Intermezzo)	Middle-of-night awakening <sup>†</sup>	Women: 1.75 mg prn Men: 3.5 mg prn	Once per night	

## ANTIPSYCHOTICS

### First-generation (typical) antipsychotics

Chlorpromazine	Psychotic disorders	200-600 mg/day (divided tid-qid)	1,000
	Acute manic states, hospitalized patients	200-800 mg/day (divided tid-qid)	2,000
Chlorpromazine injection	Acute agitation, hospitalized patients	25 mg IM, repeat 25-50 mg in 1 hour; up to 400 mg IM every 4-6 hours prn	—
Fluphenazine	Psychotic disorders	2.5-10 mg/day (divided tid-qid)	40

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); qid=four times daily (or divided into 4 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release; *Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Fluphenazine hydrochloride injection	Acute agitation	2.5–10 mg/day IM every 6–8 hours prn	10	
Fluphenazine decanoate injection	Management of psychotic disorders and schizophrenia	25–50 mg IM every 3 weeks <sup>†</sup>	—	
Haloperidol	Psychotic disorders	0.5–5 mg bid–tid	100	Ages 12 years and older: 0.01–0.02 mg/kg/day
	Tourette's disorder	0.5–5 mg bid–tid	100	Ages 6 years and older: 0.01–0.02 mg/kg/day
	Behavioral disorders, severe			Ages 6 years and older: 0.01–0.02 mg/kg/day

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
				Ages yea 5 m tid
Haloperidol lactate injection (Haldol Injection)	Acute psychosis	2-10 mg IM every 4-8 hours prn	20	
Haloperidol decanoate injection (Haldol Decanoate)	Management of psychotic disorders and schizophrenia	50-200 mg IM every month	—	
Loxapine (Loxitane)	Psychotic disorders	60-100 mg/day in divided doses	250	
Loxapine inhalation (Adasuave)	Acute agitation	10 mg/day <sup>†</sup>	10	
Perphenazine	Psychotic disorders	4-8 mg tid	24	
	Psychotic disorders, hospitalized patients	8-16 mg bid-qid	64	
Pimozide (Orap)	Tourette's disorder	2-10 mg/day	10	Ages yea 0.0! mg/

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Thioridazine	Psychotic disorders	200-800 mg/day (divided bid-qid)	800	
Thiothixene	Psychotic disorders	20-30 mg/day in divided doses	60	
Trifluoperazine	Psychotic disorders	15-20 mg/day (once daily or divided bid)	40	Ages 12-17 years: 10-20 mg/day (once daily or divided bid)
	Nonpsychotic anxiety	1-2 mg bid	6	Ages 18-20 years: 10-20 mg/day (once daily or divided bid)
<b>Second-generation (atypical) antipsychotics</b>				
Aripiprazole (Abilify)	Schizophrenia	10-15 mg/day	30	Ages 13-17 years: 5-15 mg/day
	Bipolar I disorder	10-15 mg/day	30	Ages 18-20 years: 10-15 mg/day
	MDD, adjunctive therapy	2-15 mg/day	15	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	Tourette's disorder			Ages 6-17 yea kg: mg/
	Irritability associated with autism spectrum disorder			Ages 6-17 yea kg: mg/
Aripiprazole long-acting injection (Abilify Maintena)	Schizophrenia	300-400 IM every month	—	
Aripiprazole lauroxil long-acting IM injection (Aristada)	Schizophrenia	441-882 IM every 4-6 weeks	—	
Asenapine SL (Saphris)	Schizophrenia	10-20 mg/day SL (divided bid)	20	
	Bipolar I disorder, monotherapy	10-20 mg/day SL (divided bid)	20	Ages 18-64 yea mg/ (div bid)
	Bipolar I disorder, adjunctive therapy with lithium or valproate	10 mg/day SL (divided bid)	20	
Brexipiprazole (Rexulti)	Schizophrenia	2-4 mg/day	4	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	MDD, adjunctive therapy	2 mg/day	3	
Cariprazine (Vraylar)	Schizophrenia	1.5–6 mg/day	6	
	Bipolar I disorder	3–6 mg/day	6	
Clozapine (Clozaril)	Schizophrenia, refractory	150–300 mg bid	900	
	Schizophrenia with high suicide risk	150–300 mg bid	900	
Iloperidone (Fanapt)	Schizophrenia	6–12 mg bid	24	
Lurasidone (Latuda)	Schizophrenia	40–160 mg/day	160	
	Bipolar I disorder, depressive episodes	20–80 mg/day	120	
Olanzapine (Zyprexa)	Schizophrenia	10–20 mg/day	20	Ages 18 years and older
	Bipolar I disorder	5–20 mg/day	20	Ages 18 years and older
Olanzapine IM injection (Zyprexa Intramuscular)	Acute agitation	10 mg IM; may repeat after 2 hours one time; repeat prn 4 hours after second dose	30	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		
		Usual dosage	Maximum (mg/day)	Usual dosage
Olanzapine long-acting IM injection (Zyprexa Relprevv)	Schizophrenia	Dosage titration <sup>†</sup>		
Olanzapine/fluoxetine (Symbyax)	Bipolar I disorder, acute depressive episodes	6 mg/25 mg/day–12 mg/50 mg/day	12/50	Ages 18 years and older
	Treatment-resistant depression	6 mg/25 mg/day	12/50	
Paliperidone (Invega)	Schizophrenia Schizoaffective disorder	6 mg/day	12	Ages 18 years and older
Paliperidone palmitate long-acting IM injection <sup>†</sup> Invega Sustenna		IM injection every month	—	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Invega Trinza		IM injection every 3 months	—	
Quetiapine (Seroquel)	Schizophrenia	150–750 mg/day (divided bid–tid)	750	Ages 18–65 years
	Bipolar I disorder, acute manic/mixed episodes	400–800 mg/day (divided bid)	800	Ages 18–65 years
	Bipolar I disorder, depressive episodes	300 mg/day at bedtime	300	
Quetiapine extended-release (Seroquel XR)	Schizophrenia	400–800 mg/day	800	Ages 18–65 years
	Bipolar I disorder, acute manic/mixed episodes	400–800 mg bid	800	Ages 18–65 years
	Bipolar I disorder, depressive episodes	300 mg/day at bedtime	300	
	MDD, adjunctive therapy	150–300 mg/day	300	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release. Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.



Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Risperidone (Risperdal)	Schizophrenia	4–8 mg/day (once daily or divided bid)	16	Ages yea mg/ (on or c bid)
	Bipolar I disorder, acute manic/mixed episodes	1–6 mg/day (once daily or divided bid)	6	Ages yea 2.5 (on or c bid)
	Irritability associated with autism spectrum disorder			Ages yea wei kg: mg/ (on or c bid)
Risperidone long-acting IM injection (Risperdal Consta)	Schizophrenia Bipolar I disorder	25–50 mg IM every 2 weeks	—	Ages yea wei kg: mg/ (on or c bid)
Ziprasidone (Geodon)	Schizophrenia	20 mg bid	160	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	Bipolar I disorder	80-160 mg/day (divided bid)	160	
Ziprasidone IM injection (Geodon Injection)	Acute agitation	10 mg IM every 2 hours prn or 20 mg IM every 4 hours prn	—	
<b>MOOD STABILIZERS</b>				
Carbamazepine (Tegretol)	Bipolar I disorder*	800-1,200 mg/day (divided bid-qid)	1,600	
Carbamazepine extended-release (Equetro, <sup>†</sup> Tegretol XR)	Bipolar I disorder	400-600 mg bid	1,600	
Gabapentin (Neurontin)	Postherpetic neuralgia	300-600 mg tid	1,800	
	Neuropathic pain*	300-1,200 mg tid	3,600	
	Bipolar I disorder*	600-3,600 mg/day (divided tid)	3,600	
	GAD*	600-3,600 mg/day (divided tid)	3,600	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Lamotrigine (Lamictal, Lamictal XR)	Bipolar I disorder			
	Monotherapy <sup>†</sup>	200 mg/day	200	
	With valproate <sup>†</sup>	100 mg/day	100	
	With enzyme inducers (e.g., carbamazepine) <sup>†</sup>	200 mg bid	400	
Lithium carbonate	Bipolar depression*	50-200 mg/day	200	
	Bipolar disorder	900-1,200 mg/day (divided tid-qid) <sup>†</sup>	2,400	
				Ages 12-17
				18 years and older

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); qid=four times daily (or divided into 4 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Lithium extended-release (Lithobid)		900–1,800 mg/day (divided bid–tid)	1,800	Ages 12–17: 300–600 mg/day (divided bid–tid); Ages 18 and older: 900–1,800 mg/day (divided bid–tid)
Oxcarbazepine (Trileptal)	Bipolar I disorder*	1,200–2,400 mg/day (once daily or divided bid)	2,400	
Oxcarbazepine extended-release (Oxtellar XR)				
Pregabalin (Lyrica)	GAD*	300 mg bid	600	
	Fibromyalgia	150–225 mg bid	450	
	Diabetic neuropathy	100 mg tid	300	
Topiramate (Topamax)	Bulimia nervosa*	300–400 mg/day (divided bid)	400	
	Depressive disorders, adjunctive therapy*	100–200 mg/day (divided bid)	—	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release. Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	Alcohol use disorder*	300 mg/day in divided doses	300	
Valproate, divalproex sodium (Depakote, Depakote ER)	Bipolar I disorder, manic episodes	15-20 mg/kg/day Rapid oral loading: <sup>†</sup> 20-30 mg/kg/day	60 mg/kg/day	

#### PSYCHOSTIMULANTS FOR TREATMENT OF ADHD AND NARCOLEPSY

Amphetamine/dextroamphetamine (Adderall)	ADHD	5-40 mg/day (once daily or divided bid)	40	Ages 6-12 years: 40 mg/day (once daily or divided bid); 13-17 years: 40 mg/day (once daily or divided bid); 18 years and older: 40 mg/day (once daily or divided bid)
--	------	---	----	---

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	Narcolepsy <sup>†</sup>	5-60 mg/day in divided doses	60	Ages 12-17 years: 5-60 mg/day (once daily or bid); 18 years and older: 5-60 mg/day in divided doses
Amphetamine/dextroamphetamine extended-release (Adderall XR)	ADHD	20 mg/day in morning	60	Ages 12-17 years: 20 mg/day in morning; 18 years and older: 20-60 mg/day in morning
Armodafinil (Nuvigil)	Narcolepsy Sleep apnea	150-250 mg/day in morning	250	
Modafinil (Provigil)	Narcolepsy Sleep apnea	200 mg/day in morning	400	
Dextroamphetamine (Dexedrine)	ADHD			Ages 12-17 years: 5-60 mg/day (once daily or bid); 18 years and older: 5-60 mg/day in divided doses

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
	Narcolepsy	5-60 mg/day (once daily or divided bid)	60	Ages 12 years and older; 10 mg, (once daily or divided bid)
Lisdexamfetamine (Vyvanse)	ADHD	30-70 mg/day in morning	70	Ages 12 years and older; 70 mg in morning
	Binge-eating disorder	50-70 mg/day in morning	70	
Methamphetamine (Desoxyn)	ADHD	20-25 mg/day (once daily or divided bid)	25	Ages 12 years and older; 25 mg (once daily or divided bid)
Dexmethylphenidate (Focalin)	ADHD	5-10 mg/day (divided bid)	20	Ages 12 years and older; 10 mg, (divided bid)
Dexmethylphenidate extended-release (Focalin XR)		20-40 mg/day in morning	40	Ages 12 years and older; 30 mg in morning
Methylphenidate Short-acting <sup>†</sup>				

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

Medication	Approved indications	Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Ritalin, Methylin	ADHD	20-30 mg/day (divided bid-tid)	60	Ages 6-12 yea 30 mg (div bid-
	Narcolepsy	20-30 mg/day (divided bid-tid)	60	
Intermediate-acting <sup>†</sup> Metadate ER	ADHD	20-40 mg/day (once daily or divided bid)	60	Ages 12-17 yea mg/ (on or c bid)
	Narcolepsy	20-30 mg/day (once daily or divided bid)	60	
Long-acting <sup>†</sup> Aptensio XR	ADHD	10-60 mg/day in morning	60	Ages 12-17 yea 60 mg in n

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.

*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts and Comparisons; available at: <http://www.factsandcomparisons.com>.

18-72 72 Ages



Medication	Approved indications	mg/day in Adult		Usual dosage
		Usual dosage	Maximum (mg/day)	
Daytrana Transdermal System		10-30 mg patch per day <sup>†</sup>	30	Ages 5-17
Metadate CD, Quillivant XR, Ritalin LA		20-60 mg/day in morning	60	Ages 6-17
<b>NONPSYCHOSTIMULANTS FOR TREATMENT OF ADHD</b>				
Atomoxetine (Strattera)	ADHD	80-100 mg/day (divided bid)	100	Ages 6-17

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.

*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling RL: *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: First Aid for the USMLE Step 2 Exam, 2012; Available at: <http://www.firstaid4usmle.com>.

Medication	Approved indications	Adult		Usual dose (div)
		Usual dosage	Maximum (mg/day)	
Guanfacine extended-release (Intuniv)	ADHD			0.4 mg, bid

## AGENTS FOR COGNITIVE DISORDERS

Donepezil (Aricept)	Alzheimer's disease, mild-moderate	5-10 mg/day	10
	Alzheimer's disease, moderate-severe	10-23 mg/day	23
Galantamine (Razadyne)	Alzheimer's disease, mild-moderate	8-12 mg bid	24
Galantamine extended-release (Razadyne ER)	Alzheimer's disease, mild-moderate	16-24 mg/day	24
Memantine (Namenda)	Alzheimer's disease, moderate-severe	10 mg bid	20
Memantine extended-release (Namenda XR)	Alzheimer's disease, moderate-severe	28 mg/day	28

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 3 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.

*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Firstmonline.com.

Memantine/donepezil (Namenda/Aricept) Alzheimer's 28 mg/10 28/10

Medication	Approved indications	mg/day <sup>†</sup> Adult		
		Usual dosage	Maximum (mg/day)	Usual dosage
Rivastigmine (Exelon)	Alzheimer's disease, mild-severe	3-6 mg bid	12	
	Parkinson's disease dementia	1.5-6 mg bid	12	
Rivastigmine topical patch (Exelon Transdermal)	Alzheimer's disease, mild-severe	9.5-13.3 mg patch per 24 hours	13.3	
	Parkinson's disease dementia	9.5-13.3 mg patch per 24 hours	13.3	
<b>AGENTS FOR TREATMENT OF ANTIPSYCHOTIC-INDUCED EXTRAPYRAMIDAL SIDE EFFECTS</b>				
Amantadine	Antipsychotic-induced EPS	100 mg bid	300	

Medication	Approved indications	Adult		Usual dose
		Usual dosage	Maximum (mg/day)	
Benztropine mesylate injection (Cogentin Injection)	Acute dystonic reaction	2 mg IM; repeat once after 30 minutes prn	†	
Diphenhydramine (Benadryl)	Antipsychotic-induced EPS	25-50 mg PO/IM every 6-8 hours prn	400	Ages 12-17: 25 mg PO/eve hou Ages 18-64: 50 mg PO/eve hou Ages 65+: 25 mg PO/eve hou
	Acute dystonic reaction*	50-100 mg IM/IV; repeat after 20-30 minutes prn	100 mg/dose	Ages 12-17: 50 mg IM/rep afte min prn Ages 18-64: 100 mg IM/rep afte min prn Ages 65+: 50 mg IM/rep afte min prn

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.

*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Firstmonline (Firstmonline).

Proprietary (Firstmonline) Antipsychotic- 20-120 120

Medication	Approved indications	Usual dosage	Adult		Usual dosage
			(divided tid-qid)	Maximum (mg/day)	
Trihexyphenidyl	induced akathisia* Antipsychotic-induced EPS	5-15 mg/day (divided tid-qid)		15	

#### AGENTS FOR TREATMENT OF SUBSTANCE USE DISORDERS

Acamprosate	Alcohol abstinence, maintenance	666 mg tid	†	
Bupropion sustained-release (Zyban)	Smoking cessation	150 mg bid		300
Disulfiram (Antabuse)	Management of alcohol abstinence	125-500 mg/day in morning		500
Naltrexone	Treatment of alcohol dependence	50 mg/day	†	
	Management of opioid dependence	Give 25 mg; if no withdrawal symptoms, start 50 mg/day	†	

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; tid=three times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release.  
*Source.* Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: First Aid for the USMLE Step 2.

Naltrexone injection (Vivitrol) Treatment of 380 mg IM

Medication	Approved indications	Usual dosage	Adult	
			Maximum (mg/day)	Usual dosage
	alcohol dependence	every 4 weeks <sup>†</sup>		
	Management of	380 mg IM		
	opioid dependence	every 4 weeks <sup>†</sup>		
Varenicline (Chantix)	Smoking cessation	Requires dosage titration <sup>†</sup>		

*Note.* ADHD=attention-deficit/hyperactivity disorder; CYP2D6=cytochrome P450 2D6 enzyme; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

—=not available; bid=twice daily (or divided into 2 doses); IM=intramuscular; IV=intravenous; qid=four times daily (or divided into 4 doses); SL=sublingual; tid=three times daily (or divided into 3 doses); CD=controlled delivery (extended release); CR=controlled release (extended release); ER=extended release; LA=long acting (extended release); SR=sustained release (extended release); XL, XR=extended release. Source. Athenahealth Inc.: epocrates®; Available at: <http://online.epocrates.com>; Findling R. *Adolescent Psychopharmacology*. Washington, DC, American Psychiatric Publishing, 2008; National Library of Medicine: DailyMed; available at: <http://dailymed.nlm.nih.gov>; Wolters Kluwer: Facts & Comparisons; available at: <http://eanswers.factsandcomparisons.com>.

# Index

*Page numbers in **boldface** type refer to tables or figures.*

- AADC (aromatic amino acid decarboxylase), [56-57](#), [67-68](#), [75-76](#), [245](#), [246](#)
- AADPRT (American Association of Directors of Psychiatric Residency Training), [1595](#)
- AAEP (American Association of Emergency Psychiatry), [1595](#)
- A $\beta$ . *See* [Amyloid- \$\beta\$  peptide](#)
- ABC (Aberrant Behavior Checklist), [474](#), [593](#), [743](#), [1466](#), [1467](#), [1468](#), [1472](#), [1473](#)
- Community version, [1474](#), [1475](#)
- ABCB1* gene, [212](#), [227](#), [312-313](#), [388-389](#)
- Abdominal pain
- drug-induced
- carbamazepine, [958](#)
- duloxetine, [1436](#), [1498](#)
- ketamine, [555](#)
- nefazodone, [1436](#)
- psychostimulants, [1502](#)
- SSRIs, [1434](#), [1435](#), [1447](#), [1449](#), [1497](#)
- venlafaxine, [1436](#), [1498](#)
- in serotonin syndrome, [346](#)
- Aberrant Behavior Checklist (ABC), [474](#), [593](#), [743](#), [1466](#), [1467](#), [1468](#), [1472](#), [1473](#)
- Community version, [1474](#), [1475](#)
- Abilify, Abilify Discmelt. *See* [Aripiprazole](#)
- Abnormal Involuntary Movement Scale (AIMS), [746](#), [869](#), [873](#), [1528](#)
- Absolute neutrophil count (ANC), [635-636](#), [640](#)
- Absorption of drug, [209](#), [212-214](#). *See also* [Pharmacokinetics](#)
- in elderly persons, [1506](#)
- Acamprosate, for alcohol use disorder, [87-88](#), [1288](#), [1660](#)
- in schizophrenia, [1259](#)
- Acceptance and commitment therapy, for depression, [1164](#)
- Accreditation Council for Graduate Medical Education (ACGME), [1595](#)
- ACE* gene, [1158](#)

ACE (angiotensin-converting enzyme) inhibitors, interaction with lithium, 907

Acetaldehyde, 1286

Acetaminophen, 1381, 1413

combined with codeine, 1383, 1398

combined with NSAIDs, 1398

combined with opioids, 1398, 1408

for headache, 1411

for low back pain, 1391, 1406, 1406

for osteoarthritis, 1407, 1408

use in hepatic disease, 1381–1382

Acetazolamide, interaction with carbamazepine, 964, 967

*N*-Acetylaspartate (NAA), 260, 261

in borderline personality disorder, 1326

lamotrigine effects on, 1003

Acetylcholine (ACh), 77–80, 78–79

in Alzheimer's disease, 1039, 1518, 1519, 1527

botulinum toxin prevention of release of, 867

cholinergic anti-inflammatory pathway, 186–187

in elderly persons, 1508

in sleep–wake cycle, 1350, 1351

Acetylcholine receptors, 80–81

brain distribution of, 80

muscarinic, 62, 79, 80

antagonists of, 80

drug affinity for

antihistamines, 861

aripiprazole, 734, 735

asenapine, 797

brexpiprazole, 734, 735

classic antipsychotics, 612, 618

clozapine, 626, 636, 1521

cyclic antidepressants, 308, 309, 321, 336

fluoxetine, 336

olanzapine, 650, 652, 1522

paroxetine, 386

trihexyphenidyl, 856, 858

ziprasidone, 757

nicotinic, 47, 79, 80–81, 97

drug affinity for

biperiden, 861

bupropion, 496–497, 1297

galantamine, 1041



- ketamine, [552](#)
- varenicline, [1297](#)
- in schizophrenia, [81](#)
- Acetylcholinesterase (AChE), [1040](#)
- Acetylcholinesterase inhibitors (AChEIs), [664](#), [1040–1042](#), [1045](#)
  - for Alzheimer's disease, [1040–1042](#), [1519](#), [1521](#)
  - antidepressants and, [1627–1628](#)
  - antipsychotics and, [1521](#)
  - donepezil, [1040–1041](#)
  - galantamine, [1041–1042](#)
  - huperzine A, [1042](#)
  - with memantine, [1040](#)
  - metrifonate, [1042](#)
  - in mild neurocognitive disorder, [1040](#), [1041](#)
  - to mitigate cognitive effects of ECT, [1126–1127](#)
  - nicotinic receptor agonists, [1042](#)
  - physostigmine, [1042](#)
  - recommendations for, [1040](#)
  - rivastigmine, [1041](#)
  - side effects of, [1040](#)
  - switching between, [1040](#)
  - tacrine, [1041](#)
  - for vascular cognitive impairment, [1044](#)
  - ZT-1, [1042](#)
- N-Acetylcysteine (NAC)
  - for autism spectrum disorder, [1473](#)
  - risperidone and, [1475](#)
  - for cocaine dependence, [1302–1303](#)
  - for OCD in children and adolescents, [1450](#)
  - side effects of, [1473](#)
- Acetylsalicylic acid, [1381](#)
- N-Acetyltransferase, [228](#)
- ACGME (Accreditation Council for Graduate Medical Education), [1595](#)
- ACh. *See* [Acetylcholine](#)
- AChE (acetylcholinesterase), [1040](#)
- AChEIs. *See* [Acetylcholinesterase inhibitors](#)
- Acne, lithium-induced, [1501](#)
- Acquired immune deficiency syndrome (AIDS). *See* [Human immunodeficiency virus disease](#)
- ACT (assertive community treatment), for schizophrenia, [1251](#), [1252–1253](#)
- ACTH. *See* [Adrenocorticotrophic hormone](#)
- Acupuncture

for pain, [1396](#), [1404](#), [1406](#)  
for PTSD, [1217](#)  
Acute stress disorder (ASD), [1212–1213](#), [1218–1219](#), [1602](#)  
AD. *See* [Alzheimer's disease](#)  
ADAPT (Adolescent Depression and Psychotherapy Trial), [1435](#)  
ADAS-Cog (Alzheimer's Disease Assessment Scale for Cognition), [664](#)  
Adasuve. *See* [Loxapine](#)  
ADCS-CGIC (Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change), [664](#), [692](#)  
Adderall, Adderall XR, [1085](#), [1087](#), [1092](#), [1503](#). *See also* [Amphetamines](#)  
Addiction Severity Index (ASI), [1025](#)  
Adeno-associated virus vectors for gene transfer, [18](#)  
Adenosine, [96–97](#), [1350](#)  
Adenosine deaminases that act on RNA (ADARs), [12](#)  
Adenosine receptor antagonists, [97](#)  
Adenosine receptors, [96–98](#)  
    brain distribution of, [96–97](#)  
    PET ligands to, [98](#)  
    in schizophrenia, [97–98](#)  
    subtypes of, [96–97](#)  
Adenosine triphosphate (ATP), [5](#), [83](#), [96](#), [97](#), [420](#)  
S-Adenosylmethionine (SAM-e), for depression, [1165](#)  
Adenovirus vectors for gene transfer, [18](#), [21](#)  
Adenylyl cyclase, [315](#), [948](#), [1108](#)  
    in CREB activation, [11](#)  
    inhibition by  $\alpha$  subunits of G protein, [61](#), [62](#)  
    receptor actions on, [48–49](#)  
        adrenergic receptors, [75](#), [76](#)  
        dopamine receptors, [67](#), [70](#), [71](#)  
        GABA<sub>B</sub> receptors, [94](#), [95](#)  
        muscarinic receptors, [79](#), [80](#)  
        opioid receptors, [101](#)  
        serotonin receptors, [59](#), [60](#), [61](#), [64](#), [585](#)  
ADHD. *See* [Attention-deficit/hyperactivity disorder](#)  
ADHD Rating Scale—Version IV (ADHD-RS-IV), [1087](#), [1455](#), [1472](#)  
Adinazolam, [567](#)  
Adjustment disorders, [1602](#), [1603](#)  
Adolescent Depression and Psychotherapy Trial (ADAPT), [1435](#)  
Adolescents. *See* [Child and adolescent disorders](#)  
Adoption studies, [117](#), [119](#)  
ADOS-G (Autism Diagnostic Observation Schedule—Generic), [1473](#)  
Adrafinil, [1089](#)

$\alpha_1$ -Adrenergic receptor antagonists, 1359

prazosin, 692, 712

for insomnia, 1359–1361, 1368

sleep-enhancing effects of, 1359

$\alpha_1$ -Adrenergic receptors, 76

drug affinity for

antidepressants

cyclic antidepressants, 308, 310, 322, 336

MAOIs, 286

nefazodone, 459

sertraline, 360

trazodone, 456

antipsychotics, 612

aripiprazole, 734, 735, 738, 834

asenapine, 797, 804

brexpiprazole, 734, 735, 738, 834

cariprazine, 834, 834

clozapine, 626

iloperidone, 809, 810

lurasidone, 822

olanzapine, 650, 652

quetiapine, 686, 1523

risperidone, 706, 707, 708, 1521

ziprasidone, 757

carbamazepine, 949

eslicarbazepine acetate, 949

oxcarbazepine, 949

ECT effects on, 1107

$\alpha_2$ -Adrenergic receptor agonists, 76. *See also* Clonidine; Guanfacine

$\alpha_2$ -Adrenergic receptor antagonists, 76

idazoxan, 712

$\alpha_2$ -Adrenergic receptors, 51, 76

autoreceptors, 76, 533

drug affinity for

antidepressants

cyclic antidepressants, 308, 309, 310

fluoxetine, 339

mirtazapine, 479

SNRIs, 533

antipsychotics, 612, 619

asenapine, 797

- quetiapine, 1523
- risperidone, 706, 707, **708**, 1521
- ECT effects on, 1107
- β-Adrenergic receptor antagonists
  - dosing of, **865**
  - drug interactions with, 866
    - paroxetine, **404**, 404–405
  - history and discovery of, 864
  - indications for, 865
    - acute stress disorder, 1219
    - akathisia, 864–865, **865**, 870, **871**, 1255
    - ECT, 1123, 1124, 1125
    - migraine prophylaxis, **1411**, **1414**
    - social anxiety disorder, 1199, 1202
    - trauma victims, 77
    - tremor, 865
  - mechanism of action of, 864
  - pharmacokinetics and disposition of, 864, **865**
  - pharmacological profile of, 864
  - side effects and toxicology of, 865–866
  - structure–activity relations for, 864
- β-Adrenergic receptors, 76–77
  - in Alzheimer’s disease with psychosis, 1519
  - drug affinity for
    - antidepressants, 77
      - cyclic antidepressants, 309
      - MAOIs, 286
      - SSRIs, 338–339
    - β-blockers, 864, 865
- Adrenocorticotrophic hormone (ACTH), **100**
  - bupirone effects on, 588
  - HPG axis abnormalities and, 168
  - in specific disorders
    - depression, 160, 161, 1156
    - psychosis, 162, 163
    - PTSD, 163
  - in stress response, 99, 157–158, **159**
  - synthesis of, 99
- ADRs. *See* **Dystonic reactions, acute**
- Advanced sleep phase disorder, 1072
- Adverse Events Reporting System (AERS), 1502
- Affective flattening, in schizophrenia, 1242, 1259

Affective lability, in borderline personality disorder, 1315

Aggression, 1606. *See also* [Violent behavior](#)

- in autism spectrum disorder, 1466
- causes of, 1606
- among children of depressed mothers, 1546
- in conduct disorder, 1456
- in dementia, 1518
- in disruptive mood dysregulation syndrome, 1459
- drug-induced
  - benzodiazepines, in PTSD, 1216
  - clozapine, 1364
  - gabapentin, 989
- kainate receptor abnormalities and, 90
- in oppositional defiant disorder, 1456
- in personality disorders, 1314, 1315, 1331
- serotonin and, 55
  - neuropeptide Y and, 63

Aggression treatment, 1606–1609, 1607

- in autism spectrum disorder, 1471, 1472
  - atypical antipsychotics, 1467, 1468
  - recommendations for, 1475
- benzodiazepines, 569, 1054
  - in elderly persons, 1524, 1526, 1627
- buspirone, 593
- in children and adolescents, 1456, 1457–1460
  - clinical recommendations for, 1460
  - clonidine, 1459–1460
  - lithium, 1458–1459
  - other atypical antipsychotics, 1458, 1460
  - psychostimulants, 1457
  - risperidone, 1457–1458
  - valproate, 1459

ECT, 1111, 1112

- in elderly patients, 1515, 1612, 1623–1628
  - anticonvulsants, 930–931, 1627
  - antipsychotics, 1518, 1521, 1522, 1523, 1525, 1526, 1623–1626
    - ziprasidone, 772–773
  - benzodiazepines, 1524, 1526, 1627
  - citalopram, 1521, 1525, 1628
  - dextromethorphan–quinidine combination, 1628
  - ECT, 1112
  - memantine combined with acetylcholinesterase inhibitor, 1043

- new approaches, 1628
- SSRI combined with cognitive enhancer, 1627–1628
- trazodone, 1626–1627
- emergency management, 1606–1609, **1607**
- fluoxetine, 343
- in personality disorders
  - antisocial personality disorder, 1328
  - borderline personality disorder, 1327, **1327**
    - antidepressants, **1321–1322**
    - antipsychotics, **1318–1319**
    - mood stabilizers, 1320, 1323, **1324–1325**
    - omega-3 fatty acids, 1323
  - schizotypal personality disorder, 1329
- in schizophrenia
  - for children and adolescents, 1464, 1466
  - clozapine, 631–632
- sertraline, 371
- valproate, 931
  - in borderline personality disorder, 1320, 1323, **1324–1325**
  - in children and adolescents, 1459
  - in elderly patients, 930–931

Aging. See [Elderly persons](#)

Agitation, 1606

- during alcohol withdrawal, 1613
- during barbiturate withdrawal, 1068
- during benzodiazepine withdrawal, 573, 1065
- in catatonia, 1605
- in delirium, 1612
- in dementia, 1515, 1518, 1519, 1612
- drug-induced
  - N*-acetylcysteine, 1473
  - amantadine, 863
  - amphetamine, 1086
  - aripiprazole, 746
  - brexpiprazole, 748
  - bupropion, 504, 1298
  - classic antipsychotics, **615, 719, 816**
  - iloperidone, **816**
  - methamphetamine, 1611
  - modafinil, 1090
  - olanzapine, **1370**
  - phencyclidine, 1611

- quetiapine, [693](#)
- risperidone, [693](#), [719](#), [816](#), [1463](#)
- SSRIs, [345](#), [1445](#), [1447](#), [1470](#), [1514](#)
- tranylcypromine, [295](#)
- varenicline, [1298](#)
- ECT-induced postictal, [1123-1124](#)
- in elderly persons, [1623](#)
- during nicotine withdrawal, [1255](#)
- in schizophrenia, [1244](#)
- in serotonin syndrome, [906](#)
- suicidality and, [1260](#), [1599](#)
- Agitation treatment, [1606](#)
  - in acute mania, [1610](#)
  - during alcohol withdrawal, [1613](#)
  - aripiprazole, [742](#)
  - asenapine, [803-804](#)
  - clonazepam, [569](#)
  - in delirium, [1612](#)
  - for ECT-induced postictal agitation, [1123-1124](#)
  - in elderly patients, [1515](#), [1612](#), [1623-1628](#)
    - anticonvulsants, [930-931](#), [1627](#)
    - antipsychotics, [1518](#), [1521](#), [1522](#), [1525](#), [1526](#), [1623-1626](#), [1624](#), [1626](#)
      - ziprasidone, [772-773](#)
    - benzodiazepines, [1524](#), [1526](#), [1627](#)
    - citalopram, [1521](#), [1525](#), [1628](#)
    - dextromethorphan-quinidine combination, [1628](#)
  - ECT, [1112](#)
  - memantine combined with acetylcholinesterase inhibitor, [1043](#)
  - new approaches, [1628](#)
  - SSRI combined with cognitive enhancer, [1627-1628](#)
  - trazodone, [1626-1627](#)
  - valproate, [930-931](#)
- haloperidol, [569](#), [742](#)
- lorazepam, [742](#)
- olanzapine, [663-665](#), [1522](#)
- quetiapine, [692](#), [693](#)
- risperidone, [1522](#)
- in schizophrenia, [1245](#), [1609-1610](#)
- in substance intoxication, [1611](#)
- Agomelatine
  - for depression, [469](#), [518](#)
  - for generalized anxiety disorder, [1209](#)

## Agoraphobia

gabapentin for, 987

genetics of, 121

## Agranulocytosis

absolute neutrophil count in, 635

drug-induced

benzodiazepines, 1065

carbamazepine, 1179

cariprazine, 848

classic antipsychotics, 619

clozapine, 604, 623, 628, 630, 631, 635-636, 640, 875, 1248, 1500, 1521, 1561, 1615

fluoxetine, 346

lurasidone, 825

mirtazapine, 965

treatment of, 636, 1615

AIDS (acquired immune deficiency syndrome). *See* Human immunodeficiency virus disease

AIMS (Abnormal Involuntary Movement Scale), 746, 869, 873, 1528

## Akathisia, 855-856

antipsychotic-induced, 1255

atypical antipsychotics, 871-874, 1247, 1500

aripiprazole, 742, 746, 747, 873, 1180

asenapine, 804, 873, 1464

brexpiprazole, 748, 874

cariprazine, 847, 847, 848, 849, 874, 1180

clozapine, 872

iloperidone, 816, 873-874

lurasidone, 823, 825, 873

olanzapine, 668, 669, 872, 1370

paliperidone, 873, 1463

quetiapine, 693, 872-873

risk factors for, 871

risperidone, 693, 816, 872, 1180

ziprasidone, 775, 873, 1180

classic antipsychotics, 609, 615, 617, 816, 871

in serotonin syndrome, 1615

sertraline-induced, 372

topiramate-induced, 1021

treatment of, 870-871, 1255-1256, 1607, 1614

amantadine, 863, 870

benzodiazepines, 866-867



- $\beta$ -blockers, [864–866](#), **865**, [1255](#)
  - clonidine, [870–871](#)
  - clozapine, [872](#)
  - mirtazapine, [486](#)
  - propranolol, [486](#), [1614](#)
  - trazodone, [458](#)
- Akinesia, antipsychotic-induced, [856](#), [1256](#)
- Akineton. *See* [Biperiden](#)
- Akt neuroprotective pathway, [891](#)
- AKT1* gene, [144](#)
- Alcohol
  - drug interactions with
    - barbiturates, [1068](#)
    - benzodiazepines, [230](#), [1065](#)
    - disulfiram, [1286](#)
    - pregabalin, [995](#)
    - TCAs, [326](#)
    - trazodone, [459](#)
  - GABA<sub>A</sub> receptor affinity of, [93](#), [95](#), [96](#)
- Alcohol-related disorders, [1284–1289](#)
  - benzodiazepine abuse and, [574](#), [575](#)
  - genetics of, **121**
  - incidence of, [1283](#), [1284](#)
  - mortality from, [1284](#)
  - psychiatric comorbidity with
    - antisocial personality disorder, nortriptyline for, [1328](#)
    - bipolar disorder
      - gabapentin for, [988–989](#)
      - valproate for, [932](#)
    - bulimia nervosa, [1338](#)
    - depression, [1154](#)
      - nefazodone for, [461](#)
    - schizophrenia, [1258](#), [1259](#)
  - serotonin and, [55](#)
  - smoking cessation in, [1300](#)
  - suicide and alcohol intoxication, [1598](#)
  - treatment of, [1284–1289](#)
    - acamprosate, [87–88](#), [1259](#), [1288](#)
    - amphetamine, [1093](#)
    - aripiprazole, [745](#)
    - buspirone, [592](#)
    - for detoxification, [1285–1286](#)

- disulfiram, [1259](#), [1286](#)
- mirtazapine, [484](#)
- modafinil for alcoholic brain syndrome, [1093](#)
- nalmefene, [1287-1288](#)
- naltrexone, [1259](#), [1286-1287](#)
- ondansetron, [1289](#)
- pregabalin, [994-995](#)
  - for relapse prevention, [461](#), [1283-1284](#), [1286-1289](#)
  - in schizophrenia, [1259](#)
- sertraline, [369](#)
- SSRIs, [344-345](#)
- topiramate, [1023-1024](#), [1026](#), [1288-1289](#), [1302](#)
  - for violent behavior during acute intoxication, [1611](#)
- Wernicke-Korsakoff syndrome and, [1613](#)
- Alcohol-type hypnotics, [1068-1069](#)
- Alcohol withdrawal, [1285-1286](#)
  - treatment of, [1285-1286](#), [1607](#), [1612-1613](#)
    - benzodiazepines, [1285](#), [1607](#)
    - carbamazepine, [967](#), [1286](#)
    - gabapentin, [988](#), [1286](#)
    - pregabalin, [994](#)
    - thiamine, [1613](#)
- Alcoholics Anonymous, [1024](#)
- Aldehyde dehydrogenase, [1286](#)
- Alfentanil
  - for ECT, [1122](#)
  - interaction with carbamazepine and oxcarbazepine, [963](#)
- Alleles, [122](#), [126](#)
  - case-control studies of, [132](#)
  - genotype and, [126](#)
  - population stratification of, [134-135](#)
  - positional cloning and, [16](#)
  - of single nucleotide polymorphisms, [129](#)
  - variations of, [122](#)
  - X- and Y-linked, [126](#)
- Allergic reactions to drugs. *See* [Hypersensitivity reactions to drugs](#)
- Allodynia, [1379](#)
  - in fibromyalgia, [1402](#)
- Alosetron, interaction with fluvoxamine, [425](#)
- Alprazolam, [563](#), [572](#)
  - dosing of, [1640](#)
  - drug interactions with

- carbamazepine and oxcarbazepine, [963](#), [966](#)
- fluvoxamine, [425](#)
- duration of action of, [568](#)
- indications for
  - agitation and aggression in elderly patients, [1627](#)
  - generalized anxiety disorder, [1205](#)
    - vs. imipramine, [1206](#)
    - vs. pregabalin, [993](#)–[994](#)
  - insomnia, [1353](#), [1364](#)
  - panic disorder, [563](#), [568](#), [1196](#), [1197](#), [1604](#)
  - social anxiety disorder, [1200](#), [1339](#)
- pharmacokinetics of, [566](#), [567](#), [572](#)
  - in elderly persons, [1506](#)
- side effects of, [570](#), [1196](#), [1364](#)
- structure of, [565](#)
- sustained-release, [567](#)
- use in pregnancy, [1566](#)–[1567](#)

ALS (amyotrophic lateral sclerosis), gabapentin in, [986](#), [990](#)

Alzheimer's disease (AD). *See also* [Dementia](#)

- assessment of psychopathology in, [1519](#)
- behavioral complications of, [1516](#), [1518](#), [1623](#)
- benzodiazepine use and risk of, [570](#)–[571](#), [1627](#)
- biomarkers for, [1039](#)
- early-onset autosomal dominant, [1039](#)
- genetics of, [14](#), [1039](#)
- neuropathology of, [248](#)
- neurotransmitters and receptors in, [1039](#)
  - acetylcholine, [1039](#)
  - norepinephrine, [76](#)
- PET studies in, [247](#), [248](#)
- psychosis in, [663](#), [1518](#)–[1519](#)
  - neurobiological mechanisms of, [1519](#)–[1520](#)
- rating scales for, [1519](#)
- transgenic mouse models of, [27](#)–[28](#)
- treatment of (*See* [Dementia treatment](#))
- vascular cognitive impairment and, [1044](#)

Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog), [664](#)

Alzheimer's Disease Cooperative Study— Clinical Global Impression of Change (ADCS-CGIC), [664](#), [692](#)

Amantadine, [862](#)–[863](#), [1659](#)

- dosing of, [862](#), [863](#), [1659](#)
- drug interactions with, [864](#)

- in elderly persons, [862](#)
- history and discovery of, [862](#)
- indications for
  - autism spectrum disorder, [1474](#)
  - cataplexy, [1094](#)
  - drug-induced sexual dysfunction, [399](#)
  - extrapyramidal side effects, [857](#), [862](#), [863](#), [870](#), [871](#)
  - influenza A, [862](#), [863](#)
  - neuroleptic malignant syndrome, [1614](#)
  - Parkinson's disease, [862](#), [863](#)
- mechanism of action of, [862–863](#)
- pharmacokinetics and disposition of, [862](#)
- pharmacological profile of, [862](#)
- side effects and toxicology of, [863–864](#)
- structure–activity relations for, [862](#)
- use in pregnancy, [864](#), [1566](#)
- use in renal disease, [862](#), [863](#)
- Ambien. *See* [Zolpidem](#)
- Amenorrhea. *See also* [Menstrual cycle](#)
  - antipsychotic-induced, [609](#), [618](#)
    - clozapine, [629](#)
    - risperidone, [720](#)
  - HPA axis in, [168](#)
- American Academy of Child and Adolescent Psychiatry, [1502](#)
- American Academy of Neurology, [633](#), [1002](#)
- American Academy of Pediatrics, [902](#)
- American Association of Directors of Psychiatric Residency Training (AADPRT), [1595](#)
- American Association of Emergency Psychiatry (AAEP), [1595](#)
- American College of Neuropsychopharmacology, [1625](#)
- American College of Rheumatology, [1402](#), [1404](#)
- American Diabetes Association, [638](#), [1254](#), [1499](#)
- American Psychiatric Association
  - guideline for treatment of bipolar disorder, [902](#)
  - guideline for treatment of panic disorder, [569](#)
  - monitoring guideline for antipsychotic use, [1254](#)
  - practice guideline on use of antipsychotics to treat agitation or psychosis in patients with dementia, [1626](#)
  - task force on benzodiazepine abuse, [574](#)
  - task force on electroconvulsive therapy, [1109](#), [1112](#)
    - safety in pregnancy, [1113](#)
  - task force on tardive dyskinesia, [874](#), [877–878](#)

American Society of Anesthesiology, [1122](#)  
Amfepramone, [1254](#)  
Amiloride, for lithium nephrotoxicity, [904](#)  
 $\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonists, [84–85](#), [89](#), [1045](#)  
 $\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, [51](#), [82–83](#), [84](#), [85](#), [88–89](#), [1042](#)  
brain distribution of, [85](#)  
classification of, [82](#)  
differential trafficking of subunits of, [88](#)  
drug effects on  
    antidepressant anticonvulsants, [88–89](#)  
    ketamine, [551](#), [556](#)  
    lamotrigine, [1002–1003](#)  
    lurasidone, [64](#)  
    topiramate, [1018](#)  
    vortioxetine, [64](#)  
in long-term potentiation, [88](#)  
in mouse model of Huntington's disease, [29](#)  
in regulation of synaptic plasticity, [84](#), [85](#), [88](#)  
Amino acids  
    effect of RNA editing on, [12](#)  
    excitatory, [81](#)  
    of huntington, [28–29](#)  
    mRNA coding for, [7](#)  
    neurotransmitters (See  [\$\gamma\$ -Aminobutyric acid](#); [Glutamate](#); [Glycine](#))  
    single nucleotide polymorphisms encoding exchanges of, [129–130](#)  
 $\gamma$ -Aminobutyric acid (GABA), [50](#), [92–93](#), [94–95](#), [568](#)  
    adenosine modulation of, [97](#)  
    brain distribution of, [92](#)  
    drug effects on  
        barbiturates, [1055](#), [1066](#)  
        benzodiazepines, [1054](#), [1205](#), [1353](#), [1364](#)  
        carbamazepine, [948](#)  
        gabapentin, [983–984](#)  
        lithium, [890](#)  
        topiramate, [1017](#), [1019](#)  
        vigabatrin, [1302](#)  
    glutamate modulation of, [90](#)  
    growth hormone regulation by, [165](#)  
    magnetic resonance spectroscopy studies of, [260](#), [984](#)  
        after ECT, [260](#), [1107](#)

- serotonin receptor modulation of, 64
- sleep promotion by, 1350, 1351
- in specific disorders
  - depression, 92–93, 984
  - panic disorder, 248
  - posttraumatic stress disorder, 248
  - schizophrenia, 93
- SPECT imaging of, 247, 248
- synthesis of, 92, 568
- transporter for, 58, 92
- $\gamma$ -Aminobutyric acid (GABA) receptors, 93–96
  - drug affinity for
    - alcohol, 96
    - baclofen, 96
    - barbiturates, 93, 1055, 1066–1067
    - benzodiazepines, 93, 96, 568, 866, 1054–1057, 1056, 1205, 1285, 1351, 1353
    - clozapine, 96
    - ethanol, 93, 95
    - gaboxadol, 96
    - $\gamma$ -hydroxybutyrate, 1069
    - methaqualone, 96
    - nonbenzodiazepine hypnotics, 96, 1057, 1076, 1351
    - olanzapine, 650
    - propofol, 96
    - tiagabine, 96
    - topiramate, 1017–1018
  - in encephalopathies, 87
  - GABA<sub>A</sub>, 47, 49, 87, 93–95, 568, 1054–1057
    - control of chloride ion channels by, 1054, 1055
    - molecular mechanism of benzodiazepine interaction with, 1055–1057, 1056
    - natural ligands in brain for, 1058–1060
    - structure and subunits of, 93, 568, 1054
  - GABA<sub>B</sub>, 62, 87, 93, 95–96, 568, 1068
  - GABA<sub>C</sub>, 568
  - in mouse model of Huntington's disease, 29
  - PET studies of, 247
- $\gamma$ -Aminobutyric acid transporter (GAT1), 58
  - tiagabine effects on, 96
- Aminophylline, interaction with carbamazepine, 967
- Amiodarone, interaction with iloperidone, 818

## Amitriptyline

dosing of, [311](#), [319](#), [1632](#)

drug interactions with

carbamazepine, [965](#)

SSRIs, [425](#)

indications for

borderline personality disorder, [1321](#)

depression, [306](#)

with anxiety, [317](#)

in elderly persons, [391](#)

vs. mirtazapine, [481](#)

vs. paroxetine, [390](#)

with psychotic features, [317](#)

vs. sertraline, [363](#)

insomnia, [1362](#), [1368](#)

nocturnal enuresis in children, [319](#)

pain syndromes, [319](#), [324](#), [1390](#), [1401](#), [1413](#)

fibromyalgia, [1403](#)

with fluoxetine, [344](#)

headache, [1411](#)

overdose of, [324](#)

pharmacokinetics of, [311](#), [311](#)

pharmacological profile of, [306](#), [308](#), [310](#), [326](#)

side effects of, [310](#)

anticholinergic effects, [314](#), [321](#), [326](#)

plasma concentration and, [314](#)

sedation, [322](#)

seizures, [321](#)

structure–activity relations for, [306](#), [307](#), [337](#)

Amobarbital, for catatonia, [1605](#)

Amobarbital interview, [1067](#)

## Amoxapine

antipsychotic effects of, [306](#), [317](#)

for depression, [306](#), [608](#)

with anxiety or psychotic features, [317](#)

dosing of, [311](#), [1634](#)

interaction with carbamazepine, [966](#)

pharmacokinetics of, [306](#), [310](#), [311](#), [311–312](#), [314](#)

pharmacological profile of, [308](#), [309](#)

side effects of

anticholinergic effects, [321](#)

neuroleptic malignant syndrome, [321](#)

- seizures, [321](#)
- tardive dyskinesia, [321](#)
- structure–activity relations for, [306](#), [307](#)

AMPA receptors. See [α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors](#)

Amphetamines

- abuse/dependence on, [1301–1303](#)
  - agonist replacement strategies for, [1301](#)
  - aripiprazole for, [745](#)
  - bupropion for, [504](#), [1301–1302](#)
  - laboratory screening for, [1611](#)
  - methylphenidate, [745](#)
  - modafinil for, [1302](#)
- dosing of, [1085](#), [1453](#), [1654](#)
  - in children and adolescents, [1503](#), [1654](#)
- drug interactions with, [1087](#)
- in elderly persons, [1095](#)
- FDA classification of, [1084](#)
- indications for
  - ADHD, [1084](#), [1091–1092](#), [1453](#)
    - vs. atomoxetine, [1454](#)
    - clonidine and, [1455](#)
    - valproate and, [930](#)
  - alcohol use disorder, [1093](#)
  - cataplexy, [1084](#), [1094](#)
  - cocaine abuse, [1093](#)
  - depression, [1095](#)
  - fatigue, [1094](#)
  - narcolepsy, [1084](#)
  - obesity, [1095](#)
  - stroke and traumatic brain injury patients, [1092–1093](#)
- mechanism of action of, [1086](#)
- pharmacokinetics and disposition of, [1086](#)
- pharmacological profile of, [1085](#)
- preparations of, [1085](#), [1503](#)
- side effects of, [1086–1087](#)
  - growth effects in children, [1504](#)
- psychosis
  - animal models of, [610](#), [652](#)
  - aripiprazole for, [745](#)
  - classic antipsychotics for, [610](#), [611](#)
  - olanzapine for, [652](#), [656](#)



- risperidone for, 710
- sudden death, 1504
- structure-activity relations for, 1083-1085
- stereospecificity, 1084-1085

AMPT ( $\alpha$ -methyl-*p*-tyrosine), 66-67, 72, 74-75, 315

Amygdala, 159

- in antidepressant effects of deep brain stimulation, 267
- in antidepressant effects of ketamine, 267
- cerebral blood flow in, 263
- in cocaine-seeking responses, 68
- CRH in, 158, 160
- dopamine transporter in, 69
- in fear response
  - fMRI studies of, 269
  - oxytocin modulation of, 99
- glutamate receptors in, 85, 86
- kainate receptors in, 89
- norepinephrine transporter in, 76
- in response to emotional faces, 257, 269
- serotonin receptors in, 59, 60, 64
- serotonin transporter in, 58, 263

Amyloid- $\beta$  peptide (A $\beta$ ), in Alzheimer's disease

- antiamyloid immunization, 1045
- citalopram-induced decrease in, 443

Amyloid PET imaging, 247, 248

Amyloid precursor protein (APP), 1045

- in Alzheimer's disease, 27
- expression in transgenic mice, 27

Amyotrophic lateral sclerosis (ALS), gabapentin in, 986, 990

AN. *See* [Anorexia nervosa](#)

Analgesics. *See also* [Pain management](#)

- nonopioid, 1377, 1381-1382, 1413
- opioid, 101, 1377, 1382-1390
- prevalence of use, 1377
- topical, 1393-1394, 1415

Anaphylaxis. *See also* [Hypersensitivity reactions to drugs](#)

- ketamine-induced, 555

Anemia

- aplastic, carbamazepine-induced, 957, 1179
- hemolytic, antipsychotic-induced, 619

Anesthesia

- barbiturates for, 1066, 1067

- benzodiazepine induction of, 568
- for ECT, 554, 1106, 1114, 1121, 1122–1124, 1125, 1126, 1127
- ketamine for, 540, 550–551, 552, 554, 555

Angelman syndrome, 122, 126

Anger/hostility. *See also* Aggression; Violent behavior

- benzodiazepine-induced, 570
- homicidality and, 1600
- serotonin in, 343
- in serotonin syndrome, 346
- treatment of
  - cariprazine, 846
  - clozapine, 631–632
  - fluoxetine, 343
  - quetiapine, 693

Angiotensin, 100

Angiotensin-converting enzyme (ACE) inhibitors, interaction with lithium, 907

Angiotensin receptor 1 blockers, interaction with lithium, 907

Anhedonia, 191

- in bipolar depression, 68
- in dementia, 1518
- in depression, 256, 258, 1151
- glutamate and, 260
- reward-processing paradigms and, 258
- in schizophrenia, 258, 1242, 1259, 1530
- scopolamine in, 80
- sickness behavior and, 191

Aniracetam, 1045

ANK3 gene, 141

Anorexia, drug-induced. *See* Appetite changes

Anorexia nervosa (AN), 1337, 1344–1345

- genetics of, 121
- mortality from, 666, 1344
- neuroendocrinology of, 168
- suicide and, 1344
- treatment of, 1344–1345, 1346
  - antidepressants, 1345
    - fluoxetine, 343, 1345
    - sertraline, 371
  - antipsychotics, 1345
    - olanzapine, 666–667
  - cognitive-behavioral therapy, 666
  - dialectical behavior therapy, 666

- family therapy, [1344](#)
- inpatient vs. outpatient, [1345](#)
- ANS. *See* [Autonomic nervous system](#)
- Antacid-drug interactions, [1506](#)
  - antipsychotics, [1517](#)
    - ziprasidone, [782](#)
  - benzodiazepines, [571-572](#)
  - $\beta$ -blockers, [866](#)
- Anterior capsulotomy, for OCD, [1212](#)
- Anti-NMDA receptor encephalitis, [87](#), [1113](#)
- Antiarrhythmic-drug interactions, [233](#)
  - antipsychotics, [620](#)
  - bupropion, [506](#)
  - iloperidone, [818](#)
  - paroxetine, [404](#), [404](#)
- Antibodies, [178](#)
  - $\beta$ -amyloid, [1045](#)
  - antithyroid, [165](#)
  - to botulinum toxin, [868](#)
  - HPA axis effects on formation of, [187](#), [188](#)
  - to NMDA receptor, [87](#)
  - response to vaccines, [181](#)
- Anticholinergic agents. *See also specific drugs*
  - abuse of, [860](#)
  - antihistamines, [861](#)
  - benztropine, [860-861](#)
  - biperiden, [861](#)
  - drug interactions with, [859-860](#)
  - in elderly persons, [859](#), [1508](#), [1525-1526](#)
  - indications for
    - acute psychosis, [1245](#)
    - ECT, [1122-1123](#), [1125](#)
    - extrapyramidal side effects, [614](#), [856-861](#), [857](#), [870](#), [871](#), [1255-1256](#), [1607](#)
    - avoiding in dementia patients, [1525-1526](#), [1527](#)
    - prophylaxis, [1609](#)
    - recurrence after withdrawal of, [876-877](#)
    - use in pregnancy, [1566](#)
  - tardive dystonia, [875](#), [1257](#)
- overdose of, [859](#)
- procyclidine, [861](#)
- side effects of, [858-859](#)

- delirium, 305, 614, 859, **1607**, 1615
- worsening of tardive dyskinesia, 874
- trihexyphenidyl, 856-860
- Anticholinergic effects of drugs
  - antipsychotics, 607, 612, 614, **615**, 1516, 1527
  - clozapine, 636, 1516, 1521
  - ziprasidone, 757
  - in elderly persons, 321, 614
  - paroxetine, 386, 392, 398
  - TCAs, 309, 320, 321-322, 326, 1615
- Anticoagulants. *See also specific drugs*
  - drug interactions with
    - in elderly persons, 1508
    - vitamin E, 869
  - for vascular cognitive impairment, 1043
- Anticodons, 7
- Anticonvulsants. *See also specific drugs*
  - carbamazepine, 941-970
  - drug interactions with, 233
    - carbamazepine, **963**, 964-965
    - methylphenidate, 1089
    - oxcarbazepine, **963**
    - paroxetine, **404**, 405
  - eslicarbazepine acetate, 941-942
  - gabapentin, 983-990, 995
  - lamotrigine, 1001-1012
  - oxcarbazepine, 941-970
  - pregabalin, 990-995
  - topiramate, 1017-1031
  - valproate, 923-936
- Antidepressants, 283-543, 1158-1162. *See also specific drugs and classes*
  - acute tryptophan depletion-induced depressive relapse in patients receiving, 55
  - anti-inflammatory effects of, 162, 195-196
  - assessing and optimizing response to, 1159-1161
    - ABCB1* genotyping, 227, 312-313, 388-389
    - epigenetic mechanisms, 124
    - familial aggregation of response, 123-124
    - HPA axis, 160-161, 184
    - immune system, 184
    - managing partial response, 1160
    - qEEG changes, 265

- reasons for poor response, [1161](#)
- serotonin transporter binding, [245](#)
- augmentation of, [1160](#), [1162](#)
  - atypical antipsychotics, [1160](#), [1162](#), [1515](#)
    - aripiprazole, [742-743](#)
    - brexpiprazole, [745-746](#)
    - cariprazine, [846](#)
    - quetiapine, [690](#)
    - risperidone, [716](#)
    - ziprasidone, [772](#)
  - bupropion, [459](#), [500](#)
  - buspirone, [591](#), [1160](#)
  - lamotrigine, [1007](#)
  - lisdexamfetamine, [1088](#)
  - lithium, [898](#), [1160](#), [1162](#)
  - thyroid hormone, [165](#), [1160](#), [1162](#), [1216](#)
  - topiramate, [1021](#)
- bupropion, [495-507](#)
- in children and adolescents, [1497-1498](#)
  - dosage and monitoring of, [1497](#), [1498](#)
  - side effects of, [1497-1498](#)
- choice of, [1158-1159](#), [1160](#)
- coadministered with hypnotics, [230](#)
- combinations of, [230](#)
- drug interactions with, [1159](#)
  - lithium, [906](#)
  - St. John's wort, [1165](#)
- duration of treatment with, [1159-1160](#), [1161](#)
- during ECT course of treatment, [1123](#)
- immune system effects of, [194-196](#)
- MAOIs, [283-299](#)
- mirtazapine, [479-489](#)
- nefazodone, [455](#), [459-463](#)
- pharmacogenetic studies of, [63](#)
- pharmacogenomics of, [226](#)
- with sleep-enhancing effects, [1362-1363](#)
- SSRIs
  - citalopram, [431-446](#)
  - escitalopram, [431-446](#)
  - fluoxetine, [335-350](#)
  - fluvoxamine, [419-426](#)
  - paroxetine, [385-406](#)

- sertraline, 359–373
- suicidality and, 346–347, 372, 393–395, 399–400, 425, 445–446, 1437, 1497
- switching between, 1161, 1162
- tetracyclic, 306 (*See also* Maprotiline)
  - for depression, 316
    - vs. fluvoxamine, 421
    - vs. paroxetine, 390
    - vs. trazodone, 457
  - pharmacokinetics of, 310–313, 311
  - side effects of, 320–324
  - structure–activity relations for, 306, 307
- trazodone, 455–459, 462–463
- treating side effects of, 1615–1616
- use in pregnancy and lactation, 1544–1545, 1550–1555
  - autism risk in infants after in utero exposure, 348, 1551
- vortioxetine, 64, 467–474

Antidepressants, tricyclic (TCAs), 305–326. *See also specific drugs*

- analgesic effects of, 319
- antiarrhythmic effects of, 323, 346
- in children and adolescents, 313–324, 318, 319–320, 1446
- dosing of, 311
  - in pregnancy, 1549
  - prospective dosing techniques, 315
- drug interactions with, 325–326
  - bupropion, 497
  - carbamazepine, 963, 965
  - MAOIs, 293, 325
  - methylphenidate, 1089
  - oxcarbazepine, 963
  - SSRIs, 350, 373, 404, 425, 1615
  - St. John’s wort, 1165
  - suvorexant, 1073
- in elderly persons, 313–314, 315, 318, 321, 322, 391, 392, 1507, 1510–1511
- familial aggregation of response to, 123–124
- history and discovery of, 305–306
- indications for, 316–320
  - ADHD, 318–319
  - borderline personality disorder, 1316
  - bulimia nervosa, 1338
  - depression, 306, 316–318

- with anxiety, 317
- with atypical features, 317
- in bipolar disorder, 317
- in children and adolescents, 318
- in elderly persons, 318, 391, 392
- lithium and, 898
- maintenance treatment, 316
- with melancholic features, 316–317
- vs. paroxetine, 390
- persistent depressive disorder (dysthymia), 318, 1159
- poststroke depression, 1093
- with psychotic features, 317
- in schizophrenia, 320
- vs. sertraline, 363
- treatment-resistant illness, 1162
- enuresis in children, 319–320
- generalized anxiety disorder, 396, 1206
- OCD, 318
- other disorders, 319–320
- pain syndromes, 310, 319, 1390–1391, 1400, 1401, **1413**
  - fibromyalgia, 1403, **1403**
  - headache, **1411**
  - low back pain, 1407
- panic disorder, 318, 1196–1197
- mechanism of action of, 55, **57**, 80, 305, 315
- neonatal withdrawal from, 324
- overdose of, 313, 314, 320, 321, 322, 323, 324, 326, 1316, 1390, 1511, 1615
- pharmacokinetics and disposition of, 310–315, **311**
  - absorption, 310
  - in children, 313–314
  - drug interactions and, 325–326
  - in elderly persons, 313, 1507
  - first-pass metabolism, 310
  - hepatic metabolism, 310–312
  - linear kinetics, 313
  - P-glycoprotein and blood–brain barrier, 312–313
  - plasma concentration and response, 314
  - plasma concentration and toxicity, 314–315, 320
  - plasma protein binding, 310
  - in pregnancy, 1549
  - prospective dosing techniques, 315

- steady-state concentrations, 313
- volume of distribution, 310
- pharmacological profile of, 306–310
  - receptor blockade, 306–307, 308
  - receptor sensitivity changes, 307–309
  - secondary effects, 309–310
- side effects and toxicology of, 320–325, 1390
  - anticholinergic effects, 309, 320, 321–322, 326
  - antihistaminic effects, 320, 322, 324
  - carbohydrate craving/weight gain, 324
  - cardiovascular effects, 310, 320, 322–323, 326
    - in children, 319–320
  - CNS effects, 320–321
  - cutaneous effects, 324
  - hematological effects, 324
  - hepatic effects, 323–324
  - mania, 317
  - plasma concentration and, 314–315
  - seizures, 320, 321
  - sexual dysfunction, 324
  - sweating, 324
  - teratogenicity, 324–325, 1554
  - treatment of, 1615–1616
- structure–activity relations for, 306, 307
- therapeutic blood level monitoring for, 313, 314
- use in pregnancy and lactation, 324–325, 348, 1549, 1554–1555
- Antifungal–drug interactions, 1507
  - aripiprazole, 749
  - brexpiprazole, 749
  - carbamazepine, 964, 967
  - cariprazine, 840
  - classic antipsychotics, 620
  - lurasidone, 822
  - quetiapine, 686
  - suvorexant, 1072
  - ziprasidone, 782
- Antihistamines. *See also specific drugs*
  - anticholinergic activity of, 861
  - indications for
    - extrapyramidal side effects, 857, 861–862, 1256
    - insomnia, 1068–1069, 1368
    - motion sickness, 861



- insomnia, [1068–1069](#)
- interactions with barbiturates, [1068](#)
- mechanism of action of, [80](#)
- pharmacological profile of, [861](#)
- Antihistaminic effects of drugs
  - antipsychotics, [607](#), [612](#), [618](#)
  - escitalopram, [431](#), [446](#)
  - TCAs, [320](#), [322](#), [324](#)
  - trazodone, [456](#)
  - venlafaxine, [515](#)
- Antihypertensive agents
  - interactions with aripiprazole, [749](#)
  - psychotropic drug-induced orthostatic hypotension in patients receiving TCAs, [322](#)
  - trazodone, [459](#)
  - for vascular cognitive impairment, [1043](#)
- Antimicrobial agent-drug interactions
  - antipsychotics, [620](#)
  - carbamazepine, [964](#), [967](#)
  - carbamazepine and oxcarbazepine, [963](#), [964](#), [967](#), [970](#)
  - clozapine, [641](#)
  - duloxetine, [542](#)
  - ketamine, [556](#)
  - quetiapine, [686](#)
  - suvorexant, [1072](#)
- Antioxidants, as cognitive enhancers, [1044–1045](#)
- Antiparkinsonian drugs, [856–864](#), [857](#), [870](#), [871](#)
  - amantadine, [862–864](#)
  - benztropine, [860–861](#)
  - biperiden, [861](#)
  - coadministered with antipsychotics, [230](#)
    - clozapine, [669](#)
    - olanzapine, [668–669](#)
    - risperidone, [669](#), [719](#)
  - diphenhydramine, [861–862](#)
  - procyclidine, [861](#)
  - prophylactic, [876–877](#), [1609](#)
  - trihexyphenidyl, [856–860](#)
  - use in pregnancy, [1566](#)
- Antipsychotics. *See also specific drugs*
  - atypical (second-generation; SGAs), [604](#), [620](#), [1241–1242](#), [1521](#)
    - aripiprazole and brexpiprazole, [731–750](#)

- asenapine, 797–806
- cariprazine, 831–851
- clozapine, 623–641
- iloperidone, 809–819
- lurasidone, 821–828
- olanzapine, 649–674
- quetiapine, 685–697
- risperidone and paliperidone, 705–723
- ziprasidone, 755–783
- in children and adolescents, 1462–1466, 1499–1500
  - dosage and monitoring of, 1499, **1499**
  - side effects of, 1499–1500
- choice of, 1246–1248, **1249**, 1254
- classic (first-generation; FGAs), 603–620, 1241
  - drug interactions with, 619–620
  - in elderly persons, 610, 663
  - formulations of, 609
  - history and discovery of, 603–604
  - indications for, 611–612
  - mechanism of action of, 610–611
  - pharmacokinetics of, 609–610
  - pharmacological profile of, 608–609, 612, **613**
  - side effects and toxicology of, 604, 609, 612–619, **615–616**, 620, 649, **650**, 1247
  - structure-activity relations for, 604–608, **605–606**
- coadministered with antiparkinsonian drugs, 230
- coadministered with mood stabilizers, 230
- combinations of, 230
- drug interactions with, 619–620
  - antacids, 782, 1517
  - carbamazepine, **963**, 965–966
  - classic antipsychotics, 619–620
  - lithium, 903, 905–906
  - oxcarbazepine, **963**
  - SSRIs, 350, 404, **404**, 1261
- in elderly persons, 1515–1531
- formulations of, **1249**, 1261, 1606–1609
  - intramuscular, 212–213, 221, 653, 661, 706, 1608–1609, 1610
  - long-acting injectables, 609–610, 620, 1245, 1247, **1249**, 1262
- immune system effects of, 196
- indications for, 611–612
  - augmentation of antidepressant treatment, 1160, 1162, 1515

- aripiprazole, 742-743
- brexpiprazole, 745-746
- cariprazine, 846
- quetiapine, 685, 690
- risperidone, 716
- ziprasidone, 772
- autism spectrum disorder, 1466-1469
- bipolar mania, 1179-1180
  - in children and adolescents, 1439-1440
  - in elderly persons, 1530-1531
  - vs. lithium, 892
- borderline personality disorder, 1315-1316, **1317-1319**, **1327**
- delirium, 424, 1528, 1612
- ECT-induced postictal agitation, 1123
- in elderly patients, 1518-1531
  - behavioral complications of dementia, 1517, 1518-1528, 1606-1608, **1607**, 1612
  - delirium, 1528
  - delusional disorder, 1530
  - diffuse Lewy body disease, 1528
  - mania, 1530-1531
  - OCD, 1531
  - Parkinson's disease dementia, 1528
  - schizophrenia, 1528-1530
- generalized anxiety disorder, 1209
- hiccups, 612
- Huntington's disease, 612
- insomnia, 1363, **1370**, 1371-1372
- mood disorders, 611-612
- nausea/vomiting, 607, 612
- panic disorder, 1198
- personality disorders, 611
- psychotic depression, 317, 1159, 1166
- schizophrenia and schizoaffective disorder, 267, 611, 1245-1249, **1249**
  - CATIE study, 604, 620, 631, 637, 658, 661, 669, 688, 694, **695**, 696, 697, 713, 714, 715, 718, 720, 721, 722, 764-765, 766, 767, 776, 778, 779-780, 871, 875, 1106, 1246-1247, 1250, 1253, 1254, 1255, 1524
  - in children and adolescents, 1462-1466
  - in elderly persons, 1528-1530
  - mirtazapine and, 486
- substance-induced psychosis, 611

- Tourette syndrome, 612, 1461, 1462
- mechanism of action of, 63, 71, 213
  - PET studies of, 266-267
- minimal effective concentration of, 213
- new drug development, 1261-1262
- noncompliance with, 1245, 1248, 1261
- pharmacogenomics of, 226
- pharmacological profile of, 608-609, 612, **613**
  - D<sub>2</sub> receptor blockade, 71, 213, 266-267, 607-609, 610, 612, **613**, 655, 732, **733**, 834, 869, 1241, 1242, 1262, 1518
    - extrapyramidal side effects and, 72, 609, 614, 732, **733**, 737, 869-870
- relapse after discontinuation of, 1246
- side effects and toxicology of, 424, 612-619, 620, 649, **650**, 1247-1248
  - anticholinergic effects, 607, 612, 614, **615**
  - cardiovascular effects, 424, 612, **615**, 617-618
  - in children and adolescents, 1499-1500
  - classic antipsychotics, 612-619, **615**-616
  - cognitive effects, 614, **615**
  - cutaneous effects, **616**, 619
  - in elderly persons, 1516-1517
  - endocrine effects, **616**
  - extrapyramidal side effects, 424, 604, 609, 611, 614, **615**, 617, 855-878, 1242, 1247, 1255-1256, 1316, 1614
  - gastrointestinal effects, **618**
  - hematological effects, **616**, 619
  - hyperprolactinemia, 609, 612, 618-619, 1257-1258
  - neuroleptic malignant syndrome, 617, 1257, 1614
  - ocular effects, **616**, 619
  - PET studies of, 266-267
  - sexual dysfunction, **616**, 619
  - stroke/mortality risk in elderly dementia patients, 424, 663, 717, 774, 818, 825, 848, **1370**, 1517, 1520, 1612, 1625-1626
  - tardive dyskinesia and tardive dystonia, 856, 875-876, 1256-1257
  - treatment of, **1607**, 1614-1615
  - urinary hesitancy/retention, 618
  - weight gain/metabolic effects, **616**, 618, 1247-1248, 1253-1254
    - management of, 1027-1028, 1254
    - role of 5-HT<sub>2C</sub> receptors in, 63, 64
  - use in pregnancy and lactation, 610, 1562-1566
- Antiretroviral agent-drug interactions
  - benzodiazepines, 572
  - bupropion, 506

carbamazepine and oxcarbazepine, **963**, **964**, 967  
quetiapine, **686**  
suvorexant, **1072**

Antisocial personality disorder, **121**, 1328

#### Anxiety

during alcohol withdrawal, **1285**  
in autism spectrum disorder, **1466**  
during barbiturate withdrawal, **1068**  
during benzodiazepine withdrawal, **573**, **1065**  
    rebound anxiety, **570**, **1057**, **1062**, **1205**  
borderline personality disorder and, **1315**  
bulimia nervosa and, **1338**  
Cluster C personality disorders and, **1329**  
depression and, **317**, **341**, **441–442**, **1153–1154**  
    bupropion for, **501**  
    buspirone for, **591–592**, **593**  
    SSRIs for, **341**, **441–442**, **501**  
    TCAs for, **317**

#### drug-induced

aripiprazole, **746**  
benzodiazepines, **570**  
haloperidol, **719**, **816**  
iloperidone, **816**, **817**  
methylxanthines, **97**  
risperidone, **719**, **816**  
SSRIs, **345**  
topiramate, **1029**, **1030**  
ziprasidone, **774**, **775**  
after guanfacine discontinuation, **1501**  
hyperthyroidism and, **165**  
norepinephrine transporter in, **76**  
pain and, **1378**, **1412**  
    fibromyalgia, **992**, **1402**  
in pregnancy, **1545–1546**  
psychic, **569**, **1205–1209**  
sleep disturbances and, **1075**, **1349**  
after SSRI discontinuation, **1615**  
suicide risk and, **1597**

Anxiety disorders. *See also specific anxiety disorders*

genetics of, **121**  
HPA axis in, **99**  
treatment of, **1195–1220**

- acute stress disorder, [1218–1219](#)
- in children and adolescents, [485](#), [1432](#)
- generalized anxiety disorder, [1204–1210](#)
- OCD, [1210–1212](#)
- panic disorder, [1195–1199](#)
- PTSD, [1212–1218](#)
- social anxiety disorder, [1199–1203](#)
- specific phobia, [1203–1204](#)

#### Anxiolytics

- benzodiazepines, [563–578](#), [1052](#), [1054](#), [1062](#)
- buspirone, [585–594](#)
- gabapentin, [986–987](#)
- use in children and adolescents, [1444](#), [1445](#), [1446](#), [1450](#)
- use in elderly persons, [564](#), [567](#), [572](#), [577](#), [590](#), [593](#), [1075–1076](#), [1196](#), [1285](#), [1520](#), [1524](#), [1526](#), [1627](#)
- use in pregnancy and lactation, [576–577](#), [1065](#), [1566–1568](#)

Aplastic anemia, carbamazepine-induced, [957](#), [1179](#)

Aplenzin. *See* [Bupropion](#)

Apnea-hypopnea index (AHI), [458](#), [484](#)

Apolipoprotein E (ApoE),  $\epsilon$ 4 allele, and response to mirtazapine, [483](#)

APP. *See* [Amyloid precursor protein](#)

#### Appetite changes

- in depression, [1151](#)
- drug-induced
  - asenapine, [804](#), [1439](#)
  - atomoxetine, [1472](#), [1499](#)
  - bupropion, [1498](#)
  - buspirone, [1474](#)
  - clomipramine, [1448](#), [1449](#)
  - clozapine, [626](#)
  - duloxetine, [1443](#)
  - fluoxetine, [1470](#)
  - guanfacine, [1472](#), [1501](#)
  - isocarboxazid, [290](#)
  - ketamine, [555](#)
  - mirtazapine, [487](#), [1369](#), [1471](#), [1498](#)
  - olanzapine, [1179](#), [1316](#)
  - psychostimulants, [1088](#), [1095](#), [1472](#), [1502](#)
  - quetiapine, [1316](#)
  - riluzole, [1474](#)
  - risperidone, [1458](#)
  - sertraline, [371](#)

- TCAs, [322](#)
- topiramate, [1021](#), [1029](#), [1440](#), [1502](#)
- valproate, [933](#)
- venlafaxine, [1208](#), [1436](#), [1498](#)
- Aptensio XR. *See* [Methylphenidate](#)
- Aptiom. *See* [Eslicarbazepine acetate](#)
- Arbaclofen, for autism spectrum disorder, [1473–1474](#)
- Area under the curve (AUC), [209](#), [212](#)
- Aripiprazole, [731–750](#)
  - in children and adolescents, [739–740](#), [742](#), [1438](#), [1439](#), [1449–1450](#), [1462](#), [1463](#), [1465](#), [1499](#)
  - discontinued formulations of, [736](#), [738](#)
  - dosing of, [221](#), [734–735](#), [736](#), [738](#), [739](#), [1180](#), [1646](#)
    - in children and adolescents, [1499](#), [1646](#)
    - in elderly patients, [1523](#)
  - drug interactions with, [736](#), [749](#)
    - carbamazepine, [963](#), [966](#)
    - oxcarbazepine, [963](#)
  - in elderly patients, [744](#), [1523](#)
  - formulations of, [1249](#), [1606](#)
    - intramuscular, [1608](#), [1609](#), [1610](#)
    - long-acting injectable, [221](#), [736](#), [740](#), [742](#), [747](#), [1247](#)
  - history and discovery of, [731–732](#), [831](#)
  - indications for, [738–745](#)
    - adjunctive treatment of depression, [735](#), [738](#), [742–743](#)
    - aggression in children and adolescents, [1458](#)
    - agitation, [738](#), [742](#)
    - alcohol dependence, [745](#)
    - amphetamine dependence, [745](#)
    - autism spectrum disorder, [735](#), [738](#), [743](#), [1455](#), [1466](#), [1468](#)
    - behavioral complications of dementia, [744](#), [1523](#)
    - behavioral emergencies, [1608](#), [1610](#)
    - bipolar disorder, [738](#), [741–742](#)
      - in children and adolescents, [742](#), [1438](#), [1439](#)
      - depressive episodes, [741](#)
      - maintenance treatment, [741–742](#), [1185](#)
      - mania, [738](#), [741](#), [1180](#), [1610](#)
    - borderline personality disorder, [744](#), [1319](#)
    - clozapine augmentation, [634](#)
    - cocaine abuse, [846](#)
    - OCD in children and adolescents, [1449–1450](#)
    - schizophrenia, [734](#), [738–741](#)

- behavioral emergencies, 1610
- vs. cariprazine, 840, **841**, 843
- in children and adolescents, 739–740, 1462, 1463, 1465
- maintenance treatment/relapse prevention, 738, 739, 740–741, 1249
- with substance use disorder, 1259
- SSRI augmentation, 500
- Tourette syndrome, 735, 738, 743–744, 750, 1461
- mechanism of action of, 731, 737–738
- pharmacokinetics and disposition of, 221, 734–736
- pharmacological profile of, 734, **735**, 831, 833, **834**, 836
- side effects and toxicology of, 737–738, 746–748, 750, 1180, 1439, 1461, 1463, 1468
  - extrapyramidal side effects, 746, 747, 871, 873, 1247
- structure–activity relations for, 734, **734**
- use in pregnancy and lactation, 1564
- Aripiprazole lauroxil, 736, 738, 741, 747
- Arizona Sexual Experiences Scale, 472
- Armodafinil, 1090–1091, **1654**
  - FDA classification of, **1084**
  - indications for, **1084**, 1090–1091
    - antidepressant augmentation, 1160
    - bipolar depression, 1096
    - fatigue, 1094
    - narcolepsy, 1091
    - obstructive sleep apnea, 1091
    - schizophrenia, 1096
  - interaction with carbamazepine, 966
  - pharmacokinetics of, 1091
  - single isomer, 226
  - structure–activity relations for, 1090
- Aromatic amino acid decarboxylase (AADC), **56–57**, **66–67**, **74–75**, 245, **246**
- Arrhythmias
  - drug-induced
    - amphetamine, 1086
    - citalopram, 431
    - classic antipsychotics, 424, **615**, 618
    - hydroxyzine, 1208
    - ketamine, 555
    - TCAs, 323, 326, 1390
  - ECT-induced, 1124
  - use of nicotine replacement therapies in patients with, 1297
- Artane. See **Trihexyphenidyl**



Arterial spin labeling (ASL), 262–263

Arthralgia, drug-induced

- bupropion, 504
- fluoxetine, 346

Arthritis Foundation, 1404

AS3MT gene, 143

ASD. *See* Acute stress disorder

Asenapine, 797–806

- in children and adolescents, 799, 803, 1438, 1439, 1462, 1464, **1499**, **1646**
- dosing of, 798, 799–800, 801, 806, **1646**
- in children and adolescents, **1499**
- drug interactions with, 799
- formulations of, 797, 798
- history and discovery of, 797
- indications for, 797, 799–804
- agitation, 803–804
- bipolar manic or mixed episodes, 799, 802–803, 1180
- in children and adolescents, 799, 803, 1438, 1439
- combined with lithium or valproate, 803
- vs. olanzapine, 802–803
- schizophrenia, 799, 800–802
- in children and adolescents, 1462, 1464
- maintenance treatment, 799, 801–802
- short-term efficacy, 800–801
- mechanism of action of, 797–798
- pharmacokinetics of, 798–799
- pharmacological profile of, 797–798
- side effects and toxicology of, 804–806, 1180, 1248, 1253, 1439, 1464
- extrapyramidal side effects, 801–802, 873
- structure–activity relations for, 797, **798**
- use in renal and hepatic disease, 799

Aseptic meningitis, lamotrigine-induced, 1010

ASI (Addiction Severity Index), 1025

ASL (arterial spin labeling), 262–263

Aspartate, 47, 81, 83

Aspirin, 1381, 1382

- combined with opioids, 1398
- interaction with valproate, 936
- for low-back pain, 1406
- for vascular cognitive impairment, 1043, 1044

Assaultive behavior, **1603**, 1606–1609, **1607**. *See also* Aggression; Violent behavior

Assertive community treatment (ACT), for schizophrenia, [1251](#), [1252–1253](#)

Association studies, [118](#), [128](#), [132–135](#)

- genomewide, [135–142](#)
- HapMap and 1,000 Genomes projects, [134](#), [136](#)
- linkage disequilibrium, [132–134](#), [136](#), [139](#)
- population stratification, [134–135](#)
- replication of, [134](#)

Astemizole, [861](#), [1507](#)

Asthenia, drug-induced

- gabapentin, [987](#), [989](#)
- nefazodone, [462](#)
- quetiapine, [693](#)
- risperidone, [693](#)
- SSRIs, [371](#), [398](#), [423](#), [424](#), [1448](#)

Asthma, [178](#), [193](#), [194](#), [437](#)

Astrocytes

- 5-HT<sub>1A</sub> receptor expression on, [60](#)
- role in neurotransmission, [47](#)

Ataxia

- drug-induced

  - alcohol-type hypnotics, [1069](#)
  - amantadine, [863](#)
  - benzodiazepines, [570](#), [572](#), [1065](#), [1205](#), [1627](#)
  - carbamazepine, [944](#), [957](#), [1179](#)
  - gabapentin, [987](#), [989](#)
  - lamotrigine, [1011](#), [1502](#)
  - topiramate, [1028](#)

- after SSRI discontinuation, [1615](#)
- in Wernicke-Korsakoff syndrome, [1613](#)

Atenolol, [864](#), [865](#)

Atomoxetine

- for ADHD, [76](#), [1453–1454](#), [1456](#), [1657](#)

  - with oppositional defiant disorder or conduct disorder, [1456–1457](#)
  - with tic disorders, [1454](#)

- for autism spectrum disorder, [1472–1473](#)
- dosage and monitoring of, [1498–1499](#), [1657](#)
- side effects of, [1472](#), [1499](#)

  - sudden death, [1504](#)

- suicidality and, [1499](#)

Atopic dermatitis, doxepin for, [320](#)

ATP (adenosine triphosphate), [5](#), [83](#), [96](#), [97](#), [420](#)

Atracurium, interaction with carbamazepine and oxcarbazepine, [963](#)

Atropine, [308](#)

for ECT, [1122-1123](#), [1125](#)

Attention-deficit/hyperactivity disorder (ADHD), [1452](#)

clinical features of, [1432](#)

comorbidity with

aggression, [1457-1460](#)

autism spectrum disorder, [1471](#), [1472](#), [1473](#)

bipolar disorder, [930](#), [1432](#)

conduct disorder, [1456](#)

oppositional defiant disorder, [1456](#)

Tourette syndrome, [1461](#), [1462](#)

genetics of, [127](#), [129](#), [143](#)

neurotransmitters and receptors in

dopamine D<sub>4</sub> receptor, [72](#)

dopamine transporter, [69](#)

norepinephrine transporter, [76](#)

PET studies in, [244](#), [245](#)

practice parameters for diagnosis and management of, [1502](#)

treatment of, [1452-1456](#)

atomoxetine, [76](#), [1453-1454](#)

behavior therapy, [1432](#)

bupropion, [503](#)

buspirone, [593](#)

in children with Tourette syndrome, [1461](#), [1462](#)

clinical recommendations for, [1455-1456](#)

clonidine, [76](#), [1454-1455](#), [1461](#), [1500](#)

guanfacine, [76](#), [1455-1456](#)

modafinil, [1092](#)

Multimodal Treatment of ADHD study, [1505](#)

parent training, [1458](#)

Preschool ADHD Treatment Study, [1453](#), [1505](#)

psychostimulants, [214](#), [503](#), [1084](#), [1087](#), [1091-1092](#), [1452-1453](#), [1455-1456](#), [1457](#)

risperidone, [1457-1458](#)

TCAs, [318-319](#)

valproate, [1459](#)

Attention problems

in autism spectrum disorder, [1466](#)

drug-induced

topiramate, [1028](#), [1029](#)

venlafaxine, [1471](#)

in schizophrenia, [1243](#), [1249](#)

AUC (area under the curve), [209](#), [212](#)  
Australian Register of Antiepileptic Drugs in Pregnancy, [1559](#)  
Autism Diagnostic Observation Schedule— Generic (ADOS-G), [1473](#)  
Autism spectrum disorder, [1466](#)  
    ADHD and, [1471](#), [1472](#), [1473](#)  
    clinical features of, [1466](#)  
    genetics of, [121](#), [123](#), [126](#), [127](#)  
    maternal antidepressant use and risk of, [348](#), [1550](#)  
    neuroimaging in, [262](#)  
    prevalence of, [1466](#)  
Autism spectrum disorder treatment, [1466–1475](#)  
    *N*-acetylcysteine, [1473](#), [1475](#)  
    anticonvulsants, [1471–1472](#)  
        lamotrigine, [1471](#)  
        levetiracetam, [1472](#)  
        oxcarbazepine, [1471–1472](#)  
        valproate, [1471](#)  
    antidepressants, [1469–1471](#)  
        clomipramine, [1470–1471](#)  
        mirtazapine, [1471](#)  
        reboxetine, [1471](#)  
        SSRIs, [1469–1470](#)  
            citalopram, [1470](#)  
            escitalopram, [1470](#)  
            fluoxetine, [345](#), [1469–1470](#)  
            fluvoxamine, [1470](#)  
            sertraline, [1470](#)  
        venlafaxine, [1471](#)  
    arbaclofen, [1473–1474](#)  
    atomoxetine, [1472–1473](#)  
    atypical antipsychotics, [1466–1469](#)  
        aripiprazole, [735](#), [738](#), [743](#), [1455](#), [1466](#), [1468](#)  
        olanzapine, [1468](#)  
        quetiapine, [1469](#)  
    risperidone, [716–717](#), [1466–1468](#)  
        *N*-acetylcysteine and, [1475](#)  
        amantadine and, [1474](#)  
        buspirone and, [593](#), [1474](#)  
        celecoxib and, [1474](#)  
        memantine and, [1474](#)  
        pentoxifylline and, [1474–1475](#)  
        riluzole and, [1474](#)

- ziprasidone, [1469](#)
- bumetanide, [1473](#)
- classic antipsychotics: haloperidol, [1469](#)
- clinical recommendations for, [1475](#)
- clonidine, [1472](#)
- guanfacine extended release, [1472](#)
- intranasal oxytocin, [1473](#)
- lithium, [1472](#)
- melatonin for insomnia, [1355–1356](#)
- methylphenidate, [1472](#)
- social skills training, [1432](#)
- Autoimmune disorders, [87](#), [178](#), [179](#)
  - depression and, [190](#)
    - TNF antagonists for, [191](#)
  - glucocorticoids for, [188](#)
- Autonomic nervous system (ANS)
  - during alcohol or sedative-hypnotic withdrawal, [1613](#)
  - immune system and, [186–187](#)
  - in neuroleptic malignant syndrome, [1257](#), [1516](#), [1614](#)
  - in serotonin syndrome, [1615](#)
- Autoreceptors, [50–51](#)
  - $\alpha_2$ -adrenergic, [76](#), [533](#)
  - dopamine D<sub>2</sub>, [67](#), [71](#)
  - GABA<sub>B</sub>, [95](#)
  - glutamate, [83](#), [91](#)
  - muscarinic M<sub>2</sub>, [79](#), [80](#)
  - nerve terminal, [51](#)
  - serotonin, [57](#), [59](#), [61](#), [245](#), [340](#), [533](#), [585](#)
  - somatodendritic, [50–51](#)
- Autosomes, [126](#)
- Avoidant personality disorder, [1328](#), [1329–1330](#)

- B cells, [178](#)
  - in depression, [182](#)
- Back pain, [1377](#), [1379](#), [1380](#), [1400](#), [1404-1405](#)
  - burden of, [1405](#)
  - causes of, [1405](#)
  - economic cost of, [1405](#)
  - evaluation of, [1405](#), [1406](#)
  - prevalence of, [1405](#)
  - psychosocial factors predicting outcome of, [1405](#), [1406](#)
  - sertraline-induced, [371](#)
  - treatment of, [1405-1407](#)
    - acetaminophen, [1381](#)
    - duloxetine, [1391](#)
    - maprotiline, [319](#)
    - nonpharmacological
      - cognitive-behavioral therapy, [1395](#)
      - exercise, [1399](#)
      - pain self-management programs, [1397](#)
    - opioids, [1384](#)
    - surgery, [1405](#)
- Baclofen, [96](#), [1393](#)
- BALANCE (Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation) study, [896](#)
- Balneotherapy, for fibromyalgia, [1403](#)
- Barbital, [1052](#), [1065](#)
- Barbitone, [1067](#)
- Barbiturates, [563](#), [1051](#), [1065-1068](#)
  - contraindications to, [1067](#)
  - dependence on, [1068](#)
  - drug interactions with, [1068](#)
    - TCAs, [325-326](#)
  - effects on stages of sleep, [1067](#)
  - history and discovery of, [1052](#), [1065-1068](#)
  - indications for, [1067-1068](#)
    - anxiety, [563](#)
    - catatonia, [1605](#)
  - mechanism of action of, [1066](#)
  - overdose of, [1067](#), [1068](#)
  - pharmacokinetics and disposition of, [1067](#), [1507](#)
  - pharmacological profile of, [93](#), [1066-1067](#)
  - side effects and toxicology of, [1068](#)

- structure–activity relations for, 1066
- suicidality and, 1068
- use in hepatic disease, 1067–1068
- withdrawal from, 1068

Barbituric acid, 1065, 1066

Bariatric surgery, 1254

Barnes Akathisia Rating Scale (BARS), 746, 748, 848

Basal (core) promoters, 6

Bath salts, 1611

BBB. *See* [Blood–brain barrier](#)

BChE (butyrylcholinesterase), 1040, 1041, 1042

bcl-2, 891, 926

BCRP (breast cancer resistance protein), 212

BDI (Beck Depression Inventory), 436, 666

BDNF. *See* [Brain-derived neurotrophic factor](#)

Beck Depression Inventory (BDI), 436, 666

BED. *See* [Binge-eating disorder](#)

BEHAVE-AD (Behavioral Pathology in Alzheimer’s Disease Rating Scale), 1519

Behavior therapy, for ADHD, 1432

Behavioral activation, for depression, 1164

Behavioral disinhibition, in dementia, 1518

Behavioral inhibition, in Cluster C personality disorders, 1329

Behavioral Pathology in Alzheimer’s Disease Rating Scale (BEHAVE-AD), 1519

Belsomra. *See* [Suvorexant](#)

Benadryl. *See* [Diphenhydramine](#)

Benzamide antipsychotics, 608. *See also* [Sulpiride](#)

Benzodiazepine antagonists, 1018, 1058, 1059

Benzodiazepine inverse agonists, 1058, 1059

Benzodiazepine partial agonists, 1058, 1059

Benzodiazepine receptors

- drug affinity for, 1052, 1054
  - barbiturates, 1055, 1066–1067, 1076
  - benzodiazepines, 568, 866, 1054–1057, 1076, 1205, 1285, 1351, 1353
  - carbamazepine, 948
  - nonbenzodiazepine hypnotics, 96, 1057, 1076, 1351
  - topiramate, 1017–1018

GABA<sub>A</sub>, 47, 49, 87, 93–95, 568, 1054–1057

- control of chloride ion channels by, 1054, 1055
- molecular mechanism of benzodiazepine interaction with, 1055–1057, 1056
- natural ligands in brain for, 1058–1060
- structure and subunits of, 93, 568, 1054

imaging studies of, [93](#), [247](#), [248](#)

tissue distribution of, [1054](#)

$\omega$ , [1054](#)

zolpidem binding to, [1057](#)

Benzodiazepines, [563–578](#), [1051](#), [1053–1065](#). *See also specific drugs*

abuse potential of, [574–575](#), [1057](#), [1196](#), [1353](#), [1364](#), [1446](#)

age-related use of, [564](#)

in children and adolescents, [1445](#), [1446](#), [1450](#)

coadministered with SSRIs, [230](#)

contraindications to, [1064–1065](#), [1205](#), [1285](#)

adjustment disorders, [1602](#)

delirium, [1612](#)

discontinuation of, [1065](#), [1196](#), [1198](#), [1205](#)

pregabalin for, [995](#)

rebound anxiety after, [570](#), [1057](#), [1062](#), [1205](#)

rebound insomnia after, [570](#), [1057](#), [1062](#), [1063](#)

dosing of, [1064](#)

drug interactions with, [567](#), [571–572](#)

alcohol, [230](#), [1065](#)

carbamazepine, [963](#), [966](#)

oxcarbazepine, [963](#), [968](#)

suvorexant, [1073](#)

duration of action of, [564](#), [567](#)

sustained-release formulations, [567–568](#)

effects on stages of sleep, [1060–1062](#), [1062](#)

in elderly persons, [564](#), [567](#), [572](#), [577](#), [1075–1076](#), [1196](#), [1285](#), [1520](#), [1524](#), [1526](#), [1627](#)

endogenous, [1059](#)

history and discovery of, [563–564](#), [1052](#), [1052–1053](#)

indications for, [568–569](#), [866–867](#), [1062–1064](#)

acute psychosis, [1245](#)

acute trauma exposure, [1603–1604](#)

alcohol or sedative-hypnotic withdrawal, [1285](#), [1607](#), [1613](#)

anxiety disorders, [563](#), [568](#), [1062](#)

assaultive, aggressive, or violent behavior, [1606](#), [1607](#), [1608](#)

during substance intoxication, [1611](#)

behavioral complications of dementia, [571](#), [1520](#), [1524](#), [1526](#), [1627](#)

borderline personality disorder, [1323](#)

catatonia, [1605](#)

extrapyramidal side effects, [866–867](#), [870](#), [1255](#), [1607](#)

generalized anxiety disorder, [396](#), [569](#), [589](#), [1205](#), [1210](#)

vs. buspirone, [589–590](#)



insomnia, 1063–1064, 1074, 1075, 1353–1354, **1364**  
low back pain, 1406, **1406**  
mania, 1610  
neuroleptic malignant syndrome, **1607**, 1614  
panic disorder, 568–569, 1196, 1604  
    in children and adolescents, 1445  
    combined with MAOIs, 289  
serotonin syndrome, **1607**, 1615  
social anxiety disorder, 569, 1199, 1200  
tardive dyskinesia, 867  
lipophilicity of, 216, 564, 567, 1060  
long-term use of, 563, 567, 867, 1060, 1205  
    CT brain scans, 570  
    dose escalation and, 572, 574  
mechanism of action of, 568, 866, 1351  
medicolegal issues with, 575–578  
overdose of, 1065  
pharmacokinetics and disposition of, 564–567, **566**, 572, 1060, **1061**, **1064**  
    elimination half-lives, 216, **566**, 567, 569–570, 572, 1060, 1064, **1064**  
pharmacological profile of, 1054–1057  
    benzodiazepine antagonists, partial agonists, and inverse agonists, 1058, **1059**  
    GABA<sub>A</sub> receptor affinity, 93, 96, 1054–1057, **1056**  
    natural ligands for benzodiazepine receptors in brain, 1058–1060  
side effects and toxicology of, 569–571, 1065, 1196, 1205, **1364**  
    cognitive impairment, 570–571, 1065, 1205, 1353, 1524, 1627  
        Alzheimer's disease risk and, 570–571, 1627  
    in elderly patients, 1627  
    hyperexcitability, 570  
    psychomotor impairment, 570, 577–578, 1205, 1353  
    teratogenic effects, 576, 577, 1566–1567  
structure–activity relations for, 564, **565**, 1053, **1053**  
switching between, 572  
tolerance and dependence on, 570, 572, 573–574, 590, 1065, 1075, 1205, 1524, 1627  
use in pregnancy and lactation, 576–577, 1065, 1566–1568  
use in renal or hepatic disease, 567, 572, 1285  
withdrawal from, 570, 572–573, 574, 1065, 1205, 1613, 1627  
    buspirone during, 590  
    carbamazepine for, 966  
    neonatal, 576, 1567  
Benztropine, 860–861

- for acute psychosis, [1245](#)
- dosing of, [860](#), [861](#), [1659](#)
- for extrapyramidal side effects, [857](#), [860–861](#), [870](#), [1607](#)
  - vs. amantadine, [863](#)
  - recurrence after withdrawal of, [867](#)
- history and discovery of, [860](#)
- mechanism of action of, [80](#), [860](#)
- pharmacokinetics and disposition of, [860](#)
- side effects of, [860](#), [869](#)
- use in pregnancy, [1566](#)
- Betapace. *See* [Sotalol](#)
- Betaxolol, [865](#), [865](#)
- Bethanechol, [290](#), [322](#)
- Bibliotherapy, for depression, [1164](#)
- Bifeprunox, for cocaine abuse, [846](#)
- Binge-eating disorder (BED), [1337](#), [1342–1344](#)
  - obesity and, [1342](#)
  - psychiatric comorbidity with, [1342](#)
  - treatment of, [1342–1344](#), [1346](#)
    - antidepressants, [1342–1343](#)
      - fluvoxamine, [423–424](#)
      - sertraline, [371](#)
    - comprehensive treatment, [1344](#)
    - lisdexamfetamine, [1087–1088](#), [1343](#), [1344](#), [1346](#)
    - orlistat, [1343](#)
    - sibutramine, [1343–1344](#)
    - topiramate, [1022–1023](#), [1343](#), [1346](#)
    - zonisamide, [1343](#)
- Bini, Lucio, [1106](#), [1113](#)
- Bioavailability of drug, [214](#), [214–215](#), [219](#)
  - food effects on, [215](#)
- Biofeedback, for pain, [1396](#), [1397](#)
- Biperiden, [857](#), [861](#)
- Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) study, [896](#)
- Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) trial, [894](#)
- Bipolar disorder. *See also* [Mania](#)
  - alcohol use disorder and, [932](#), [988–989](#)
  - baseline evaluation of patients with, [956](#)
  - in children and adolescents, [1432](#), [1438](#)

- depression in, [68](#), [85](#), [86](#), [260](#), [317](#), [495](#), [501](#), [518](#), [662](#), [689–690](#), [741](#),  
[771](#), [824](#), [844](#), [846](#), [893–894](#), [927](#), [942](#), [1003](#), [1004–1006](#), [1020](#), [1088](#),  
[1096](#), [1181–1183](#)
- genetics of, [121](#)
  - cross-disorder studies, [143](#)
  - genomewide association studies, [140–141](#)
- machine learning to profile risk of, [265–266](#)
- mania in, [1177–1181](#)
- migraine and, [986](#)
- neuroimaging in
  - MRS, [260](#)
  - PET, [69](#), [244](#)
- neurotransmitters and receptors in
  - dopamine, [68](#), [69](#)
  - norepinephrine, [55](#), [59](#)
  - serotonin, [55](#), [59](#)
- postpartum, [1545](#)
- prevalence of, [907](#)
- rapid-cycling, [633](#), [894–895](#), [988](#), [1006](#)
  - hypothyroidism and, [165](#)
- smoking and, [1299](#)
- suicide and, [55](#), [59](#), [898–899](#), [907](#), [1598](#)
- Bipolar disorder treatment, [1177–1186](#)
  - for acute depressive episodes, [86](#), [1181–1183](#), [1186](#)
    - antidepressants, [1182–1183](#)
      - bupropion, [501](#), [1020](#), [1183](#)
      - paroxetine, [393](#), [689–690](#), [927](#)
      - tranylcypromine, [317](#), [1183](#)
      - venlafaxine, [518](#)
    - aripiprazole, [741](#)
    - armodafinil, [1096](#)
    - carbamazepine, [1182](#)
    - ECT, [1183](#)
    - goal of, [1181](#)
    - ketamine, [85](#)
    - lamotrigine, [662](#), [942](#), [943](#), [1003](#), [1004–1006](#), [1012](#), [1182](#)
      - international guidelines, [1005](#)
    - lisdexamfetamine, [1088](#)
    - lithium, [689–690](#), [893–894](#), [1181](#)
    - lurasidone, [824](#), [825](#), [1005](#), [1182](#)
    - mifepristone, [1183](#)
    - modafinil, [1096](#)

- novel treatments, 1183
- olanzapine, 662–663, 1181
- olanzapine-fluoxetine combination, 662, 1005, 1181–1182
  - vs. lamotrigine, 1005–1006, 1182
- pramipexole, 1183
- psychotherapy, 1183
- quetiapine, 689–691, 894, 1005, 1181
- stepped-care approach, 961
- TCAs, 317
- topiramate, 1020
- tranlycypromine, 317
- valproate, 927, 1182
- ziprasidone, 771
- for acute manic and mixed episodes, 1177–1181, 1186
  - atypical antipsychotics, 1179–1180, 1610
    - aripiprazole, 738, 741, 1180, 1610
    - asenapine, 799, 802–803, 1180
    - cariprazine, 71, 844, 844, 845, 1180
    - clozapine, 632
    - in elderly persons, 1530–1531
    - olanzapine, 661–662, 663, 1179, 1610
    - paliperidone, 1181
    - quetiapine, 689, 892, 1180, 1610
    - risperidone, 716, 899–900, 930, 1179–1180, 1610
    - ziprasidone, 770, 770–771, 892–893, 1180, 1610
  - benzodiazepines, 1610
  - carbamazepine, 893, 941, 942, 950, 951–952, 1179
  - classic antipsychotics, 1179
  - ECT, 1110–1111, 1180–1181
  - emergency management, 1610
  - eslicarbazepine acetate, 950, 951–952
  - gabapentin, 987
  - goal of, 1177
  - lamotrigine, 1007
  - lithium, 891–893, 1178
    - vs. antipsychotics, 892–893
    - vs. carbamazepine, 893
    - ECT and, 1110
    - gabapentin and, 893
    - in psychotic mania, 893
    - vs. valproate, 893
  - oxcarbazepine, 941, 942, 947, 950, 951–952, 1179

- tamoxifen, 1181
- valproate, 738, 741, 803, 923, 926-927, 1178-1179
  - vs. lithium, 893
- carbamazepine, 941-970
- in children and adolescents, 1432, 1438-1443
  - aripiprazole, 742, 1438, 1439
  - asenapine, 799, 803, 804, 805-806, 1438, 1439
  - clinical recommendations for, 1442-1443
  - clozapine, 1443
  - combination treatment, 1441-1442
  - comparator studies of, 1441
  - ECT, 1443
  - lamotrigine, 1440-1441
  - lithium, 899-900, 1438-1439, 1441-1442
  - maintenance treatment, 1442
  - olanzapine, 663, 1438, 1439, 1441
  - oxcarbazepine, 1440
  - quetiapine, 1438, 1439-1440, 1441, 1442
  - risperidone, 899-900, 930, 1438, 1439
  - topiramate, 1440
  - valproate, 899-900, 930, 1440, 1441-1442
  - ziprasidone, 773, 1438, 1440
- combination drug therapy, 960-961
- with comorbid alcohol use disorder
  - gabapentin, 988-989
  - valproate, 932
- gabapentin, 987-988, 995
- lamotrigine, 1001-1012
- lithium, 889-907
  - in children and adolescents, 899-900, 1438-1439, 1441-1442
  - in elderly persons, 900-901
  - in pregnancy, 901-902
- maintenance therapy/relapse prevention, 1183-1186
  - aripiprazole, 741-742, 1185
  - carbamazepine, 946, 953-955, 954, 1185
  - in children and adolescents, 1442
  - ECT, 1186
  - eslicarbazepine acetate, 955
  - goal of, 1183
  - lamotrigine, 896, 928, 929, 1003-1004, 1006, 1012, 1184
  - lithium, 662, 895-897, 927-929, 1183-1184
    - vs. carbamazepine, 953-955, 954

- vs. lamotrigine, 1003–1004
- olanzapine, 662, 896–987, 929, 1185
- oxcarbazepine, 953, 954
- paliperidone, 1185
- polarity index for, 896
- psychotherapy, 1186
- quetiapine, 690, 896, 1185
- valproate, 895, 896, 927–929, 936, 1184–1185
- ziprasidone, 771–772, 929, 1185
- oxcarbazepine, 941–970
  - predictors of response to, 956
- pregabalin, 990–995
- in pregnancy, 1544
  - lithium, 901–902
- quetiapine, 685, 687, 689–690
- for rapid cycling
  - clozapine, 633
  - gabapentin, 988
  - lamotrigine, 1006
  - lithium, 894–895
- topiramate, 1017, 1019, 1020
- for treatment-resistant illness
  - clozapine, 633
  - gabapentin, 988
- trials of
  - Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation, 896
  - Bipolar Clinical Health Outcomes Initiative in Comparative Effectiveness, 894
- valproate, 923–936
  - predictors of response to, 932, 936
- Birth defects. *See* Teratogenic effects of drugs
- Bleeding, drug-related
  - NSAIDs, 1382
  - SSRIs, 345, 1508, 1514
  - valproate, 933
  - venlafaxine, 522
- Blepharospasm
  - antipsychotic-induced, 1256
  - botulinum toxin for, 867, 868
- $\beta$ -Blockers. *See*  $\beta$ -Adrenergic receptor antagonists
- Blood dyscrasias. *See* Hematological effects of drugs

Blood oxygenation level-dependent (BOLD) signal in fMRI, [240](#), [251–255](#), [252](#), [255](#), [258–259](#)

Blood pressure. *See* [Hypertension](#); [Hypotension](#)

Blood–brain barrier (BBB), [46](#), [83](#)

P-glycoprotein at, [212](#), [312](#)

permeation of

choline, [79](#)

cytokines, [189](#), [189](#)

drugs, [212](#)

amphetamine, [1086](#)

antidepressants, [388](#)

benzodiazepines, [564](#)

classic antipsychotics, [610](#)

clozapine, [627](#)

fetal drug exposure and, [1550](#)

nefazodone, [460](#), [461](#)

trihexyphenidyl, [858](#)

valproate, [924](#)

radiotracers, [241](#)

L-tryptophan, [54](#)

L-tyrosine, [65](#)

translocator protein signal at, [249](#)

transporters contributing to function of, [212](#)

BMI. *See* [Body mass index](#)

BMS-820836, [69](#)

BN. *See* [Bulimia nervosa](#)

Body dysmorphic disorder

fluoxetine for, [342](#)

fluvoxamine for, [423](#)

Body mass index (BMI)

depression and, [183](#), [184](#)

inflammation and, [183](#)

monitoring during treatment with atypical antipsychotics, [1499](#)

in obesity, [502–503](#)

BOLD (blood oxygenation level-dependent) signal in fMRI, [240](#), [251–255](#), [252](#), [255](#), [258–259](#)

Bone mineral density, drug effects on

antipsychotics, [609](#), [618](#)

carbamazepine, [959](#)

oxcarbazepine, [960](#)

SSRIs, [372](#)

Borderline personality disorder (BPD)

- binge-eating disorder and, 1342
- clinical features of, 1315
- endocannabinoid system in, 1326
- habituation capacity in, 1326
- oxytocin in, 1326
- prevalence of, 665
- prognosis for, 1315
- PTSD and, 1326
- schizotypal personality disorder and, 1329
- suicide and, 1599
- treatment of, 1315–1328, **1603**
  - antidepressants, 343, 665, 1316, 1320, **1321–1322**
  - atypical antipsychotics, 1316, **1318–1319**
    - aripiprazole, 744
    - olanzapine, 665–666, 1316
    - quetiapine, 693, 1316
  - benzodiazepines, 1323
  - classic antipsychotics, 1315–1316, **1317–1318**
  - clonidine, 1323
  - guidelines for, 1326–1328, **1327**
  - mood stabilizers, 1007, 1027, 1320, 1323, **1324–1325**
  - neuropeptides and other future directions, 1323, 1326
  - omega-3 fatty acids, 1323
- Botulinum toxin, 867–868
  - development of antibodies to, 868
  - drug interactions with, 868
  - history and discovery of, 867
  - indications for, 867, 868
    - drug-induced dystonia, 868
    - neuropathic pain, 1400
    - social anxiety disorder, 1202
  - mechanism of action of, 867–868
  - pharmacokinetics and disposition of, 867
  - pharmacological profile of, 867
  - side effects and toxicology of, 868
  - structure–activity relations for, 867
  - use in pregnancy, 868
- Bowel obstruction, clozapine-induced, 639
- BPD. *See* **Borderline personality disorder**
- BPRS (Brief Psychiatric Rating Scale), 592, 657, 658, 659, 660, 692, 739, 744, 763, 764, 765, 768, 769, 773, 811, **812–813**, 823, 920, 1031, 1523, 1528



BPRS-C (Brief Psychiatric Rating Scale for Children), [1462](#), [1464](#)

## Bradycardia

### drug-induced

- $\beta$ -blockers, [866](#)
- clonidine, [1454](#), [1500](#)
- clozapine, [636](#)
- ketamine, [555](#)
- lithium, [905](#)
- olanzapine, [672](#)

ECT-induced, [1122](#), [1125](#), [1127](#)

QTc interval prolongation and, [782](#)

Bradykinesia, antipsychotic-induced, [611](#), [614](#), [1256](#)

## Brain

adenosine receptors in, [96–97](#)

in Alzheimer's disease, [1519–1520](#)

AMPA receptors in, [85](#)

aspartate in, [83](#)

autopsy studies of ECT patients, [1127](#)

benzodiazepine receptors in, [1054](#)

natural ligands for, [1058–1059](#)

central executive network of, [259](#)

cholinergic receptors in, [80](#)

CRH receptors in, [98](#)

default mode network of, [259–260](#)

dopamine in, [65](#)

dopamine receptors in, [70–72](#)

endogenous opioids in, [99](#)

excitatory amino acid transporters in, [84](#)

GABA in, [92](#)

glutamate in, [82–83](#), [83](#), [84](#)

immune system interactions with, [177–197](#) (*See also* [Immune system](#))

neurocircuitry of depression, [1107–1108](#)

ECT effects on, [1108](#)

NMDA receptors in, [85](#)

norepinephrine in, [72](#), [74](#)

norepinephrine transporter in, [73](#)

oxytocin in, [99](#)

salience network of, [260](#)

in schizophrenia, [1244](#)

in schizotypal personality disorder, [1328](#)

serotonergic neurons in, [54](#), [56–57](#), [335](#)

serotonin receptors in, [59–64](#)

- vasopressin in, [99](#)
- Brain-derived neurotrophic factor (BDNF), [48](#), [71](#), [73](#), [144](#)
  - in antidepressant response, [388](#), [1157](#)
  - ECT and, [1108](#)
  - rTMS and, [1129](#)
  - specific drugs and
    - citalopram, [435](#)
    - clozapine, [628](#)
    - escitalopram, [435](#)
    - ketamine, [551–552](#), [556](#)
    - lithium, [891](#)
    - paroxetine, [398](#)
    - valproate, [926](#)
  - suicidality and, [445](#)
- Brain imaging. *See* [Neuroimaging](#)
- Breast cancer
  - hyperprolactinemia and, [619](#)
  - psychotropic drug use in
    - paroxetine, [398](#), [404](#), [405](#)
    - sertraline, [370](#)
- Breast cancer resistance protein (BCRP), [212](#)
- Breast milk, drugs in. *See also* [Pregnancy and lactation](#)
  - aripiprazole, [1564](#)
  - benzodiazepines, [577](#), [1065](#), [1568](#)
  - carbamazepine, [959](#), [1560](#)
  - clozapine, [1563](#)
  - desvenlafaxine, [522](#)
  - duloxetine, [541](#), [1554](#)
  - eslicarbazepine acetate, [960](#)
  - lamotrigine, [1562](#)
  - lithium, [902](#), [1556](#)
  - mirtazapine, [488](#), [1544](#)
  - olanzapine, [1563](#)
  - oxcarbazepine, [960](#)
  - phenothiazines, [1566](#)
  - quetiapine, [1564](#)
  - risperidone, [1564](#)
  - SSRIs, [348](#), [403](#), [1553](#)
  - TCAs, [324–325](#)
  - valproate, [935](#), [1558](#)
  - venlafaxine, [522](#), [1554](#)
  - ziprasidone, [1565](#)

Brexpiprazole, 731–750, 831  
dosing of, 736–737, 1647  
drug interactions with, 749  
formulations of, 1249  
history and discovery of, 731–732  
indications for, 745–746  
    adjunctive treatment of depression, 737, 745–746  
    schizophrenia, 737, 745  
pharmacokinetics and disposition of, 736–737  
pharmacological profile of, 734, 735, 831, 833, 834, 836  
side effects and toxicology of, 737–738, 748–749, 750  
    extrapyramidal side effects, 732, 748, 874, 1247  
structure–activity relations for, 734, 734  
Brief motivational therapy, for alcohol use disorder, 1284  
Brief Pain Inventory, 1417  
Brief Pain Inventory—Short Form, 539  
Brief Psychiatric Rating Scale (BPRS), 592, 657, 658, 659, 660, 692, 739, 744, 763, 764, 765, 768, 769, 773, 811, 812–813, 823, 930, 1021, 1523, 1528  
Brief Psychiatric Rating Scale for Children (BPRS-C), 1462, 1464  
Brief Social Phobia Scale, 365, 1199  
Bright light therapy, for depression, 1163, 1166  
Brintellix. *See* Vortioxetine  
Brisdelle. *See* Paroxetine  
Brofaromine, 284  
    for bulimia nervosa, 1338  
    for social anxiety disorder, 1201  
Bromazepam  
    pharmacokinetics of, 572  
    for social anxiety disorder, 1200  
Bromocriptine  
    for neuroleptic malignant syndrome, 1257, 1614  
    use in serotonin syndrome, 1615  
Bronchospasm,  $\beta$ -blocker-induced, 865  
Brotizolam, 566, 570  
Brunner syndrome, 285  
*BRUNOL4* gene, 815  
Buccal drugs, 213  
Bulimia nervosa (BN), 1337–1342  
    age at onset of, 1337  
    bupropion contraindicated in, 1339  
    genetics of, 121

- medical complications of, 1338
- psychiatric comorbidity with, 1338
  - depression, 1338, **1341**
- treatment of, 1338-1342, 1345-1346
  - antidepressants, 1338-1339
    - combined with cognitive-behavioral therapy, 1339-1342, 1345-1346
    - desipramine, 1338, 1339
    - duration of, 1339
    - fluoxetine, 342-343, 1338, 1339
    - MAOIs, 289
    - sertraline, 371
    - trazodone, 342-343, 458
  - comprehensive treatment, 1340-1342, **1341**
  - inpatient vs. outpatient, 1340
  - topiramate, 1022, 1339
- Bumetanide, 1473
- Buprenorphine
  - combined with naloxone for pain, 1390
  - interaction with carbamazepine and oxcarbazepine, 968
  - mechanism of action of, 102
  - for opioid use disorder
    - clonidine augmentation, 1291
    - detoxification, 1290
    - dosing of, 1289
    - maintenance treatment, 1292
      - buprenorphine implants, 1293
      - combined with naloxone, 1290, 1292-1293, 1390
      - vs. methadone, 1292
      - during pregnancy, 1294
- Bupropion, 495-507
  - abuse potential of, 497, 504
  - in children and adolescents, 1436, 1438, 1498, **1498**
  - contraindications to, 1297
    - eating disorders, 1297, 1337
    - seizure disorders, 1498
  - dosing of, 221, 496, **1638, 1660**
    - in children and adolescents, **1498, 1638**
  - drug interactions with, 506
    - carbamazepine, 506, **963**, 965
    - duloxetine, 542
    - MAOIs, **293**, 1297
    - oxcarbazepine, **963**

- sertraline, 362, 373
- vortioxetine, 473
- in elderly persons, 392, 498, 500, 1508, 1515
- formulations of, 213–214, 496, 504
- history and discovery of, 495–496
- indications for, 495, 498–504, 506–507
  - ADHD, 503
  - amphetamine use disorder, 504
  - depression, 495, 498–501, 1159
    - with anxiety, 501
    - augmentation of other antidepressants, 495, 500, 1160
    - in bipolar disorder, 501, 1020, 1183
    - in children and adolescents, 1436, 1438
    - with decreased energy, interest, and pleasure, 500–501
    - in elderly persons, 392, 500
    - escitalopram and, 482
    - maintenance treatment, 499
    - mirtazapine and, 481
    - vs. paroxetine, 391
    - prevention of seasonal depressive episodes, 501
    - vs. trazodone, 457
  - drug-induced sexual dysfunction, 372, 399, 503–504, 1160
  - generalized anxiety disorder, 1208
  - obesity, 502–503
  - panic disorder, 1197
  - smoking cessation, 495, 497, 501–502, 1297, 1660
    - combined with varenicline, 1298
    - in patients with psychiatric disorders, 1299–1300
    - in schizophrenia, 1259
- mechanism of action of, 495, 498, 506
- overdose of, 505
- pharmacokinetics and disposition of, 497–498
  - in elderly persons, 1508
- pharmacological profile of, 69–70, 496–497
- racemic, 226
- side effects and toxicology of, 495, 504–506, 1436, 1498
  - seizures, 221, 496, 504, 505, 506, 1297
- structure–activity relations for, 496, 496
- suicidality and, 1298
- TNF- $\alpha$  production reduced by, 195
- use in pregnancy and lactation, 498, 505–506, 1553
- use in renal or hepatic disease, 498, 1508

Bupropion/naltrexone, for obesity, 502–503

BuSpar. *See* [Buspirone](#)

Buspirone, 585–594

- antidepressant effects of, 588, 591

- in children and adolescents, 1444, 1446

- dosing and administration of, 593, 1642

- drug interactions with, 594

  - carbamazepine and oxcarbazepine, 963

  - MAOIs, 293

- in elderly persons, 590, 593, 1524

- history and development of, 586–587

- indications for, 589–593

  - antidepressant augmentation, 591, 1160

  - autism spectrum disorder, 593, 1474

  - behavioral complications of dementia, 593, 1524, 1612

  - drug-induced sexual dysfunction, 399

  - generalized anxiety disorder, 589–590, 1205–1206, 1210

    - in children and adolescents, 1444

    - effect of prior benzodiazepine treatment on therapeutic response to, 593–594, 1206

    - vs. venlafaxine, 1207

  - methamphetamine and cocaine dependence, 71

  - mixed anxiety–depression, 591–592, 593

  - OCD, 1212

  - panic disorder, 590–591, 1197

  - schizophrenia, 592–593

  - social anxiety disorder, 1201–1202

  - substance use disorders, 592

- mechanism of action of, 57, 61, 71, 588–589

- overdose of, 594

- pharmacokinetics of, 588

- pharmacological profile of, 587–588

- side effects and toxicology of, 594.1474

- use in pregnancy and lactation, 1568

- use in renal or hepatic disease, 588

Butyrophenones. *See also* [Antipsychotics](#)

- side effects of, 615–616

- structure–activity relations for, 606, 607

Butyrylcholinesterase (BChE), 1040, 1041, 1042

C-reactive protein (CRP), [178](#)  
  in depression, [162](#), [182–183](#)  
  in medically ill patients, [190](#)  
  monitoring during clozapine treatment, [637](#)  
*CACNA1C* gene, [141](#), [143](#)  
*CACNB2* gene, [143](#)  
CAFE (Comparison of Atypicals in First Episode Psychosis) study, [687](#), [696](#)  
Caffeine, [96](#), [97](#), [216](#), [228](#)  
  drug interactions with  
    fluvoxamine, [425](#)  
    lithium, [907](#)  
  effect on lithium tremor, [903](#)  
Calcitonin gene-related peptide, [100](#), [186](#)  
Calcium  
  adenosine A<sub>1</sub> agonist inhibition of, [97](#)  
  in CREB activation, [11](#)  
  CRH effects on, [98](#)  
  modulation of neurotransmitter release by, [51](#)  
  opioid effects on, [101](#)  
  in psychopathology, [143](#)  
    schizophrenia, [140](#)  
  signaling interactions in learning and memory, [87](#)  
Calcium channel blocker-drug interactions  
  β-blockers, [866](#)  
  carbamazepine, [963](#), [964](#), [966–967](#), [969](#)  
  lithium, [906–907](#)  
  oxcarbazepine, [963](#), [968](#)  
Calcium ion channels, [51](#), [62](#), [71](#), [76](#), [80](#), [86](#), [87](#), [95](#), [95](#)  
  drug effects on  
    carbamazepine, [949](#)  
    gabapentin, [984](#)  
    lamotrigine, [1002](#)  
    opioids, [101](#)  
    oxcarbazepine, [949](#)  
    pregabalin, [990](#)  
    topiramate, [1018](#)  
Calgary Depression Scale for Schizophrenia (CDSS), [813](#), [814](#)  
Calmodulin-dependent protein kinases (CaMKs), [11](#), [49](#), [70](#), [83](#), [86](#), [87](#)  
CAM. *See* [Complementary and alternative medicine](#)  
CaMKs (calmodulin-dependent protein kinases), [11](#), [49](#), [70](#), [83](#), [86](#), [87](#)  
cAMP. *See* [Cyclic 3′-5′-adenosine monophosphate](#)

cAMP response element-binding protein (CREB), [9](#), [10](#), [11](#), [48](#), [101](#), [445](#), [891](#), [1108](#)

cAMP response elements (CREs), [10](#)

CAMS (Child Anxiety Multimodal Study), [1446](#)

Canadian Network for Mood and Anxiety Treatments, [1005](#)

Cancer

- depression and, [1153](#), [1154](#)
  - fluoxetine for, [345](#)
  - psychostimulants for, [1095](#)
  - sertraline for, [370](#)
- economic costs of, [1377](#)
- immune system in, [179](#), [181](#)
- mirtazapine for nausea in, [484–485](#)
- pain management in, [424](#), [1377](#), [1380](#), [1382](#), [1383](#), [1384](#)
  - for low back pain, [1405](#), [1406](#)
  - for neuropathic pain, [1392](#), [1400](#), [1401](#)
- psychostimulants for fatigue in, [1094](#)
- smoking and, [1254](#)

Cannabinoid (CB) receptors, [98](#), [247](#), [1394](#)

Cannabinoids, [98](#), [1394–1395](#)

Cannabis use disorder

- psychosis and
  - AKT1* gene and, [144](#)
  - schizophrenia, [1258](#)
- treatment of
  - buspirone, [592](#)
  - gabapentin, [989](#)

CAPS (Clinician-Administered PTSD Scale), [344](#), [367](#), [423](#), [668](#), [1026](#), [1213](#), [1219](#)

CAPS-CA (Clinician-Administered PTSD Scale—Child and Adolescent Version), [1451](#)

Capsaicin, [1393–1394](#), [1400](#), [1401](#), [1415](#)

Carbamazepine (CBZ), [941–970](#)

- in children and adolescents, [1440](#), [1441](#), [1451](#), [1501](#)
- cognitive effects in children exposed in utero to, [935](#), [959](#)
- dosing of, [944](#), [946](#), [957](#), [1650](#)
  - in children and adolescents, [1501](#)
- drug interactions with, [947](#), [960–967](#), [963](#), [964](#), [969–970](#)
  - antidepressants, [965](#)
  - antipsychotics, [965–966](#)
  - aripiprazole, [749](#)
  - benzodiazepines, [966](#)



- bupropion, 506, 965
- calcium channel blockers, 966–967
- fluoxetine, 350
- fluvoxamine, 425
- lamotrigine, 964, 1012
- lithium, 905, 962
- MAOIs, 293
- mood stabilizers and anticonvulsants, 962–965
- nefazodone, 462
- olanzapine, 673
- oral contraceptives, 231
- paroxetine, 405
- psychostimulants, 966
- quetiapine, 686
- sedative-hypnotics, 966
- substances of abuse, 967
- valproate, 934, 962–964
- ziprasidone, 782
- formulations of, 942, 943–944
- generic, 944
- history and discovery of, 042
- indications for, 949–953
  - alcohol withdrawal, 967, 1286
  - behavioral complications of dementia, 1524, 1612, 1627
  - bipolar disorder, 969
    - in children and adolescents, 1440, 1441
    - depressive episodes, 1182
    - maintenance treatment, 946, 953–955, 954, 1185
    - mania, 893, 941, 942, 950, 951–952, 1179
    - predictors of response to, 956
  - borderline personality disorder, 1320, 1324, 1327
  - depression, 953, 953
  - obsessive-compulsive personality disorder, 1330
  - PTSD, 1216
    - in children and adolescents, 1451
  - seizures, 942, 944, 949–950, 964
  - trigeminal neuralgia, 943, 949, 1393
- mechanism of action of, 97
- pharmacokinetics and disposition of, 944–946, 945, 1507
- pharmacological profile of, 943
- side effects and toxicology of, 944, 956–959, 1179, 1440
  - gastrointestinal effects, 958

- hematological effects, [957](#), [958](#)
- hyponatremia, [957](#), [959](#), [962](#)
- monitoring for, [957](#), [958](#)
- neurotoxic effects, [957](#)
- rash, [957-958](#)
- teratogenic effects, [959](#), [1559-1560](#)
- structure-activity relations for, [943](#)
- suicidality and, [958](#)
- use in pregnancy and lactation, [959](#), [1549](#), [1559-1560](#)
  - fetal carbamazepine syndrome, [1559](#)
  - folate supplementation and, [1560](#)
  - monitoring of nursing infants, [1570](#)
- Carbamazepine 10,11-epoxide (CBZ-E), [944](#), [945](#), [946](#), [960](#), [962](#), [963](#), [964](#), [966](#), [967](#), [968](#)
- Carbatrol. *See* [Carbamazepine](#)
- Carbidopa, discontinuation before ECT, [1124](#)
- Carbinoxamine maleate, [861](#)
- Carbohydrate craving
  - in bulimia nervosa, [343](#)
  - drug-induced
    - MAOIs, [290](#)
    - TCAs, [324](#)
- $\beta$ -Carbolines, [1058](#)
- Carbonic anhydrase, topiramate inhibition of, [1018](#), [1029](#), [1030](#)
- Cardiometabolic risk factors, [777](#), [779](#)
- Cardiomyopathy, clozapine-induced, [636-637](#), [640](#), [641](#)
- Cardiovascular disease patients
  - chronic stress in, [181](#)
  - depression in, [161](#), [183](#), [190](#), [1153](#), [1154](#), [1509](#)
  - drug use in
    - amantadine, [863](#)
    - antidepressants
      - escitalopram, [442-443](#)
      - MAOIs, [290](#), [294](#), [295](#)
      - paroxetine, [393](#)
      - sertraline, [369-370](#)
    - $\beta$ -blockers, [865-866](#)
    - lithium, [905](#)
    - nicotine replacement therapies, [1297](#)
    - NSAIDs, [1382](#)
    - psychostimulants, [1504](#)
  - ECT in, [1124-1125](#)

inflammation in, [178](#), [183](#), [190](#)  
Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram  
Treatment study, [442-443](#)  
vascular cognitive impairment in, [1043](#)  
Cardiovascular effects  
of drugs  
  alcohol-type hypnotics, [1069](#)  
  amphetamines, [1086](#)  
  anticholinergic agents, [858](#), [859](#)  
  antipsychotics, [1516](#)  
  asenapine, [804](#)  
  barbiturates, [1068](#)  
   $\beta$ -blockers, [864](#), [865-866](#), [1452](#)  
  carbamazepine, [958](#)  
    in infants after in utero exposure, [1559](#)  
  citalopram, [370](#), [431](#), [444](#), [446](#)  
  classic antipsychotics, [424](#), [612](#), [615](#), [617-618](#), [719](#)  
  clonidine, [1500](#)  
  clozapine, [626](#), [636-637](#), [640](#), [641](#), [1248](#), [1500](#)  
  dofetilide, [233](#)  
  escitalopram, [446](#)  
  eslicarbazepine acetate, [960](#)  
  fluvoxamine, [425](#)  
  hydroxyzine, [1208](#)  
  iloperidone, [815](#), [818](#), [1248](#)  
  ketamine, [555](#)  
  lamotrigine, [1011](#)  
  levomilnacipran, [541-542](#)  
  lithium, [905](#)  
    Ebstein's anomaly in infants after in utero exposure, [901](#), [1555](#)  
  methadone, [1289-1290](#), [1292](#), [1390](#)  
  methylphenidate, [1089](#)  
  milnacipran, [541](#)  
  modafinil, [1090](#)  
  nefazodone, [462](#)  
  NSAIDs, [1382](#)  
  olanzapine, [672](#)  
  paliperidone, [1248](#)  
  paroxetine, [401](#)  
  quetiapine, [697](#), [1516](#)  
  risperidone, [718](#), [719](#), [721](#), [722](#), [1516](#)  
  sertraline, [369](#), [370](#)

- sotalol, [233](#)
- SSRIs, [346](#)
  - fluvoxamine, [425](#)
  - in infants after in utero exposure, [1549-1550](#)
  - paroxetine, [400-401](#)
  - sertraline, [369-370](#)
- TCAs, [310](#), [321](#), [322-323](#), [326](#), [370](#), [1390](#)
  - in children, [319-320](#)
  - plasma concentration and, [314](#)
- trazodone, [456](#), [457](#), [458](#), [459](#)
- valproate, in infants after in utero exposure, [1557](#)
- venlafaxine, [322](#), [521](#), [522](#), [1514](#)
- vortioxetine, [473](#)
- ziprasidone, [755](#), [780-782](#), [1248](#), [1469](#)
- of ECT, [1124-1125](#)
- Cariprazine, [71](#), [831-851](#)
  - in children and adolescents, [840](#), [848](#)
  - dosing of, [840](#), [1647](#)
  - drug interactions with, [838-840](#)
  - in elderly persons, [840](#), [848](#)
  - formulations of, [1249](#)
  - high dosage and overdose of, [849](#)
  - history and discovery of, [831](#), [832](#)
  - indications for, [831](#), [833](#), [840-846](#)
    - augmentation of antidepressant treatment, [846](#)
    - bipolar depression, [844](#), [846](#)
    - bipolar manic or mixed episodes, [71](#), [844](#), [844](#), [845](#), [1180](#)
    - cocaine abuse, [846](#)
    - ongoing trials, [850-851](#)
    - schizophrenia, [840-844](#), [841-843](#)
      - for hostility, [846](#)
  - pharmacokinetics of, [837-838](#), [839](#)
  - pharmacological profile of, [831](#), [833-837](#), [851](#)
    - compared with other dopamine receptor partial agonists, [831-833](#), [834](#)
    - PET studies of dopamine receptor occupancy, [836-837](#)
  - side effects and toxicology of, [847](#), [847-849](#)
    - extrapyramidal side effects, [848](#), [874](#), [1247](#)
  - structure-activity relations for, [833](#), [835](#)
  - use in pregnancy and lactation, [849-850](#)
  - use in renal or hepatic disease, [837](#)
- Carisoprodol, [1393](#)
- Carotenoids, [1044](#)

Carotid endarterectomy, [1043–1044](#)

CARS (Childhood Autism Rating Scale), [1473](#)

CAS (Clinical Anxiety Scale), [441](#)

Case management, for schizophrenia, [1245](#), [1250](#)

Case-control studies, [126](#), [132](#), [135](#), [138](#), [139](#), [140](#), [142](#), [144](#)

Caspofungin, interaction with carbamazepine and oxcarbazepine, [963](#)

Catalepsy, [1605](#)

- antipsychotic-induced, [609](#), [623](#), [627](#), [651](#), [652](#), [705](#), [709](#)

Cataplexy

- narcolepsy with, [1051](#), [1072](#)
- treatment of
  - amphetamine, [1084](#), [1094](#)
  - γ-hydroxybutyrate, [1069](#)

Cataracts, drug-induced

- cariprazine, [847](#)
- quetiapine, [697](#)

Catatonia, [1605](#)

- antipsychotic-induced, [609](#)
- ECT for, [1111](#), [1112](#)
- medical evaluation of, [1605](#)
- neuroleptic malignant syndrome and, [1257](#)
- topiramate for, [1022](#)

Catechol-*O*-methyltransferase (COMT), [130](#), [420](#), [1110](#)

CATIE (Clinical Antipsychotic Trials of Antipsychotic Effectiveness), [604](#), [620](#), [631](#), [637](#), [658](#), [661](#), [669](#), [688](#), [694](#), [695](#), [696](#), [697](#), [713](#), [714](#), [715](#), [718](#), [720](#), [721](#), [722](#), [764–765](#), [766](#), [767](#), [776](#), [778](#), [779–780](#), [871](#), [875](#), [1106](#), [1246–1247](#), [1250](#), [1253](#), [1254](#), [1255](#), [1524](#)

CATIE-AD (Clinical Antipsychotic Trials of Antipsychotic Effectiveness—Alzheimer’s Disease), [664](#), [692](#), [717](#), [1524](#), [1529](#), [1624](#), [1626](#)

Cauda equina syndrome, [1405](#)

CB (cannabinoid) receptors, [98](#)

CBF. *See* [Cerebral blood flow](#)

CBP (CREB-binding protein), [10](#), [11](#)

CBT. *See* [Cognitive-behavioral therapy](#)

CBZ. *See* [Carbamazepine](#)

CBZ-E (carbamazepine 10,11-epoxide), [944](#), [945](#), [946](#), [960](#), [962](#), [963](#), [964](#), [966](#), [967](#), [968](#)

CD. *See* [Conduct disorder](#)

CD4:CD8 cell ratio, in depression, [182](#), [182](#)

CDH (chronic daily headache), [1411](#)

CDP-choline (cytidine 5′-diphosphocholine), for vascular cognitive impairment, [1044](#)

CDRS-R (Children's Depression Rating Scale— Revised), [440](#), [1433](#), [1434](#),  
[1435](#), [1436](#), [1437](#), [1442](#)

CDSS (Calgary Depression Scale for Schizophrenia), [813](#), [814](#)

Celecoxib, [1474](#)

Celexa. *See* [Citalopram](#)

Celiac disease, [294](#)

CEN (central executive network), [259](#)

Central executive network (CEN), [259](#)

Central nervous system (CNS) depressants

- alcohol-type hypnotics, [1068–1069](#)
- barbiturates, [563](#), [1051](#), [1065–1068](#)
- benzodiazepines, [563–578](#), [1051](#), [1053–1065](#)
- $\beta$ -blockers, [864](#)
- drug interactions with
  - barbiturates, [1068](#)
  - diphenhydramine, [862](#)
  - trazodone, [459](#)
- $\gamma$ -hydroxybutyrate, [1069](#), [1611](#)
- melatonin, [1070–1071](#), [1355–1356](#)
- sedative-hypnotics, [1051–1076](#)

Central nervous system (CNS) effects of drugs

- alcohol-type hypnotics, [1069](#)
- amantadine, [863](#), [864](#)
- amphetamine, [1086](#)
- antihistamines, [861](#)
- aripiprazole, [746](#), [747](#), [1180](#)
- asenapine, [804](#), [805](#), [806](#), [1439](#)
- benzodiazepines, [570](#), [572](#), [1065](#), [1205](#), [1627](#)
- brexpiprazole, [748](#)
- bupropion, [221](#), [496](#), [504](#), [505](#), [506](#), [1297](#), [1436](#), [1498](#)
- bupirone, [593](#)
- carbamazepine, [944](#), [957](#), [1179](#)
- cariprazine, [847](#), [847](#), [848](#)
- classic antipsychotics, [612](#), [614](#), [616](#), [719](#), [816](#)
- clomipramine, [1448](#), [1449](#)
- clonidine, [1500](#)
- clozapine, [221](#), [633](#), [635](#), [638](#), [640](#), [641](#), [875](#), [1248](#), [1464](#), [1500](#), [1521](#)
- dihydropyridine, [70](#)
- diphenhydramine, [1368](#)
- doxylamine, [1368](#)
- duloxetine, [472](#), [540](#), [1436](#), [1443](#), [1498](#)
- eslicarbazepine acetate, [960](#)

fluoxetine, [1434](#)  
gabapentin, [987](#), [989](#), [1401](#), [1404](#)  
guanfacine, [1501](#)  
γ-hydroxybutyrate, [1069](#)  
iloperidone, [809](#), [816](#), **816**, [817](#)  
lamotrigine, [1011](#), [1182](#), [1502](#)  
lithium, [903](#), [1438](#), [1439](#), [1458](#)  
lurasidone, [825](#)  
MAOIs, [290](#), [291](#), [297](#)  
mirtazapine, [487](#), [1498](#)  
modafinil, [1090](#), [1092](#)  
nefazodone, [462](#), [1436](#)  
olanzapine, [804](#)  
opioids, [1385](#)  
oxcarbazepine, [1440](#), [1502](#)  
paliperidone, [1463](#)  
paroxetine, [392](#), [398](#), [1435](#)  
prazosin, **1368**  
pregabalin, [992](#), [995](#), [1393](#), [1401](#), [1404](#)  
psychostimulants, [1502](#)  
quetiapine, **693**, [694](#), [804](#), [1180](#), [1440](#), [1463](#)  
risperidone, **693**, [718](#), **719**, **816**, [1439](#), [1457](#), [1463](#)  
selegiline transdermal system, [1436](#)  
sertraline, [372](#), [1435](#)  
SSRIs, [345](#), [371](#), [398](#), [424](#), [443](#), [1434](#), [1435](#), [1445](#), [1447](#), [1449](#), [1451](#), [1497](#)  
suvorexant, [1359](#), **1367**  
TCAs, [314](#), [320–321](#), [324](#), **1368**, [1615](#)  
topiramate, [1028](#), [1029](#)  
trazodone, [457](#), **1369**  
venlafaxine, [522](#), [1498](#)  
ziprasidone, [774](#), [1180](#), [1440](#)  
zolpidem, **1365**

CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) Behavior Rating Scale, [1519](#)

Cerebellar dysfunction, lithium-induced, [903](#)

Cerebral blood flow (CBF)  
fMRI studies of, [251](#)  
PET studies of, [242–244](#), **243**  
postictal decrease after ECT, [1107](#)

Cerebrovascular disease patients, MAOI use in, [294](#), [295](#)

Cerivastatin, [1507](#)

*CERKL* gene, [815](#)

Cerletti, Ugo, [1106](#), [1113](#)  
CFS. See [Chronic fatigue syndrome](#)  
CGAS (Children's Global Assessment Scale), [1442](#)  
CGI (Clinical Global Impressions) Scale, [363](#), [364](#), [365](#), [367](#), [369](#), [390](#), [422](#),  
[481](#), [484](#), [485](#), [486](#), [591](#), [664](#), [667](#), [691](#), [739](#), [740](#), [741](#), [743](#), [744](#), [745](#),  
[746](#), [763](#), [764](#), [765](#), [771](#), [773](#), [800](#), [803](#), [812-813](#), [814](#), [841-842](#), [843](#),  
[844](#), [845](#), [950](#), [1004](#), [1006](#), [1007](#), [1021](#), [1026](#), [1087](#), [1088](#), [1091](#), [1204](#),  
[1217](#), [1433](#), [1434](#), [1435](#), [1437](#), [1438](#), [1439](#), [1441](#), [1444](#), [1445](#), [1446](#),  
[1447](#), [1458](#), [1462](#), [1464](#), [1465](#), [1466](#), [1467](#), [1468](#), [1469](#), [1470](#), [1471](#),  
[1472](#)  
cGMP (cyclic guanosine monophosphate), [34](#), [62](#), [551](#), [890](#)  
Chamomile, [1210](#)  
Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14), [472](#)  
CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology)  
Consortium, [140](#)  
"Cheeking" of medications, [1606](#)  
Chest pain  
  drug-induced  
    methamphetamine, [1611](#)  
    sertraline, [371](#)  
  in panic disorder, [1604](#)  
Child and adolescent disorders, [1431-1475](#)  
  ADHD, [1432](#), [1452-1456](#)  
  anorexia nervosa, [666-667](#)  
  anxiety disorders, [485](#), [1432](#), [1443-1446](#), [1445-1446](#)  
    generalized anxiety disorder, [1443-1444](#)  
    mixed anxiety disorders, [1445-1446](#)  
    panic disorder, [1445](#)  
    separation anxiety disorder, [1202-1203](#), [1443](#), [1445](#), [1446](#)  
    social anxiety disorder, [1202-1203](#), [1444-1445](#)  
  autism spectrum disorder, [1466-1475](#)  
  bipolar disorder, [663](#), [1179](#), [1432](#), [1438-1443](#)  
  child abuse, [1596](#), [1601](#)  
  depression, [318](#), [485](#), [1152](#), [1433-1438](#)  
  differential diagnosis of, [1432](#)  
  disruptive behavior disorders and aggression, [1456-1460](#)  
    aggression, [1457-1460](#)  
    conduct disorder, [1456-1457](#)  
    oppositional defiant disorder, [1456-1457](#)  
  nocturnal enuresis, [319-320](#)  
  nonpharmacological interventions for, [1432](#)  
  OCD, [1447-1450](#)



- pharmacotherapy for, 1431–1433
  - clinical issues affecting response to, 1431–1432
  - comorbid disorders and, 1432
  - compliance with, 1432
  - diagnostic accuracy for, 1432
  - evaluation for, 1431
  - evidence base for, 1433
  - informed consent for, 1432–1433
  - psychosocial factors and, 1432
- PTSD, 1450–1452
- schizophrenia, 1462–1466
- smoking cessation, 1299
- specific drugs for, 1497–1504
  - N*-acetylcysteine, 1450
  - antidepressants, 1497–1498
    - bupropion, 1436, 1438, 1498, **1498**
    - citalopram, 439, 1434, 1435, 1444–1445, 1449, 1451, 1470, **1498**
    - clomipramine, 1211, 1448–1449, 1470–1471
    - desvenlafaxine, 520–521, 1436
    - dosage and monitoring of, 1497, **1498**
    - duloxetine, 1436, 1443, 1446, 1498, **1498**
    - escitalopram, 439–440, 1434, 1435, 1444, 1470, **1498**
    - fluoxetine, 1211, 1433–1434, 1434–1435, 1444, 1445, 1446, 1447–1448, **1498**
    - fluvoxamine, 421, 423, 1202, 1445–1446, 1448, 1470
    - mirtazapine, 1436, 1438, 1471, 1498, **1498**
    - nefazodone, 1436
    - paroxetine, 393–395, 396, 1435, 1444, 1445, 1449, **1498**
    - selegiline transdermal system, 1436
    - sertraline, 361, 367, 371, 1202–1203, 1211, 1434–1435, 1444, 1445, 1446, 1447, 1451, **1498**
    - side effects of, 1497–1498
    - suicidality and, 346–347, 372, 393–395, 399–400, 425, 445–446, 1437, 1497
    - TCAs, 313–314, 313–324, 318, 319–320, 323, 1446
    - venlafaxine, 520–521, 1202, 1336, 1435–1436, 1438, 1443–1444, 1445, 1446, 1471, 1498, **1498**
  - atomoxetine, 1453–1454, 1456–1457, 1472–1473, 1498–1499
    - dosage and monitoring of, 1498–1499
    - side effects of, 1499
  - atypical antipsychotics, 1462–1466, 1499–1500

aripiprazole, 739–740, 742, 1438, 1439, 1449–1450, 1458, 1461, 1462, 1463, 1465, **1499**  
asenapine, 799, 803, 1438, 1439, 1462, 1464, **1499**  
cariprazine, 840, 848  
clozapine, 634, 1443, 1464, 1465, 1466, **1499**  
dosage and monitoring of, 1499, **1499**  
iloperidone, 810  
olanzapine, 634, 654, 659–660, 663, 672, 1438, 1439, 1441, 1458, 1462, 1464–1465, 1468, **1499**  
paliperidone, 1462, 1463, 1465, **1499**  
quetiapine, 659, 687, 689, 1438, 1439–1440, 1441, 1442, 1452, 1458, 1462, 1463, 1469, **1499**  
risperidone, 659, 712, 899–900, 930, 1438, 1439, 1441–1442, 1449, 1452, 1457–1458, 1462–1463, 1464–1465, 1466–1468, 1474–1475, **1499**  
side effects of, 1499–1500  
ziprasidone, 773, 1438, 1440, 1458, 1462, 1463–1464, **1499**  
benzodiazepines, 1445, 1446, 1450  
buspirone, 1444, 1446  
classic antipsychotics  
haloperidol, 659, 1464, 1465, 1469  
loxapine, 1465  
molindone, 1465  
pimozide, 1461, 1462  
thioridazine, 1465  
thiothixene, 1465  
clonidine, 1451, 1454–1455, 1459–1460, 1459–1461, 1472, 1500  
dosage and monitoring of, 1500  
side effects of, 1500  
D-cycloserine, 1450, 1452  
guanfacine, 1451, 1455, 1459, 1460–1461, 1500–1501  
dosage and monitoring of, 1500–1501  
side effects of, 1501  
modafinil, 1090  
mood stabilizers, 1501–1502  
carbamazepine, 1440, 1441, 1451  
dosage and monitoring of, 1501, **1501**  
lamotrigine, 1440–1441, 1471  
lithium, 899–900, 1438–1439, 1441–1442, 1458–1459, 1472  
oxcarbazepine, 1179, 1440, 1471–1472  
side effects of, 1501–1502  
topiramate, 1019, 1440

- valproate, [899–900](#), [930](#), [1440](#), [1441–1442](#), [1459](#), [1471](#)
- prazosin, [1452](#)
- propranolol, [1452](#)
- psychostimulants, [1452–1453](#), [1455–1456](#), [1457](#), [1459–1460](#), [1502–1504](#)
  - dosage and monitoring of, [1502](#), **[1503](#)**
  - side effects of, [1502–1504](#)
- riluzole, [1450](#)
- Tourette syndrome, [1460–1462](#)
- Child Anxiety Multimodal Study (CAMS), [1446](#)
- Childhood abuse/trauma. *See also* [Early life stress](#)
  - borderline personality disorder and, [1326](#)
  - depression and, [1153](#)
    - HPA axis and, [161–162](#), [1153](#), [1156](#)
    - 5-HTTLPR polymorphism and, [59](#), [144](#)
    - immune system and, [1153](#)
  - functional somatic syndromes and, [1402](#)
  - oxytocin deficits and, [1326](#)
  - PTSD and, [163–164](#), [185](#), [1326](#)
    - FKBP5* polymorphism and, [121](#), [144](#)
    - immune function and, [185](#)
  - stress-related disorders and, [143](#)
- Childhood Autism Rating Scale (CARS), [1473](#)
- Children’s Depression Rating Scale—Revised (CDRS-R), [440](#), [1433](#), [1434](#), [1435](#), [1436](#), [1437](#), [1442](#)
- Children’s Global Assessment Scale (CGAS), [1442](#)
- Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS), [1447–1449](#), [1450](#), [1470](#)
- China, Oxford, and Virginia Commonwealth University Experimental Research on Genetic Epidemiology (CONVERGE) Consortium, [140](#)
- ChIP (chromatin immunoprecipitation), [21–22](#)
- Chloral hydrate, [1068–1069](#), [1219](#)
- Chlordiazepoxide, [563](#), [1052](#), [1106](#)
  - for alcohol withdrawal, [1285](#)
  - dosing of **[1641](#)**
  - pharmacokinetics of, [212](#), [564](#), **[566](#)**, [572](#), [1060](#), **[1061](#)**
  - structure of, **[565](#)**
  - use in pregnancy, [1567–1568](#)
- Chloride ion channels, [33](#), [47](#), **[49](#)**, [1054](#), [1055](#)
- para-Chlorophenylalanine (pCPA), [585](#), [588](#), [589](#)
- m*-Chlorophenylpiperazine (mCPP), [456](#), [460](#), [463](#)
- D-Chlorpheniramine, **[308](#)**
- Chlorpromazine

- dosing of, [1643](#)
- drug interactions with
  - carbamazepine and oxcarbazepine, [963](#), [966](#)
  - propranolol, [866](#)
- formulations of, [1249](#), [1610](#)
- history and discovery of, [603](#), [604](#), [1052](#), [1106](#), [1241](#)
- indications for
  - anorexia nervosa, [666](#)
  - bipolar mania, [892](#), [1179](#)
    - ECT and, [1181](#)
  - hiccups, [612](#)
  - schizophrenia
    - behavioral emergencies, [1610](#)
    - treatment-resistant illness, [630](#)
  - serotonin syndrome, [1615](#)
- mechanism of action of, [80](#)
- receptor affinities of, [613](#)
- side effects of, [614](#), [615](#)–[616](#), [618](#), [619](#), [1516](#)
  - extrapyramidal side effects, [855](#), [872](#)
- structure–activity relations for, [605](#), [607](#)
- use in pregnancy and lactation, [1565](#)–[1566](#)

Chlorprothixene, [606](#), [607](#)

Chlorzoxazone, [1393](#)

Cholecystokinin, [100](#)

Cholestatic jaundice, antipsychotic-induced, [618](#)

Cholesterol level. *See* [Dyslipidemia](#); [Lipid profile](#)

Cholestyramine–drug interactions, [1506](#)

- $\beta$ -blockers, [866](#)

Cholinergic anti-inflammatory pathway, [186](#)–[187](#)

Cholinergic system. *See* [Acetylcholine](#)

Chondroitin, for osteoarthritis, [1408](#), [1409](#)

Chromatin, [7](#)–[8](#)

Chromatin immunoprecipitation (ChIP), [21](#)–[22](#)

Chromosomes

- abnormalities of, [124](#)–[126](#)
  - deletions, [125](#)
  - duplications, [126](#)
  - numerical, [124](#)–[125](#)
  - translocations, [125](#)
- autosomes, [126](#)
- crossing over, [131](#)
- gene distribution on, [6](#)

- linkage studies of, [3](#), [16](#), [118](#), [128](#), [130](#), [131–132](#), [141](#), [144](#)
- number of, [124](#)
- positional cloning and, [16](#)
- X and Y, [124](#), [125](#), [126](#)
- Chronic daily headache (CDH), [1411](#)
- Chronic fatigue syndrome (CFS), [1401](#)
  - fluoxetine for, [345](#)
  - immune system in, [185](#)
- Chronic obstructive pulmonary disease, treatment of insomnia in, [1356](#), [1359](#), [1366](#)
- CIBIC (Clinician's Interview-Based Impression of Change) scale, [664](#)
- Ciliary neurotrophic factor (CNTF), [814–815](#)
- Cimetidine–drug interactions
  - benzodiazepines, [567](#), [572](#)
  - carbamazepine, [964](#)
  - classic antipsychotics, [620](#)
  - moclobemide, [297](#)
  - paroxetine, [404](#), [405](#)
  - propranolol, [866](#)
  - ziprasidone, [782](#)
- Cingulotomy, for OCD, [1212](#)
- Ciprofloxacin–drug interactions
  - clozapine, [641](#)
  - duloxetine, [542](#)
- Circadian. *See* [Melatonin](#)
- Circadian rhythm–based sleep disorders
  - advanced sleep phase disorder, [1072](#)
  - delayed sleep phase disorder, [1070](#), [1072](#)
  - jet lag, [1070](#), [1072](#), [1074](#)
  - melatonin for, [1070](#), [1356](#)
  - melatonin receptor agonists for, [1071–1072](#)
  - non-24-hour sleep–wake cycle, [1070](#), [1071](#)
  - shift work sleep disorder, [1070](#), [1072](#), [1074](#), [1084](#), [1089](#), [1097](#)
- cis*-Regulatory elements, [6](#), [10](#), [12](#)
- Cisapride, [1507](#)
- Cisatracurium, interaction with carbamazepine and oxcarbazepine, [963](#)
- Cisplatin, interaction with carbamazepine, [967](#)
- Citalopram, [431–446](#)
  - bupropion augmentation of, [500](#)
  - in children and adolescents, [439](#), [1434](#), [1444–1445](#), [1449](#), [1451](#), [1470](#), [1498](#)
  - discontinuation syndrome with, [444–445](#)

dosing of, 436, 1525, **1634**  
in children and adolescents, **1498**  
drug interactions with, 446  
carbamazepine and oxcarbazepine, **963**, 965  
in elderly patients, 436, 1513–1514, 1525  
fMRI studies of effects of, 269  
generic, 431  
history and discovery of, 421–432  
indications for, 436–442, 446  
autism spectrum disorder, 1470  
behavioral complications of dementia, 1521, 1525, 1628  
bulimia nervosa, 1338  
depression, 436, 446  
with anxiety, 441–442  
in children and adolescents, 439, 1434  
maintenance treatment, 436  
vs. mirtazapine, 481  
vs. paroxetine, 391  
STAR\*D study, 435, 436, 445  
generalized anxiety disorder, 440  
OCD, 442  
in children and adolescents, 1449  
mirtazapine and, 484  
quetiapine and, 1211  
panic disorder, 440–441, 1195  
in children and adolescents, 1445  
maintenance treatment, 1198  
PTSD in children and adolescents, 1451  
social anxiety disorder, 441  
in children and adolescents, 1444–1445  
investigational use in Alzheimer's disease, 442–443  
mechanism of action of, 434–436  
PET studies of receptor binding affinity of, 59  
pharmacogenetics of, 63  
pharmacokinetics and disposition of, 433–434  
pharmacological profile of, 432–433  
*R*-enantiomer of, 321, 431, 433  
racemic, 226, 432, 434  
*S*-enantiomer of (See *Escitalopram*)  
side effects and toxicology of, 443–444, 446, 1434, 1449, 1451, 1470  
structure–activity relations for, 336, **337**, **432**  
suicidality and, 445–446

Civil commitment laws, [1595](#)

CIWA (Clinical Institute Withdrawal Assessment), [1613](#)

CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol, Revised), [1285](#)

Clarithromycin-drug interactions

- carbamazepine, [964](#), [967](#)
- ketamine, [556](#)
- suvorexant, [1072](#)

Clearance of drug, [209](#), [218–219](#), [225](#), [227](#). *See also* [Pharmacokinetics](#)

- drug interactions affecting, [231](#)
- in elderly persons, [1507–1508](#)

Clinical Antipsychotic Trials of Antipsychotic Effectiveness (CATIE), [604](#), [620](#), [631](#), [637](#), [658](#), [661](#), [669](#), [688](#), [694](#), [695](#), [696](#), [697](#), [713](#), [714](#), [715](#), [718](#), [720](#), [721](#), [722](#), [764–765](#), [766](#), [767](#), [776](#), [778](#), [779–780](#), [871](#), [875](#), [1106](#), [1246–1247](#), [1250](#), [1253](#), [1254](#), [1255](#), [1524](#)

Clinical Antipsychotic Trials of Antipsychotic Effectiveness—Alzheimer’s Disease (CATIE-AD), [664](#), [692](#), [717](#), [1524](#), [1529](#), [1624](#), [1626](#)

Clinical Anxiety Scale (CAS), [441](#)

Clinical Global Impressions (CGI) Scale, [363](#), [364](#), [365](#), [367](#), [369](#), [390](#), [422](#), [481](#), [484](#), [485](#), [486](#), [591](#), [664](#), [667](#), [691](#), [739](#), [740](#), [741](#), [743](#), [744](#), [745](#), [746](#), [763](#), [764](#), [765](#), [771](#), [773](#), [800](#), [803](#), [812–813](#), [814](#), [841–842](#), [843](#), [844](#), [845](#), [950](#), [1004](#), [1006](#), [1007](#), [1021](#), [1026](#), [1087](#), [1088](#), [1091](#), [1204](#), [1217](#), [1433](#), [1434](#), [1435](#), [1437](#), [1438](#), [1439](#), [1441](#), [1444](#), [1445](#), [1446](#), [1447](#), [1458](#), [1462](#), [1464](#), [1465](#), [1466](#), [1467](#), [1468](#), [1469](#), [1470](#), [1471](#), [1472](#)

Clinical Institute Withdrawal Assessment (CIWA), [1613](#)

Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar), [1285](#)

Clinician-Administered PTSD Scale (CAPS), [344](#), [367](#), [423](#), [668](#), [1026](#), [1213](#), [1219](#)

Clinician-Administered PTSD Scale—Child and Adolescent Version (CAPS-CA), [1451](#)

Clinician’s Interview-Based Impression of Change (CIBIC) scale, [664](#)

Clobazam

- for generalized anxiety disorder, [590](#)
- interaction with carbamazepine, [966](#)
- structure of, [1053](#)

Clomethiazole, [1068](#)

Clomipramine

- in children and adolescents, [1211](#), [1448–1449](#), [1470–1471](#)
- dosing of, [311](#), [1633](#)
- drug interactions with
  - carbamazepine, [965](#)
  - SSRIs, [318](#), [425](#)
- indications for

- autism spectrum disorder, 1470-1471
- depression, 316
  - in elderly persons, 391
  - vs. paroxetine, 390
- maintenance treatment for panic disorder, 1198
- OCD, 306, 318, 342, 396, 1210-1211
  - in children and adolescents, 1211, 1448-1449
  - cognitive-behavioral therapy and, 1212
  - fluvoxamine and, 1211
  - intravenous clomipramine, 1211
  - maintenance treatment/relapse prevention, 1211
- pain syndromes, 319
- overdose of, 324
- pharmacokinetics of, 311
- pharmacological profile of, 306, 308
- side effects of, 321, 324, 1448, 1449
- structure-activity relations for, 306, 307, 337

Clonazepam, 572

- dosing of, 1641
- drug interactions with
  - bupropion, 506
  - carbamazepine, 963, 966
  - oxcarbazepine, 963
- duration of action of, 568
- indications for
  - acute trauma exposure, 1604
  - benzodiazepine withdrawal, 1198
  - extrapyramidal side effects, 866, 867
  - insomnia, 1353, 1364
  - OCD, 1211-1212
    - in children and adolescents, 1450
  - panic disorder, 563, 568, 1196
    - in children and adolescents, 1445
  - psychotic agitation, 569
  - social anxiety disorder, 1200, 1204
    - maintenance treatment, 1203
  - specific phobia, 1204
  - tardive dyskinesia, 866, 867, 874-875
- pharmacokinetics of, 566
- side effects of, 1364

Clonidine

- in children and adolescents, 1451, 1454-1455, 1459-1460, 1472, 1500



- dosage and monitoring of, 1500, **1657**
- side effects of, 1500
- contraindications to, 1614
- discontinuation of, 1500
- drug interactions with
  - methylphenidate, 1500
  - TCAs, 325
  - trazodone, 459
- growth hormone release induced by, 165
- indications for
  - ADHD, 76, 1454–1455, 1456, 1500
    - with aggression, 1459–1460
  - akathisia, 870–871
  - autism spectrum disorder, 1472
  - borderline personality disorder, 1323
  - opioid withdrawal, 76, 1291, 1613–1614
  - PTSD in children and adolescents, 1451
  - smoking cessation, 1298
  - Tourette syndrome, 1460–1461, 1500
- overdose of, 1500
- side effects of, 871, 1454, 1500
- transdermal, 1451, 1461, 1472, 1500
- Clopidogrel, interaction with bupropion, 506
- Clorazepate
  - dosing of, **1641**
  - for generalized anxiety disorder, 589–590
  - pharmacokinetics of, 564, 571–572, 1060, **1061**
  - structure of, **565**
  - sustained-release, 567
- Clorgyline, **284**, 286
- Clozapine, 623–641
  - augmentation of, 634
  - in children and adolescents, 634, 1443, 1464, 1466, **1499**
  - dosing of, 220–221, 627, **1647**
    - in children and adolescents, **1499**
  - drug interactions with, 640–641
    - carbamazepine, **963**, 966
    - fluvoxamine, 425
    - lithium, 906
    - oxcarbazepine, **963**
    - paroxetine, 404, **404**
  - in elderly persons, 1507–1508, 1516, 1521, 1525, 1528, 1624

- formulations of, [1249](#)
- history and discovery of, [604](#), [623-624](#), [649-650](#)
- indications for, [630-635](#)
  - behavioral complications of dementia, [1521](#), [1525](#)
  - bipolar disorder
    - in children and adolescents, [1443](#)
    - mania, [632](#)
    - treatment-resistant and rapid-cycling illness, [633](#)
  - borderline personality disorder, [1318](#)
  - extrapyramidal side effects, [871](#), [872](#)
  - Parkinson's disease psychosis, [633](#), [1528](#)
  - polydipsia-hyponatremia syndrome, [635](#)
  - psychotic depression, [633](#)
  - schizoaffective disorder, [630](#), [632](#), [633](#)
  - schizophrenia, [630](#), [1521](#)
    - augmentation strategies, [634](#)
    - in children and adolescents, [634](#), [1464](#), [1466](#)
    - ECT and, [1111](#)
    - with high suicide risk, [632](#), [1261](#)
    - with hostility/aggression, [631-632](#)
    - maintenance treatment, [634-635](#)
    - with substance use disorder, [632](#), [1259](#)
    - topiramate and, [1021-1022](#)
    - treatment-resistant illness, [604](#), [623](#), [630-631](#), [1247](#), [1248](#)
  - tardive dyskinesia, [617](#), [635](#), [875](#), [876](#), [1257](#)
  - tardive dystonia, [875](#), [876](#)
- mechanism of action of, [63](#), [72](#), [623-624](#), [628-630](#)
  - exceptional antipsychotic efficacy, [629-630](#)
  - low propensity to cause extrapyramidal side effects, [628-629](#)
- monitoring treatment with, [636](#)
- pharmacogenetics and response to, [628](#)
- pharmacokinetics and disposition of, [627-628](#), [1507](#)
- pharmacological profile of, [624-627](#), [706](#), [707](#), [708](#), [1521](#)
  - animal studies of, [626-627](#)
- side effects and toxicology of, [626](#), [635-640](#), [1248](#), [1464](#), [1500](#), [1521](#)
  - agranulocytosis/hematological effects, [604](#), [623](#), [628](#), [630](#), [631](#), [635-636](#), [640](#), [875](#), [1248](#), [1464](#), [1500](#), [1521](#), [1561](#), [1615](#)
  - anticholinergic effects, [636](#), [639](#)
  - cardiac effects, [626](#), [636-637](#), [1248](#), [1516](#)
  - discontinuation and reinitiation due to, [640](#)
  - hepatic effects, [639-640](#)
  - neuroleptic malignant syndrome, [639](#)

- obsessive-compulsive symptoms, [640](#)
- respiratory effects, [639](#)
- sedation, [639](#)
- seizures, [221](#), [638](#), [640](#), [875](#), [1248](#)
- sexual dysfunction, [640](#)
- sialorrhea, [639](#)
- weight gain/metabolic effects, [626](#), [628](#), [637–638](#), [639](#), [669](#), [1253](#), [1254](#)
- smoking and, [641](#)
- structure-activity relations for, [606](#), [624](#), [625](#)
- use in pregnancy and lactation, [1562–1563](#)
- Clozapine National Registry, [635](#)
- Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program, [635](#), [636](#)
- CLPS (Collaborative Longitudinal Personality Disorders Study), [1315](#)
- Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system, [22–23](#), [24](#)
- CMAI (Cohen-Mansfield Agitation Inventory), [744](#), [1519](#), [1523](#)
- CNS. *See* [Central nervous system](#)
- CNTF (ciliary neurotrophic factor), [814–815](#)
- CNVs. *See* [Copy number variants](#)
- CO-MED (Combination Medication to Enhance Depression Outcomes) study, [482](#)
- Cocaine- and amphetamine-related transcript, [73](#), [100](#)
- Cocaine use disorder, [1301](#), [1611](#)
  - benzodiazepine abuse and, [574](#), [575](#)
  - depression and, [1154](#)
  - dopamine and, [68–69](#), [70](#), [71](#), [1302](#)
  - effects of AMPA receptor antagonists on hyperactivity induced by, [84–85](#)
  - norepinephrine and, [73](#)
  - psychosis and, [1611](#)
  - schizophrenia and, [1259](#)
  - suicide and cocaine intoxication, [1598](#)
  - tolerance in, [224](#)
  - treatment of, [1301–1303](#)
    - N*-acetylcysteine, [1302–1303](#)
    - agonist replacement strategies, [1301](#)
    - aripiprazole, [846](#)
    - bifeprunox, [846](#)
    - bupropion, [1301–1302](#)
    - buspirone, [71](#), [592](#)
    - cariprazine, [846](#)
    - classic antipsychotics, [611](#)
    - desipramine, [1259](#)

- disulfiram, [1302](#)
- imipramine, [1259](#)
- ketamine, [554](#)
- modafinil, [1093](#), [1302](#)
- psychostimulants, [1093](#)
- topiramate, [1024–1025](#), [1302](#)
- vigabatrin, [1302](#)
- for violent behavior during acute intoxication, [1611](#)

Codeine, [228](#), [1384](#), [1388](#), [1408](#)

- combined with acetaminophen, [1383](#), [1398](#)

Codons, [7](#), [12](#)

- stop, [7](#), [64](#)

Cogentin. See [Benztropine](#)

Cognitive-behavioral analysis, for depression, [1164](#)

Cognitive-behavioral therapy (CBT)

- for anorexia nervosa, [666](#)
- for binge-eating disorder, [1023](#), [1344](#)
- for bipolar disorder, [1183](#), [1186](#)
- for bulimia nervosa, [1339–1342](#), [1341](#)
- for child and adolescent disorders, [1432](#)
  - depression, [521](#), [1434](#), [1435](#), [1437](#)
  - OCD, [1447](#), [1449](#), [1450](#)
  - panic disorder, [1446](#)
  - PTSD, [1450](#)
  - social anxiety disorder, [1202–1203](#)
- for depression, [1108](#), [1164–1165](#), [1166](#)
  - with alcohol use disorder, [461](#)
  - in children and adolescents, [521](#), [1434](#), [1435](#), [1437](#)
  - nefazodone and, [461](#)
  - neuroimaging to identify patients for, [267](#)
  - in postpartum period, [363](#)
- for generalized anxiety disorder, [1210](#)
- for insomnia, [1350](#)
- for OCD, [1211](#), [1212](#)
  - in children and adolescents, [1447](#), [1449](#), [1450](#)
  - SSRIs and, [366](#), [1211](#)
- for pain syndromes, [1395–1397](#), [1396](#)
  - fibromyalgia, [1403](#), [1404](#)
- for panic disorder, [1198–1199](#)
  - in children and adolescents, [1446](#)
  - clonazepam and, [1196](#)
  - paroxetine and, [395](#)

- sertraline and, 366
- for PTSD, 1218
  - in children and adolescents, 1450
  - prevention after trauma exposure, 1603
- for schizophrenia, 1251, 1252, 1261
  - prodromal illness, 1262
- for smoking cessation, 1255
- for social anxiety disorder, 1203
  - in children and adolescents, 1202–1203
  - with D-cycloserine, 1202
- for substance use disorders, 1284
- for suicidality, 1600
- Cognitive Drug Research System Attention Battery Tests, 843
- Cognitive effects
  - of drugs
    - amantadine, 863
    - anticholinergic agents, 859
    - antipsychotics, 612, 614, 615, 1527
    - benzodiazepines, 570–571, 1065, 1205, 1353, 1364, 1524, 1627
    - carbamazepine, 944, 957
    - citalopram, 1470
    - clozapine, 1521
    - fluoxetine, 346
    - ketamine, 555
    - lithium, 902–903, 1178
    - nonbenzodiazepine hypnotics, 1365
    - opioids, 1385–1386
    - pregabalin, 995
    - sedative-hypnotics, 1076
    - TCAs, 320
    - topiramate, 1021, 1028, 1029, 1339, 1502
    - valproate, 934, 1178
    - vortioxetine, 469
  - of ECT, 1115–1116, 1117, 1125–1127, 1162
- Cognitive enhancers, 1039–1045
  - cholinesterase-related therapies, 664, 1040–1042
    - donepezil, 1040–1041
    - galantamine, 1041–1042
    - huperzine A, 1042
    - metrifonate, 1042
    - nicotinic receptor agonists, 1042
    - physostigmine, 1042

- recommendations for, [1040](#)
- rivastigmine, [1041](#)
- NMDA-related therapies, [1042-1043](#)
  - memantine, [1043](#)
  - recommendations for, [1042-1043](#)
- other therapies, [1044-1045](#)
  - antiamyloid immunization, [1045](#)
  - antioxidants, [1044-1045](#)
  - ginkgo biloba*, [1044](#)
- vascular and inflammation-related therapies, [1043-1044](#)
  - acetylcholinesterase inhibitors, [1044](#)
  - recommendations for, [1044](#)
- Cognitive impairment. *See also* [Delirium](#); [Dementia](#)
  - in borderline personality disorder, [1315](#)
  - in depression, [1125](#)
  - mild, [1040](#)
  - neurotransmitter systems in, [1039](#)
  - in schizophrenia, [611](#), [1242-1244](#), [1249-1250](#), [1262](#)
    - in CATIE trial, [1250](#)
    - lurasidone for, [826-827](#)
    - olanzapine vs. risperidone for, [659](#)
    - perphenazine, [1250](#)
    - ziprasidone for, [766](#)
  - in schizotypal personality disorder, [1328](#), [1329](#)
  - vascular, [1043-1044](#)
  - in Wernicke-Korsakoff syndrome, [1613](#)
- Cognitive therapy, for social anxiety disorder, [1199](#), [1200](#)
- CogState Computerized Cognitive Battery, [827](#)
- Cohen-Mansfield Agitation Inventory (CMAI), [744](#), [1519](#), [1523](#)
- Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, [140](#)
- Colestipol, interaction with  $\beta$ -blockers, [866](#)
- Collaborative Longitudinal Personality Disorders Study (CLPS), [1315](#)
- Collaborative Perinatal Project, [1566](#)
- Color Trails Test, [843](#)
- Columbia Suicide Severity Rating Scale, [848](#)
- Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD), [1519](#)
- Combination Medication to Enhance Depression Outcomes (CO-MED) study, [482](#)
- Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study, [1287](#), [1288](#)

Comparison of Atypicals in First Episode Psychosis (CAFE) study, [687](#), [696](#)  
Compazine. *See* [Prochlorperazine](#)  
Complement system, [178](#)  
Complementary and alternative medicine (CAM)  
    for depression, [1165](#)  
    for generalized anxiety disorder, [1209–1210](#)  
    for pain, [1378](#), [1396–1397](#), [1416](#)  
        fibromyalgia, [1404](#)  
        osteoarthritis, [1408](#)  
Complex regional pain syndrome  
    ECT for, [1113](#)  
    ketamine for, [552](#)  
Computed tomography (CT) of brain, in long-term benzodiazepine users, [570](#)  
COMT (catechol-*O*-methyltransferase), [130](#), [420](#), [1110](#)  
Concentration difficulty  
    in depression, [1151](#)  
    drug-induced  
        amantadine, [863](#)  
        citalopram, [1470](#)  
        classic antipsychotics, [614](#)  
        pregabalin, [995](#)  
        topiramate, [1028](#), [1029](#)  
Concerta. *See* [Methylphenidate](#)  
Conduct disorder (CD), [1456–1457](#)  
    ADHD and, [1456](#)  
    treatment of, [1456–1457](#)  
        bupropion, [503](#)  
        clinical recommendations for, [1460](#)  
        haloperidol, [1458](#)  
        lithium, [1458–1459](#)  
        psychostimulants, [1456](#)  
        valproate, [930](#)  
Confidentiality, [1594](#)  
    breach of, in emergency situations  
        duty to warn potential victims of harm, [1600–1601](#)  
        suicidal patients, [1597](#)  
        suspected child or elder abuse or neglect, [1597](#)  
Confusion  
    drug-induced  
        antipsychotics, [612](#), [614](#)  
        benzodiazepines, [1065](#), [1627](#)  
        ketamine, [555](#)

- TCAs, [320](#)
- topiramate, [1028](#)
- after SSRI discontinuation, [1615](#)
- in Wernicke-Korsakoff syndrome, [1613](#)
- Congenital anomalies. *See* [Teratogenic effects of drugs](#)
- Conivaptan, interaction with suvorexant, [1072](#)
- Connectomics, [253](#)
- Conners Behavior Checklist, [1460](#)
- Conners Parent Rating Scale (CPR), [1087](#)
- Conotruncal anomaly face syndrome, [125](#)
- Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavior Rating Scale, [1519](#)
- Constipation, drug-induced
  - N*-acetylcysteine, [1473](#)
  - anticholinergic agents, [859](#)
  - antipsychotics, [1516](#)
  - aripiprazole, [746](#), [1180](#)
  - bupropion, [504](#)
  - cariprazine, [848](#)
  - classic antipsychotics, [612](#), [618](#), [719](#), [816](#)
  - clomipramine, [1448](#), [1449](#)
  - clozapine, [626](#), [639](#), [1521](#)
  - diphenhydramine, [1368](#)
  - doxylamine, [1368](#)
  - duloxetine, [540](#)
  - iloperidone, [816](#)
  - lamotrigine, [1502](#)
  - levomilnacipran, [541](#)
  - MAOIs, [290](#)
  - mirtazapine, [1369](#), [1498](#)
  - muscarinic receptor antagonists, [80](#)
  - nefazodone, [462](#)
  - olanzapine, [1179](#), [1370](#)
  - opioids, [1385](#)
  - paroxetine, [386](#), [398](#)
  - quetiapine, [1180](#)
  - risperidone, [719](#)
  - TCAs, [321](#), [1368](#), [1369](#)
  - treatment of, [639](#), [1398](#)
  - ziprasidone, [774](#)
- Contingency management, for substance use disorders, [1284](#), [1292](#), [1299](#)
- Continuous positive airway pressure (CPAP), for obstructive sleep apnea



- armodafinil and, 1091
- modafinil and, 1095
- Contrave. *See* Bupropion/naltrexone
- Controlled-release drug formulations, 213–214
- Controlled Substances Act of 1970, 1383
- CONVERGE (China, Oxford, and Virginia Commonwealth University Experimental Research on Genetic Epidemiology) Consortium, 140
- Conversion disorder, 1605
- Coordination problems, eslicarbazepine acetate-induced, 960
- Copy number variants (CNVs), 126, 127, 129, 145
  - in ADHD, 127
  - in autism spectrum disorder, 127
  - genomewide analysis of, 130, 141
  - in schizophrenia, 127
- Corgard. *See* Nadolol
- Cortical brain stimulation, 268
- Corticosterone, buspirone effects on, 588–589
- Corticotropin-releasing hormone (CRH), 98–99, 100, 186
  - in depression/suicidality, 99, 160–162, 181, 193, 389, 1156
    - antidepressant effects on, 195
  - effects on HPG axis, 168
  - hypothalamic secretion of, 98, 157
  - immune system and, 187–188, 193
  - in pregnancy, 167
  - receptors for, 98–99
  - in stress response, 99, 157–158, 159, 435–436
    - escitalopram effects on, 436
  - synthesis of, 98
- Cortisol
  - in borderline personality disorder, 1326
  - drug effects on
    - carbamazepine, 949
    - mirtazapine, 480
  - effects on hypothalamic-pituitary-gonadal axis, 168
  - immune system and, 181, 184, 187, 193, 195
  - regulation of secretion of, 157–158
  - in specific disorders
    - depression, 158, 160–162, 181, 184, 193, 1156
    - psychosis, 162
    - PTSD, 163–164
  - in stress response, 158, 159, 179, 181

Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study—band 2 (CUTLASS-2), [631](#), [1247](#)

Cotinine analogues, as cognitive enhancers, [1042](#)

Cough, drug-induced

- duloxetine, [1443](#)
- haloperidol, [719](#)
- paroxetine, [1435](#)
- risperidone, [719](#)
- suvorexant, [1359](#), [1367](#)

Cough syrups, interaction with MAOIs, [292](#)

COX (cyclo-oxygenase) inhibitors, [1382](#)

CPK (creatine phosphokinase), in neuroleptic malignant syndrome, [1257](#), [1614](#)

CPR (Conners Parent Rating Scale), [1087](#)

Cre-loxP recombination technology, [30](#)

Creatine phosphokinase (CPK), in neuroleptic malignant syndrome, [1257](#), [1614](#)

CREB (cAMP response element-binding protein), [9](#), [10](#), [11](#), [48](#), [101](#), [445](#), [891](#), [1108](#)

CREB-binding protein (CBP), [10](#), [11](#)

CREs (cAMP response elements), [10](#)

CRH. *See* [Corticotropin-releasing hormone](#)

CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 system, [22–23](#), [24](#)

Cross-disorder studies, [142–143](#)

Cross-National Collaborative Panic Study, [1196](#)

CSFQ-14 (Changes in Sexual Functioning Questionnaire Short Form), [472](#)

CT (computed tomography) of brain, in long-term benzodiazepine users, [570](#)

Curare, [81](#)

CUSPAD (Columbia University Scale for Psychopathology in Alzheimer's Disease), [1519](#)

Cutaneous effects of drugs

- benzodiazepines, [1065](#)
- botulinum toxin, [868](#)
- bupropion, [504](#), [1436](#)
- carbamazepine, [957–958](#), [1179](#), [1440](#)
- citalopram, [1470](#)
- classic antipsychotics, [616](#), [619](#)
- clonidine patch, [1500](#)
- eslicarbazepine acetate, [960](#)
- ketamine, [555](#)
- lamotrigine, [1008–1009](#), [1010](#), [1441](#), [1502](#)

- lithium, [1501](#)
- modafinil, [1090](#)
- oxcarbazepine, [958](#), [960](#), [1440](#), [1502](#)
- selegiline transdermal system, [298](#), [1436](#)
- TCAs, [324](#)
- ziprasidone, [775](#)
- CUtLASS-2 (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study—band 2), [631](#), [1247](#)
- CY-BOCS (Children’s Yale-Brown Obsessive Compulsive Scale), [1447–1449](#), [1450](#), [1470](#)
- Cyclic 3′-5′-adenosine monophosphate (cAMP), [10](#), [11](#), [34](#)
  - acetylcholine actions on, [78](#)
  - adenosine actions on, [96](#)
  - CRH actions on, [98](#)
  - dopamine actions on, [66](#)
  - drug effects on  $\beta$ -adrenergic-stimulated production of cyclic antidepressants, [309](#)
  - SSRIs, [338](#)
  - lithium effects on, [890](#)
  - norepinephrine actions on, [75](#)
  - protein kinase A mediation of, [49](#)
  - serotonin receptor actions on, [56](#), [60](#), [61](#)
  - somatodendritic autoreceptor effects on, [51](#)
- Cyclic guanosine monophosphate (cGMP), [34](#), [62](#), [551](#), [890](#)
- Cyclo-oxygenase (COX) inhibitors, [1382](#)
- Cyclobenzaprine
  - interaction with MAOIs, [293](#)
  - for pain, [1393](#), [1403](#), [1413](#)
- Cycloplegia, drug-induced
  - classic antipsychotics, [619](#)
  - trihexyphenidyl, [858](#)
- D-Cycloserine, [86](#), [92](#), [553](#)
  - for OCD in children and adolescents, [1450](#)
  - for PTSD, [1218](#)
  - in children and adolescents, [1451](#)
  - for social anxiety disorder, [1202](#)
  - for specific phobia, [1204](#)
- Cyclosporine–drug interactions
  - buspirone, [594](#)
  - carbamazepine and oxcarbazepine, [963](#)
  - nefazodone, [462](#)
- Cyproheptadine

- for drug-induced sexual dysfunction, [290](#), [399](#)
- for myoclonus, [290](#)
- for serotonin syndrome, [1615](#)

#### Cystitis

- interstitial, [1401](#)
- ketamine-induced, [555](#)

Cytidine 5'-diphosphocholine (CDP-choline), for vascular cognitive impairment, [1044](#)

Cytochrome P450 (CYP) enzymes, in drug metabolism, [215](#), [228-230](#), [229-230](#), [231](#), [1507-1508](#)

- amphetamine, [1087](#)

#### antidepressants

- bupropion, [497](#), [506](#)
- citalopram, [434](#), [446](#)
- citalopram, in elderly persons, [1505](#)
- desvenlafaxine, [523](#)
- duloxetine, [534](#), [542](#)
- escitalopram, [446](#)
- escitalopram, in elderly persons, [1505](#)
- fluoxetine, [340](#), [349-350](#), [1507](#)
- fluvoxamine, [425](#), [1507](#)
- ketamine, [550](#), [556](#)
- mirtazapine, [480](#), [488](#)
- paroxetine, [387](#), [393](#), [403-405](#)
- paroxetine, in elderly persons, [1505](#)
- sertraline, [360](#), [361-362](#), [373](#)
- TCAs, [305](#), [312](#), [325-326](#), [1506](#), [1615](#)
- trazodone, [456](#)
- venlafaxine, [522-523](#), [1506](#)
- vortioxetine, [468](#)

#### antipsychotics, [610](#), [619-620](#), [1625](#)

- aripiprazole, [736](#), [749](#)
- asenapine, [799](#)
- brexpiprazole, [737](#), [749](#)
- cariprazine, [838](#), [840](#)
- clozapine, [627](#), [628](#), [640-641](#), [1507](#)
- iloperidone, [810](#)
- lurasidone, [822](#)
- olanzapine, [653](#), [673-674](#)
- quetiapine, [686](#)
- risperidone, [709-710](#), [722](#)
- ziprasidone, [760](#), [782](#)

- anxiolytics
  - benzodiazepines, [566](#)
  - buspirone, [589](#)
- drug interactions and, [231-233](#), [1506-1507](#)
- in elderly persons, [1505](#), [1506-1507](#)
- genetic variations of
  - CYP2D6* copy number variants, [127](#), [312](#)
  - genotyping of, [228](#)
- modafinil, [1089](#), [1090](#)
- mood stabilizers
  - carbamazepine, [944](#), [961-962](#), [1507](#)
  - eslicarbazepine acetate, [968](#)
  - oxcarbazepine, [968](#)
  - topiramate, [1018](#)
- normal, extensive, ultrarapid, and poor metabolizers, [228-229](#), [229](#), [312](#)
- suvorexant, [1072](#)
- Cytogenetic studies, [130-131](#)
- Cytokines, [178](#). *See also* [Interleukins](#)
  - anti-inflammatory, [183-184](#), [195](#)
  - proinflammatory, [178](#)
    - antidepressant effects on, [195](#), [1157](#)
    - in borderline personality disorder, [1326](#)
    - CRH effects on production of, [187-188](#)
    - in depression, [182-184](#), [1157](#)
    - effects on brain, [189](#), [189-190](#)
    - effects on HPA axis, [192-194](#)
    - effects on monoamine neurotransmitters, [191-192](#)
    - effects on thyroid axis, [191-192](#)
    - inhibition by vagus nerve stimulation, [186](#)
    - pathways by which neuropsychiatric disturbance are produced by, [191](#), [191-194](#)
    - in psychophysical disorders, [185](#)
    - in schizophrenia, [185](#)
    - in seasonal affective disorder, [185](#)
- sickness behavior induced by, [189](#), [190-191](#)
  - antidepressant efficacy for, [195](#), [196](#)
  - CRH and, [193](#)
- stress-induced production of, [180](#)
- T cell release of, [158](#)

DA. *See* [Dopamine](#)

DAG (diacylglycerol), [56-57](#), [63](#), [74-75](#), [78-79](#), [90](#)

Dalmane. *See* [Flurazepam](#)

Danazol, interaction with carbamazepine, [964](#)

Dantrolene, [1393](#)

    for neuroleptic malignant syndrome, [1257](#), [1607](#), [1614](#)

DAT. *See* [Dopamine transporter](#)

Davidson Trauma Scale (DTS), [1213](#)

Daytrana patch (Daytrana Transdermal System), [1503](#), [1657](#)

DBS. *See* [Deep brain stimulation](#)

DBT. *See* [Dialectical behavior therapy](#)

DCAR (desmethyl-cariprazine), [833](#), [835](#), [837-838](#), [839](#), [840](#)

DDCAR (didesmethyl-cariprazine), [833](#), [835](#), [837-838](#), [839](#), [840](#)

Deep brain stimulation (DBS), [268](#), [1133-1134](#)

    EEG guidance for, [265](#)

    indications for, [1163](#)

        depression, [1108](#), [1133](#), [1163](#)

        OCD, [1133](#), [1163](#), [1212](#)

        Parkinson's disease, [1134](#), [1163](#)

    neuroimaging studies of acute and delayed effects of, [268](#)

    PET imaging and, [244](#)

Deep vein thrombosis, antipsychotics and, [1516](#)

Default mode network (DMN), [259-260](#)

Dehydroaripiprazole, [734](#), [735](#), [736](#), [749](#)

Dehydroepiandrosterone (DHEA), [934](#), [1045](#), [1054](#), [1165](#)

Dehydroxynorketamine (DHNK), [550](#)

Deinstitutionalization, [603-604](#), [1593](#)

Delavirdine, interaction with carbamazepine and oxcarbazepine, [963](#)

Delayed sleep phase syndrome, [1070](#), [1356](#)

Delirium, [1604](#), [1612](#)

    alcohol-withdrawal, [1607](#), [1612-1613](#)

    causes of, [1612](#)

    drug-induced

        amantadine, [863](#)

        anticholinergic agents, [305](#), [614](#), [859](#), [1607](#)

        ketamine, [555](#)

        lithium, [903](#)

        TCAs, [320](#), [322](#)

    ECT-induced interictal, [1110](#), [1124](#)

    in elderly patients

        antipsychotics for, [1528](#)

- melatonin receptor agonists for prevention of, 1071
- in serotonin syndrome, 346
- superimposed on dementia, 1612
- treatment of, **1607**, 1612
  - antipsychotics, 424, 1528, 1612
  - fluvoxamine, 424
- Delirium tremens (DTs), 1285, **1607**, 1612–1613
- Delusional disorder, late-onset, 1530
- Delusions
  - in Alzheimer's disease, 1518–1519
    - olanzapine for, 663
  - antipsychotics for, 611
  - during benzodiazepine withdrawal, 573
  - during cocaine intoxication, 1611
  - nihilistic, suicide risk and, 1597
  - in Parkinson's disease, clozapine for, 633
  - in schizophrenia, 1242, 1243
    - vs. obsessive-compulsive symptoms, 1261
- Dementia
  - of Alzheimer's type (See [Alzheimer's disease](#))
  - assessment of psychopathology in, 1519
  - behavioral complications of, 1516, 1518, 1623
  - benzodiazepine use and risk of, 571
  - delirium superimposed on, 1612
  - diffuse Lewy body disease, 1528
  - lithium-induced, 903
  - in Parkinson's disease, 1528
  - prevalence of, 1515–1516
  - psychosis in, 1515, 1516, 1518–1519
    - neurobiological mechanisms of, 1519–1520
  - rating scales for, 1519
- Dementia praecox, 123
- Dementia treatment
  - for behavioral complications, 1520–1528, 1624–1628
    - agitation and aggression, 1624–1628
    - antipsychotics, 663–665, 1520–1528, 1612, 1624–1626
      - vs. anticonvulsants and other agents, 1524–1525
    - aripiprazole, 744, 1523
    - vs. benzodiazepines, 1524
  - CATIE-AD study, 664, 692, 717, 1524, 1529, 1624, 1626
  - choice of, 1525
  - classic antipsychotics, 1520–1521

- clozapine, [1521](#), [1525](#)
- comparative studies of, [1523-1524](#)
- for diffuse Lewy body disease, [1528](#)
- dosing of, [1525](#)
- duration of treatment with, [1526-1527](#)
- effects on cognition and activities of daily living, [1527](#)
- efficacy studies of, [1520](#)
- olanzapine, [663-665](#), [1522-1523](#), [1524](#), [1525](#)
- paliperidone, [1522](#)
- for Parkinson's disease dementia, [1528](#)
- quetiapine, [692](#), [1523](#), [1524](#), [1525](#)
- risperidone, [717](#), [1521-1522](#), [1523-1524](#), [1525](#), [1526](#)
- side effects of, [1525](#)
- stroke/mortality risk in elderly patients, [424](#), [663](#), [717](#), [774](#), [818](#), [825](#), [848](#), [1370](#), [1517](#), [1520](#), [1612](#), [1625-1626](#)
- treatment monitoring of target behavioral symptoms of, [1527-1528](#)
- use of concomitant psychotropics with, [1525-1526](#)
- benefits of early intervention, [1039](#)
- benzodiazepines, [571](#), [1520](#), [1524](#), [1627](#)
- buspirone, [593](#), [1524](#), [1612](#)
- carbamazepine, [1524](#), [1612](#), [1627](#)
- citalopram, [1521](#), [1525](#), [1628](#)
- cognitive enhancers, [1039-1045](#)
  - cholinesterase-related therapies, [664](#), [1040-1042](#)
  - NMDA-related therapies, [1042-1043](#)
  - other therapies, [1044-1045](#)
  - SSRIs and, [1627-1628](#)
  - vascular and inflammation-related therapies, [1043-1044](#)
- dextromethorphan-quinidine combination, [1628](#)
- ECT, [1112](#)
- propranolol, [1524](#), [1612](#)
- trazodone, [1626-1627](#)
- valproate, [930-931](#), [1524](#), [1612](#), [1627](#)
- for depression
  - citalopram, [443](#)
  - mirtazapine, [485-486](#)
  - selegiline, [297](#)
  - sertraline, [368-369](#)
  - trazodone, [457](#)
- Dental caries, [859](#), [1338](#)
- Deoxyhemoglobin, [251](#), [254](#), [254-255](#)
- Deoxyribonucleic acid (DNA)



- in cell nucleus, [4](#)
- chromosomal, [5](#), [6](#)
- cloning of, [14–16](#), [15](#)
  - polymerase chain reaction, [14–16](#)
  - positional cloning, [16](#)
- complementary (cDNA), [14](#), [16–18](#)
- CpG islands of, [8](#)
- delivery of recombinant DNA into mammalian cells, [17–19](#)
  - vectors for, [17–18](#)
- DNA libraries, [14](#)
- genes and, [5–6](#)
- genome-editing technologies, [2–25](#), [24](#)
- “junk,” [144](#)
- methylation of, [7–9](#), [141](#)
- microarray technology, [22](#), [130](#), [228](#)
- noncoding, [6](#)
- occurrence of linkage disequilibrium, [132–133](#)
- replication of, [6](#)
  - origin of, [6](#)
  - semiconservative, [6](#)
- shotgun sequencing of, [33](#)
- structure of, [5](#)
- transcription of, [6](#)

Dependent personality disorder, [1329](#)

Depression, [1151–1158](#)

- age at onset of, [1152](#)
- with anxious distress, [317](#), [341](#), [441–442](#), [483](#), [501](#), [591–592](#), [1153–1154](#)
- with atypical features, [286–288](#), [294](#), [317](#), [1159](#)
- bipolar, [68](#), [85](#), [86](#), [260](#), [317](#), [495](#), [501](#), [518](#), [662](#), [689–690](#), [741](#), [771](#), [824](#),  
[844](#), [846](#), [893–894](#), [927](#), [942](#), [1003](#), [1004–1006](#), [1020](#), [1088](#), [1096](#),  
[1181–1183](#)
- in children and adolescents, [318](#), [485](#), [1152](#), [1433](#)
- clinical course of, [1151](#)
- clinical features of, [1151](#)
  - cognitive deficits, [1125](#)
  - neurovegetative symptoms, [1151](#), [1155](#), [1259](#)
  - sleep disturbances, [182](#), [1073](#), [1075](#), [1349](#)
- dexamethasone suppression test in, [99](#), [160–161](#), [162](#)
  - immune system and, [184](#), [193](#), [194](#)
- disease burden/disability due to, [1151](#), [1154–1155](#)
- drug-induced
  - benzodiazepines, [1205](#)

- $\beta$ -blockers, 866
  - cariprazine, 848
  - clonidine, 1500
  - interferon- $\alpha$ , 192, 1157
    - paroxetine for prevention of, 393, **394**
  - reserpine, 283, 315
  - topiramate, 1029, 1030
- economic cost of, 1155
- in elderly persons, 318, 1152, 1508–1509
- gender distribution of, 1152
- genetics of, 14, **121**, 1153, 1158
  - candidate gene studies, 1158
  - genomewide association studies, 140, 141
  - 5-HTTLPR polymorphism, 59, 127–128, 134, 388
  - twin studies, 123, 140, 1153
- immune function and, 178, 181–184, **182**, 1153, 1157
- inositol depletion and, 891
- medical illness and, 1153, **1154**
  - cardiovascular disease, 161, 183, 190, 1153, **1154**, 1509
  - fibromyalgia, 992
  - immune system and, 190–191
  - Parkinson's disease, 368
  - stroke, 345, 1093
  - thyroid disease, 192
- with melancholic features, 288, 316–317
- minor, 1152
- neurobiology of, 1155–1158
- neurocircuitry of, 1107–1108
- neuroendocrinology of, 1156–1157
  - growth hormone, 165
  - HPA axis, 99, 158–162, 181, 184, 389, 1153, 1156–1157
    - dexamethasone suppression test, 99, 160–161, 162, 1156
  - ECT effects on, 1107
  - HPG axis, 166–167
  - hypothyroidism, 165
  - prolactin, 165–166
- neuroimaging in
  - MRI, 163, 261–262, 263
  - PET, 59, 61, 69, **243**, 245, 248
- neurotransmitters and receptors in, 1155–1156
  - dopamine, 68–69
  - GABA, 92–93, 984

- glutamate, 1156
- norepinephrine, 73, 76
- serotonin, 55, 192, 263
  - 5-HT<sub>1A</sub> receptor, 61, 245
- neurotrophic hypothesis of, 1157–1158
- pain and, 1378, 1412
- perimenopausal, 167
- postpartum, 166, 167, 363, 1544
  - effects on infant development, 1546
- in pregnancy, 167, 1544–1546
- prevalence of, 1151, 1152
- psychiatric comorbidity with, 1153–1154
  - anxiety disorders, 1153–1154
  - binge-eating disorder, 1342
  - bulimia nervosa, 1338, **1341**
  - dementia, 485–486, 1518
  - functional somatic syndromes, 1402
  - generalized anxiety disorder, 1204
  - schizophrenia, 766–767, 1244, 1259–1260
  - substance use disorders, 1154, 1165
- with psychotic features, 296, 317, 421, 633, 1159, 1530
- risk factors for, 1152–1154
  - negative cognitive bias, 269
- subsyndromal, 1152
- suicidality and, 1151, 1154, 1155
- treatment-resistant (TRD), 1161–1162

Depression treatment, 1158–1166

- anti-inflammatory agents, 194
- antidepressants, 283–543, 1158–1162, 1165
  - assessing and optimizing response to, 1159–1161
  - augmentation of
    - antipsychotics in elderly persons, 1515
    - aripiprazole, 742–743
    - brexpiprazole, 745–746
    - bupropion, 459, 500
    - cariprazine, 846
    - quetiapine, 690
    - risperidone, 716
    - thyroid hormone, 165, 1160
    - ziprasidone, 772
- choice of, 1158–1159, **1160**
- duration of treatment with, 1159–1160, 1161

- in children and adolescents, 1433-1438
  - bupropion, 1436
  - clinical recommendations for, 1437-1438
  - desvenlafaxine, 520-521, 1436
  - duloxetine, 1436
  - mirtazapine, 485
  - nefazodone, 1436
  - selegiline transdermal system, 1436
  - SSRIs, 1433-1435
    - citalopram, 439, 1434
    - escitalopram, 439-440, 1434
    - fluoxetine, 1433-1434
    - paroxetine, 393-395, 1435
    - sertraline, 361, 371, 1434-1435
  - TCAs, 318, 391
  - for treatment-resistant illness, 1436
  - venlafaxine, 520-521, 1435-1436
- complementary and alternative medicine approaches, 1165
  - omega-3 fatty acids, 1165
  - SAM-e, 1165
  - St. John's wort, 1165
- for depressive subtypes
  - anxious depression, 317, 341, 441-442, 483, 501, 591-592, 593 (*See also Anxiety, depression and*)
  - atypical depression, 286-288, 294, 317, 1159
  - bipolar depression, 85, 86, 317, 393, 495, 501, 518, 662, 689-691, 741, 771, 824, 825, 844, 846, 893-894, 927, 942, 1003, 1004-1006, 1020, 1088, 1096, 1181-1183(*See also Bipolar disorder treatment*)
  - melancholic depression, 288, 316-317
  - persistent depressive disorder, 288, 318, 483, 1109, 1159
  - postpartum depression, 363, 364, 406
  - poststroke depression, 1093
  - psychotic depression, 296, 317, 421, 633, 1159, 1162, 1166, 1530 (*See also Psychotic depression*)
- in elderly persons, 1509-1515
  - antipsychotic augmentation of antidepressants, 1515
  - bupropion, 392, 1515
  - duloxetine, 1514-1515
  - mirtazapine, 483, 1515
  - SSRIs, 1512-1514
    - citalopram, 1513-1514
    - escitalopram, 1513-1514

- fluoxetine, 392, 1512
- fluvoxamine, 420
- paroxetine, 391-392, 1513
- sertraline, 361, 364, 368-369, 1512-1513
- side effects and safety of, 1514
- TCAs, 313-314, 315, 318, 321, 322, 391, 392, 1507, 1510-1511
  - nortriptyline, 318, 392, 1510-1511
  - side effects and safety of, 1511
- trazodone, 457
- venlafaxine, 1514
- goals of, 1151, 1159
- lifestyle interventions, 1165, 1166
- maintenance therapy
  - bupropion, 499
  - citalopram, 436
  - ECT, 1127-1129
  - escitalopram, 437
  - fluoxetine, 341-342
  - nefazodone, 461
  - paroxetine, 391, 392-393
  - sertraline, 363-364
  - TCAs, 316
  - venlafaxine, 391, 518-519
- neuroimaging to guide selection of, 267
- in pain patients, 1412
- in pregnancy, 1544-1545
- psychotherapies, 1163-1165, 1166
  - cognitive-behavioral therapy, 1108, 1163-1165
  - interpersonal therapy, 1164-1165
  - mindfulness-based cognitive therapy, 1164
  - other types of, 1164
- qEEG to predict response to, 265
- in schizophrenia, 1260
- somatic therapies, 1162-1163
  - bright light therapy, 1163, 1166
  - deep brain stimulation, 1108, 1133, 1163
  - ECT, 1105-1129, 1162, 1163, 1166
    - compared with rTMS and VNS, 1130-1131
    - ketamine and, 553-554
  - transcranial direct current stimulation, 1131-1133
  - transcranial magnetic stimulation, 1129-1130, 1163
  - vagus nerve stimulation, 1130, 1162-1163

specific drugs for

- agomelatine, 469, 518
- bupropion, 495, 498–501
- buspirone, 591–592, 593
- carbamazepine, 953, **953**
- citalopram, 436, 446
- clozapine, 633
- cyclic antidepressants, 306, 316–318
- duloxetine, 534–535, **536–537**
- escitalopram, 436–437, 446, 1159
- fluoxetine, 341–342
- fluvoxamine, 421
- ketamine, 85, 267–268, 553–554, 1156, 1162
- lamotrigine, 1007
- levomilnacipran, 535, **539**
- lisdexamfetamine, 1088.1095
- lithium, 897–898
- MAOIs, 286–288
- milnacipran, 535, **538**
- mirtazapine, 481–483, 1159
- nefazodone, 461
- paroxetine, 390–395
- sertraline, 362–364, 368–370, 1159
- topiramate, 1020–1021
- trazodone, 456–457
- venlafaxine, 517–519, 1159
- vortioxetine, 468–469, **470–471**

for treatment-resistant depression (TRD), 1161–1162, 1166

- aripiprazole, 742–743
- BMS-820836, 69
- brexpiprazole, 745–746
- in children and adolescents, 1437
- deep brain stimulation, 1108
- ECT, 1162
- lamotrigine, 1007
- lithium, 898
- olanzapine–fluoxetine combination, 663
- paroxetine, 391
- quetiapine, 690
- risperidone, 716
- vortioxetine, 469
- ziprasidone, 772

- trials of
  - Combination Medication to Enhance Depression Outcomes (CO-MED), [482](#)
  - Genome-Based Therapeutic Drugs for Depression (GENDEP), [312](#), [438-439](#), [445](#)
  - International Study to Predict Optimized Treatment in Depression (iSPOT-D), [437-438](#)
  - STAR\*D, [63](#), [288](#), [312](#), [435](#), [436](#), [445](#), [482](#), [500](#), [591](#), [898](#), [1106](#)
- Desalkylflurazepam, [566](#), [1060](#)
- Designer drugs, [1610-1611](#)
- Desipramine
  - dosing of, [311](#), [315](#), [1632](#)
  - drug interactions with, [325-326](#)
    - bupropion, [497](#), [506](#)
    - carbamazepine, [965](#)
    - sertraline, [360](#)
  - immune system effects of, [195](#)
  - indications for
    - ADHD, [318-319](#)
    - bulimia nervosa, [1338](#), [1339](#)
      - cognitive-behavioral therapy and, [1340](#)
    - cocaine use disorder in schizophrenia, [1259](#)
    - depression, [306](#)
      - with anxious distress, [317](#)
    - persistent depressive disorder (dysthymia), [318](#)
    - OCD, [1212](#)
  - mechanism of action of, [73](#)
  - pharmacokinetics of, [311](#), [311-312](#), [313-314](#)
  - pharmacological profile of, [308](#), [310](#)
  - side effects of, [310](#)
    - anticholinergic effects, [321](#), [322](#)
    - cardiovascular effects, [321](#), [322](#)
      - sudden death in children, [319](#), [323](#)
    - hepatic effects, [323](#)
  - structure-activity relations for, [306](#), [307](#)
- Desmethyl-cariprazine (DCAR), [833](#), [835](#), [837-838](#), [839](#), [840](#)
- N*-Desmethyloclozapine (NDMC), [626](#), [630](#)
- Desmethyldiazepam, [566](#), [572](#), [576](#), [1059](#), [1060](#), [1061](#), [1065](#)
- Desmethylimipramine, [313](#), [1197](#)
- Desmethylmirtazapine, [480](#), [488](#)
- 4'-*N*-Desmethyloanzapine, [653](#), [673](#)
- N*-Desmethylselegiline, [297](#)
- Desmethylertraline, [360](#), [361](#)

O-Desmethylvenlafaxine (ODV), 515, 516, 523. *See also* Desvenlafaxine

Desoxyn. *See* Methamphetamine

Desvenlafaxine, 515–523

- discontinuation syndrome with, 522

- dosing of, 517

- history and discovery of, 515

- indications for

  - depression, 519

  - in children and adolescents, 520–521, 1436

  - vasomotor menopausal symptoms, 520

- mechanism of action of, 517

- overdose of, 522

- pharmacokinetics and disposition of, 516–517

- pharmacological profile of, 515–516

- side effects and toxicology of, 521–522

- structure–activity relations for, 515, 516

- use in pregnancy and lactation, 522, 1554

- use in renal disease, 516

Desyrel. *See* Trazodone

Dexamethasone, interaction with carbamazepine and oxcarbazepine, 963, 967

Dexamethasone/corticotropin-releasing hormone (CRH) test, 99, 160, 162, 193

Dexamethasone suppression test (DST)

- in depression, 99, 160–161, 162, 1156

- immune system and, 184, 193, 194

- effects of weight loss on, 168

- in PTSD, 163–164

- ECT response and, 1110

Dexedrine, Dexedrine Spansules. *See* Dextroamphetamine

Dexmedetomidine, 1123

Dexmethylphenidate, 226, 1084, 1085, 1088, 1452, 1503, 1655

Dextroamphetamine, 1085, 1087, 1453

- dosing in children and adolescents, 1503, 1654

- indications for

  - ADHD, 1085, 1087

  - cocaine dependence, 1093, 1301

  - fatigue, 1094

  - poststroke aphasia, 1092–1093

  - schizophrenia, 1096–1097

- interaction with MAOIs, 293

- structure–activity relations for, 1084–1085

Dextromethorphan



- combined with quinidine, for agitation in elderly patients, [1628](#)
- drug interactions with
  - MAOIs, [293](#)
  - paroxetine, [404](#), [405](#)
  - sertraline, [360](#)
- Dextrostat. *See* [Dextroamphetamine](#)
- DHEA (dehydroepiandrosterone), [934](#), [1045](#), [1054](#), [1165](#)
- DHNK (dehydroxynorketamine), [550](#)
- Diabetes insipidus, nephrogenic, lithium-induced, [903](#), [904](#), [962](#)
- Diabetes mellitus, [122](#)
  - antipsychotic-induced, [618](#), [1253](#)
    - clozapine, [626](#), [637-638](#), [1253](#)
    - in elderly patients, [1516](#)
    - lurasidone, [825](#)
    - olanzapine, [671-672](#), [696](#), [1253](#)
    - risperidone, [717](#)
    - screening for, [638](#)
  - chronic stress and, [181](#)
  - management in schizophrenia, [1253-1254](#)
  - topiramate for obesity in, [1019](#), [1028](#)
  - vascular cognitive impairment and, [1043](#)
- Diabetic ketoacidosis (DKA)
  - clozapine and, [638](#), [906](#)
  - in elderly patients, [1516](#)
  - olanzapine and, [672](#)
  - risperidone and, [672](#)
  - in schizophrenia, [1253](#)
- Diabetic neuropathy, [1379](#), [1400](#), [1401](#)
  - carbamazepine, [1393](#)
  - duloxetine for, [529](#), [534](#), [1391](#), [1399-1400](#), [1401](#)
  - fluoxetine for, [344](#)
  - fluvoxamine for, [424](#)
  - gabapentin for, [985](#), [990](#), [1392](#), [1401](#)
  - opioids for, [1384](#)
  - pregabalin for, [990](#), [991-992](#), [995](#), [1392](#), [1401](#)
  - trazodone for, [458](#)
- Diacylglycerol (DAG), [56-57](#), [63](#), [74-75](#), [78-79](#), [90](#)
- Dialectical behavior therapy (DBT)
  - for anorexia nervosa, [371](#)
  - for borderline personality disorder, [666](#)
- Dialysis patients
  - hypotension in, [370](#)

psychotropic drug use in

fluoxetine, [340](#)

fluvoxamine, [420](#)

lithium, [900](#)

sertraline, [362](#), [370](#)

Diaphoresis. *See* [Sweating](#)

Diarrhea

drug-induced

*N*-acetylcysteine, [1473](#)

carbamazepine, [958](#)

duloxetine, [540](#)

mirtazapine, [487](#)

selegiline transdermal system, [298](#)

SSRIs, [371](#), [443](#), [444](#), [1435](#), [1447](#), [1470](#)

topiramate, [1029](#), [1440](#), [1502](#)

valproate, [933](#)

in serotonin syndrome, [346](#)

Diazepam, [563](#), [572](#), [575](#)

dosing of, [1641](#)

drug interactions with

bupropion, [506](#)

fluvoxamine, [425](#)

endogenous, [1059](#)

GABA<sub>A</sub> receptor affinity of, [93](#), [95](#), [1054](#)

indications for

acute trauma exposure, [1604](#)

akathisia, [866](#)

alcohol withdrawal, [1285](#)

behavioral emergencies, [1608](#)

generalized anxiety disorder, [457](#), [1205](#)

vs. buspirone, [589](#)

vs. imipramine, [569](#), [1206](#)

insomnia, [1064](#)

restless legs syndrome, [866](#)

seizures, [1060](#)

intramuscular, [1608](#)

intravenous emulsion, [1060](#)

pharmacokinetics of, [216](#), [564](#), [566](#), [567](#), [572](#), [1060](#), [1061](#)

side effects of, [569](#)

structure of, [565](#), [1053](#)

sustained-release, [567](#)

use in pregnancy and lactation, [576–577](#), [1567](#)

Diazepam binding inhibitors, 1059

Dibenzazepines, 605, 624

Dibenzepines, 624

Dibenzodiazepines, 624

Dibenzothiazpines, 685

Dibenzoxazepines, 624. *See also* Loxapine

    side effects of, 615–616

    structure–activity relations for, 606, 607–608

Diclofenac, 1413

Dicumarol, interaction with carbamazepine, 967

Didesmethyl-cariprazine (DDCAR), 833, 835, 837–838, 839, 840

Diet

    for constipation, 639

    effect on valproate protein binding, 924

    food effects on drug absorption and bioavailability

        asenapine, 798, 806

        cariprazine, 837–838

        lurasidone, 822

        selegiline, 297

        sertraline, 361

        suvorexant, 1072

        ziprasidone, 759, 760–761

    MAOI interactions with, 283, 291–292, 292, 296–297

        selegiline transdermal system, 298

    restrictive, in bulimia nervosa, 1337–1338

    sodium-restricted, effect on serum lithium level, 907

Diethylpropion, 1254

Differential display technique, 16–17

Diffuse Lewy body disease (DLBD), 1528

Diffusion tensor imaging (DTI), 240, 252, 259, 262

DiGeorge syndrome, 125

Digit Symbol Substitution Task (DSST), 469

Digitoxin

    interaction with barbiturates, 1068

    pharmacokinetics in elderly persons, 1506

Digoxin, 227

    drug interactions with

        antipsychotics, 619

        nefazodone, 462

        paroxetine, 404, 405

    pharmacokinetics in elderly persons, 1506

Dihydropyridine, 70

Dihydroindoles. *See also* [Molindone](#)

side effects of, [615–616](#)

structure–activity relations for, [606](#), [608](#)

L-Dihydroxyphenylalanine (L-dopa), [65](#)

Diltiazem, [1507](#)

interaction with carbamazepine, [964](#), [966](#)

Dimenhydrinate, [861](#)

Diphenhydramine, [861–862](#)

acute intoxication with, [1606](#)

dosing of, [862](#), [1659–1660](#)

drug interactions with, [862](#)

in elderly persons, [862](#)

history and discovery of, [861](#)

indications for, [862](#)

extrapyramidal side effects, [857](#), [862](#), [870](#), [1607](#), [1614](#)

insomnia, [1068](#), [1368](#)

in adjustment disorders, [1602](#)

mechanism of action of, [862](#)

pharmacokinetics and disposition of, [861](#)

pharmacological profile of, [861](#)

side effects of, [862](#), [1368](#)

structure–activity relations for, [861](#)

use in pregnancy, [1566](#)

Diphenylbutylpiperidines. *See also* [Pimozide](#)

side effects of, [615–616](#)

structure–activity relations for, [606](#), [608](#)

Diplopia. *See* [Visual disturbances](#)

Disability

chronic pain and, [1377](#), [1378](#), [1382](#), [1395](#), [1412](#), [1417](#)

low back pain, [1405](#), [1406](#), [1407](#)

neuropathic pain, [1400](#)

osteoarthritis, [1407](#)

depression and, [1151](#), [1154–1155](#), [1260](#), [1378](#)

generalized anxiety disorder and, [1206](#), [1209](#)

with inability to care for self, [1596](#), [1601](#)

OCD and, [1210](#)

PTSD and, [1213](#), [1214](#)

schizophrenia and, [1245](#), [1246](#), [1260](#)

social anxiety disorder and, [1199](#), [1330](#)

specific phobia and, [1203](#)

*DISC1* and *DISC2* genes, [125](#), [130–131](#), [1158](#)

Discontinuation of drug. *See also* [Withdrawal from substance](#)

- barbiturates, 1067
- benzodiazepines, 1065, 1196, 1198, 1205
  - pregabalin for, 995
  - rebound anxiety after, 570, 1057, 1062, 1205
  - rebound insomnia after, 570, 1057, 1062, **1063**
- clonidine, 1500
- guanfacine, 1500, 1501
- methylphenidate, 1089
- selegiline, 297
- SSRIs, 340, 348–349, 372–373, 401, 420, 444–445, 1196, **1608**, 1615
- tranylcypromine, 295
- venlafaxine, 522, 1208, 1615
- vortioxetine, 472
- Disorientation, drug-induced
  - anticholinergic agents, 859
  - benzodiazepines, 1065
  - MAOIs, 290
- Disrupted in schizophrenia genes (*DISC1* and *DISC2*), 125, 130–131, 1158
- Disruptive mood dysregulation syndrome, 1459
- Dissociation, 1604–1605
  - in borderline personality disorder, 1315
  - ketamine-induced, 551, 555
- Distribution of drug, 216–218. *See also* Pharmacokinetics
  - in elderly persons, 1506
  - significance of drug transporters in, 211–212
- Disulfiram
  - for alcohol use disorder, 1286, **1660**
  - in schizophrenia, 1259
  - for cocaine dependence, 1302
- Diuretics
  - interaction with lithium, 900, 906
  - use in bulimia nervosa, 1338
- Divalproex. *See* Valproate
- Dizocilpine (MK-801), 86, 710, 711, 826
- Dizziness
  - drug-induced
    - amitriptyline, **1368**
    - aripiprazole, 746, 747
    - asenapine, 804, 1439
    - benzodiazepines, 1065
    - bupropion, 504
    - buspirone, 593

carbamazepine, 944  
classic antipsychotics, 612, **719**, **816**  
clomipramine, 1448, 1449  
clonidine, 1500  
diphenhydramine, **1368**  
doxylamine, **1368**  
duloxetine, 540, 1443  
eslicarbazepine acetate, 960  
gabapentin, 987, 989, 1401, 1404  
guanfacine, 1501  
iloperidone, 809, 816, **816**, 817  
lamotrigine, 1011  
lithium, 1439  
MAOIs, 290, 297  
mirtazapine, 1498  
nefazodone, 462, 1436  
opioids, 1385  
oxcarbazepine, 1440, 1502  
paroxetine, 392, 398, 1435  
prazosin, **1368**  
pregabalin, 992, 995, 1393, 1401, 1404  
quetiapine, **693**, 694, 1180, 1440, 1463  
risperidone, **693**, 718, **719**, **816**, 1463  
topiramate, 1028, 1029  
trazodone, 457, **1369**  
venlafaxine, 1498  
ziprasidone, 774, 1180, 1440  
zolpidem, **1365**  
after SSRI discontinuation, 1615  
DKA. See [Diabetic ketoacidosis](#)  
DLBD (diffuse Lewy body disease), 1528  
DM-3411, 737  
DMN (default mode network), 259–260  
DNA. See [Deoxyribonucleic acid](#)  
Dofetilide, 233  
Donepezil, 1040–1041  
for Alzheimer's disease, 1040–1041  
antipsychotics and, 1521  
combined with memantine, 1043  
combined with risperidone in schizophrenia, 1529  
depression relapse in older adults and, 309  
dosing of, 1040, **1658**

- formulations of, 1040
- in mild neurocognitive disorder, 1041
- for vascular cognitive impairment, 1044
- Dopamine (DA), 65–68, **66–67**
  - brain distribution of, 65, **66**, 834
  - in brain reward circuits, 65, **66**
  - conversion to norepinephrine, 72
  - cytokine effects on, 192
  - drug effects on
    - amphetamine, 1086
    - bupropion, 495, 496
    - buspirone, 587
    - carbamazepine, 948
    - fluoxetine, 339, 346
    - γ-hydroxybutyrate, 1069
    - methylphenidate, 1088
    - moclobemide, 295
    - olanzapine, 651–652
    - oxcarbazepine, 949
    - risperidone, 711
    - selective 5-HT<sub>2</sub> receptor antagonists, 711
    - sertraline, 359, 362
  - in elderly persons, 1508, 1517–1518
  - inhibition of prolactin release by, 608
  - PET studies of, 69, 129, 245, **246**
  - in specific disorders
    - borderline personality disorder, 1315–1316
    - cocaine dependence, 68–69, 70, 71, 1302
    - Parkinson's disease, 65, 245
    - schizophrenia, 84, 266, 610–611, 710, 732
    - Tourette syndrome, 612
  - synthesis of, 65
- Dopamine β-hydroxylase, 72
- Dopamine receptors, 70–72
  - in Alzheimer's disease with psychosis, 1520
- D<sub>1</sub>, 70
- D<sub>2</sub>, 51, 70–71
  - antipsychotic blockade of, 71, 213, 266–267, 607–609, 610, 612, **613**, 655, 732, **733**, 834, 869, 1241, 1242, 1262, 1518
  - autoreceptors, **67**, 71
  - modulation of ECT response by, 1110
  - in mouse model of Huntington's disease, 29

- in schizophrenia, 71
- D<sub>3</sub>, 70, 71
- D<sub>4</sub>, 70, 71–72
- D<sub>5</sub>, 70
  - in depression, 69
  - drug affinity for
    - antipsychotics, 71, 213, 266–267, 607–609, 610, 612, **613**, 614, 732, 1241, 1242, 1262, 1518
    - aripiprazole, 731, 732, 734, **735**, 737, 831, 833, **834**
    - asenapine, 797–798
    - brexpiprazole, 731, 732, 734, **735**, 737, 831, 833, **834**
    - cariprazine, 831, 833–836, **834**, 851
    - clozapine, 624, 628–630
    - iloperidone, 809–810
    - lurasidone, 821
    - olanzapine, 651, 652, 1522
    - quetiapine, 685–686, 1523
    - risperidone, 705–707, **708**, 710–712, 1521
    - ziprasidone, 756, 775, 783
  - buspirone, 587, 588, 589
  - cocaine, 71
  - cyclic antidepressants, 306–307, **308**
  - methylphenidate, 71
  - pergolide, 1329
  - SSRIs, 339, 359
- in elderly persons, 1518
- kissing cousin receptors, 70
- PET and SPECT studies of, 245, **246**, 266
- subtypes of, 70
- TaqIA polymorphism of, 70
  - transgenic mouse studies of, 71
- Dopamine transporter (DAT), **66**, 68–70
  - drug effects on
    - amphetamines, 68, 1086
    - BMS-820836, 69
    - bupropion, 69–70, 496, 498
    - cocaine, 68–69
    - methylphenidate, 1088
  - PET studies of, 245
  - in specific disorders
    - bipolar disorder, 69
    - depression, 69



- Parkinson's disease, 69
- SPECT studies of, 69, 129
- structure of, 58
- Doral. *See* Quazepam
- Dosage regimen, 209–210, 221–222
- Dose–effect relationship, 210–211, **211**
  - pharmacodynamics and, 210–211, **211**, **222**, 222–223
  - pharmacokinetics and, 210–211, **211**, 230
  - sources of variability in, 225–233
    - active metabolites, 225–226
    - drug interactions, 230–233, **232**
    - pharmacogenomics, 226–230, **229**, **231**
    - stereochemistry, 226
- Down syndrome, 125
- Doxacurium, interaction with carbamazepine and oxcarbazepine, **963**, 967
- Doxepin
  - dosing of, **311**, 1356, **1633**
    - for insomnia, 1356, 1357, 1358
  - indications for, 1356
    - depression, 306, 1356
      - with anxious distress, 317
    - vs. paroxetine, 390
  - insomnia, 320, 1070, 1351–1352, 1356–1358, 1362, **1367**, **1369**
  - pruritus, 320
  - interaction with carbamazepine, 965
  - pharmacokinetics of, **311**
  - pharmacological profile of, **308**, 309, 310, 1356–1357
  - side effects of, 320, 322, **1367**, **1369**
  - sleep-promoting effect of, 1351–1352
  - structure–activity relations for, 306, **307**
  - use during lactation, 1555
- Doxorubicin, interaction with carbamazepine, 967
- Doxycycline, interaction with carbamazepine and oxcarbazepine, **963**, 967
- Doxylamine, **1368**
- DRD2* gene, 1288
- Dreams, vivid. *See also* Nightmares
  - after SSRI discontinuation, 1615
  - suvorexant-induced, 1359, **1367**
- DRESS syndrome. *See* Drug rash with eosinophilia and systemic symptoms
- Driving safety
  - barbiturates and, 1068
  - benzodiazepines and, 577

- opioids and, [1386](#)
  - suvorexant and, [1072](#)
  - trazodone and, [459](#)
- Dronabinol, [1394](#)
- Droperidol, [606](#)
- Drowsiness, drug-induced. *See also* [Somnolence](#)
  - antipsychotics, [612](#)
  - benzodiazepines, [567](#), [570](#)
  - buspirone, [593](#), [1474](#)
  - citalopram, [1451](#)
  - gabapentin, [989](#)
  - guanfacine, [1472](#)
  - hypnotics, [1051](#)
  - lamotrigine, [1011](#)
  - opioids, [1385](#)
  - sertraline, [1444](#)
- Drug interactions, [230–234](#). *See also specific drugs*
  - cytochrome P450 enzyme-mediated, [231–233](#), [1506–1507](#)
  - effects on plasma drug concentration, [231](#), [232](#)
  - with grapefruit juice, [215](#)
  - in vitro methods for prediction of, [233](#)
  - P-glycoprotein in, [227](#)
  - pharmacodynamic, [230](#)
  - pharmacokinetic, [230–231](#)
  - plasma protein-binding displacement interactions, [217–218](#)
- Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)
  - carbamazepine and, [958](#)
  - lamotrigine and, [1008](#)
  - ziprasidone and, [775](#)
- Drugs
  - absorption of, [212–214](#), [214](#)
  - bioavailability of, [214](#), [214–215](#), [219](#)
  - in children and adolescents, [1431–1475](#)
  - clearance of, [218–219](#), [225](#), [227](#)
  - coadministration of, [230](#)
  - development of, [209](#)
  - distribution of, [216–218](#), [217](#), [218](#)
  - dosing of, [209–210](#), [221–222](#)
  - duration of therapy with, [209](#)
  - in elderly persons, [1505–1531](#)
  - elimination half-life of, [213](#), [214](#), [219](#)
  - elimination of, [218–219](#)

formulations of, 213-214, **214**  
metabolism of, 214-216  
metabolites of, 225-226  
minimal effective concentration of, 213, **214**, 216, 217, **217**, 220, **221**  
multiple dosing to steady state, 219-221, **221**  
plasma concentration of, 209-210  
in pregnancy and lactation, 1543-1570  
presystemic elimination of, 214-216  
protein binding of, 217-218, **218**  
racemic mixtures of, 226  
renal excretion of, 217, 218, 225, 227  
routes of administration of, 212, 213, **214**, 215  
stereochemistry of, 226  
transporters for, 211-212, 227-228

Dry mouth, drug-induced

- antipsychotics, 1516
- buspirone, 593
- classic antipsychotics, 612, 618, **816**
- clomipramine, 1448, 1449
- clonidine, 1500
- clozapine, 639, 1521
- desvenlafaxine, 521
- diphenhydramine, 862, **1368**
- doxylamine, **1368**
- duloxetine, 540
- gabapentin, 987, 989
- iloperidone, 816, **816**
- lamotrigine, 1182
- MAOIs, 290
- mirtazapine, 487, **1369**, 1498
- muscarinic receptor antagonists, 80
- nefazodone, 462
- olanzapine, 1179
- opioids, 1385
- prazosin, **1368**
- pregabalin, 995
- quetiapine, 688, **693**, 1180, 1316
- risperidone, **693**, 722, **816**
- SSRIs, 345, 371, 386, 398, 443, 1435, 1444, 1497
- suvorexant, 1359, **1367**
- TCAs, 321, **1368**, **1369**
- topiramate, 1029

- trazodone, [1369](#)
- trihexyphenidyl, [858-859](#)
- venlafaxine, [521](#), [1498](#)
- Dry skin, citalopram-induced, [1470](#)
- DSM-5, [144](#)
- DSST (Digit Symbol Substitution Task), [469](#)
- DST. *See* [Dexamethasone suppression test](#)
- DTS (Davidson Trauma Scale), [1213](#)
- DTs (delirium tremens), [1285](#), [1607](#), [1612-1613](#)
- Duloxetine
  - in children and adolescents, [1436](#), [1443](#), [1446](#), [1498](#), [1498](#)
  - dosing of, [529](#), [532](#), [533](#), [535](#), [540](#), [542](#), [1637](#)
    - in children and adolescents, [1498](#)
  - drug interactions with, [542](#)
    - vortioxetine, [473](#)
  - in elderly persons, [1514-1515](#)
  - history and discovery of, [529](#)
  - indications for, [534](#)
    - borderline personality disorder, [1320](#), [1322](#)
    - depression, [534-535](#), [543](#)
      - in children and adolescents, [1436](#)
      - vs. SSRIs, [391](#), [535-536](#), [536](#)
      - vs. vortioxetine, [469](#), [470-471](#), [537](#)
  - generalized anxiety disorder, [1208](#)
    - in children and adolescents, [1443](#)
  - pain syndromes, [344](#), [535](#), [539](#), [1391](#), [1399](#), [1414](#)
    - fibromyalgia, [539](#), [1391](#), [1403](#), [1403-1404](#)
    - low back pain, [1406](#)
    - neuropathic pain, [1401](#)
    - osteoarthritis, [1391](#), [1408](#)
  - stress urinary incontinence, [539-540](#)
- overdose of, [543](#)
- pharmacokinetics and disposition of, [533](#), [534](#)
- pharmacological profile of, [530-533](#), [531](#)
- side effects and toxicology of, [540-541](#), [1404](#), [1436](#), [1443](#), [1498](#)
- structure-activity relations for, [529](#), [530](#)
- use in pregnancy and lactation, [541](#), [1553](#), [1554](#)

- Duty to warn potential victims of harm, [1600-1601](#)
- Dynorphins, [99](#), [100](#), [101](#)
- Dyskinesias, drug-induced. *See also* [Tardive dyskinesia](#)
- aripiprazole, [746](#)
- sertraline, [372](#)

## Dyslipidemia

### drug-induced

- antipsychotics, 618, **695**, 1254, 1499
  - aripiprazole, 696, 747
  - asenapine, 805
  - clozapine, 638, 1254
  - iloperidone, 818
  - lurasidone, 825
  - monitoring for, 1499
  - olanzapine, 669, 670, **695**, 747, 931, 1254, 1462
  - quetiapine, **695**, 696, 1254
  - risperidone, **695**, 696, 718, 931, 1458
  - ziprasidone, **695**, 696, 779–780
- β-blockers, 864
- vascular cognitive impairment and, 1043, 1044

## Dyspepsia, drug-induced

- aripiprazole, 746
- cariprazine, **848**, 1180
- haloperidol, **719**, **816**
- iloperidone, 816, **816**
- paroxetine, 1435
- quetiapine, **693**
- risperidone, **693**, 718, **719**, **816**, 1180, 1458
- sertraline, 1447
- topiramate, 1029
- valproate, 933

## Dysthymia. *See* Persistent depressive disorder (dysthymia)

## Dystonic reactions, acute (ADRs), 855. *See also* Tardive dystonia

- antipsychotic-induced, 1255, 1256
  - classic antipsychotics, 609, 614, **615**, **816**, 1458, 1469
  - iloperidone, **816**
  - oculogyric crisis, 614, 1256, 1614
  - onset of, 855
  - quetiapine, **693**
  - risperidone, **693**, 719, **816**
- cervical dystonia, 868, 875
- laryngeal dystonia, 614, 868, 872, 875, 1256
- in neuroleptic malignant syndrome, 1257
- prophylaxis for, 876
- risk factors for, 876, **877**
- sertraline-induced, 372
- vs. tardive dystonia, 856

- treatment of, [614](#), [856–864](#), [857](#), [870](#), [1256](#), [1607](#), [1614](#)
  - amantadine, [862–864](#)
  - benzodiazepines, [866–867](#)
  - benztropine, [860–861](#), [1614](#)
  - biperiden, [861](#)
  - botulinum toxin, [867–868](#), [875](#)
  - diphenhydramine, [861–862](#), [1614](#)
  - procyclidine, [861](#)
  - trihexyphenidyl, [856–860](#)
- E-cigarettes, [1299](#)
- EAATs (excitatory amino acid transporters), [84](#)
- Early life stress, [157](#). *See also* [Childhood abuse/trauma](#)
  - depression and
    - HPA axis effects, [159](#), [162](#), [389](#), [1153](#)
    - immune system effects, [183](#)
  - psychophysical disorders and, [185](#)
- Eating Attitudes Test, [666](#)
- Eating disorders, [1337–1346](#)
  - anorexia nervosa, [1337](#), [1344–1345](#)
  - binge-eating disorder, [1337](#), [1342–1344](#)
  - bulimia nervosa, [1337–1342](#)
  - bupropion contraindicated in, [1297](#), [1339](#)
  - depression and, [1337](#)
  - gender distribution of, [1337](#), [1342](#)
  - prevalence of, [1337](#)
  - treatment of
    - fluoxetine, [342–343](#)
    - fluvoxamine, [423–424](#)
    - sertraline, [371](#)
    - topiramate, [1017](#), [1022–1023](#)
- Ebstein's anomaly, lithium-induced, [901](#), [1555](#)
- Echolalia, [1605](#)
- Echopraxia, [1605](#)
- Ecstasy. *See* [3,4-Methylenedioxy-N- methamphetamine](#)
- ECT. *See* [Electroconvulsive therapy](#)
- Edema, drug-induced
  - MAOIs, [290](#)
  - pregabalin, [995](#), [1393](#)
- EEG. *See* [Electroencephalography](#)
- Efavirenz, interaction with bupropion, [506](#)

Efficacy of Monotherapy Seroquel in BipOLar DEpression (EMBOLDEN I and II) studies, [689](#), [694](#)

Ejaculatory dysfunction. *See also* [Sexual dysfunction](#)

drug-induced

citalopram, [443](#)

classic antipsychotics, [619](#)

duloxetine, [540](#)

escitalopram, [444](#)

MAOIs, [290](#)

paroxetine, [398](#)

risperidone, [720](#)

sertraline, [371](#)

treatment of premature ejaculation fluoxetine, [344](#)

paroxetine, [344](#), [399](#)

sertraline, [370](#)

Ekbom syndrome. *See* [Restless legs syndrome](#)

Elderly persons, [1505–1531](#)

abuse of, [1596](#), [1601](#)

dementia in, [1515–1516](#)

depression in, [318](#), [1152](#), [1508–1509](#)

diabetic ketoacidosis in, [1516](#)

dopamine in, [1508](#), [1517–1518](#)

dose-effect relationship in, [210](#)

drug interactions in, [1517](#)

drug use in

alcohol-type hypnotics, [1068–1069](#)

amantadine, [862](#)

amphetamine, [1095](#)

anticholinergic drugs, [859](#), [1508](#), [1525–1526](#)

antidepressants, [1508–1515](#), [1509–1515](#), [1627–1628](#)

antipsychotic augmentation of, [1515](#)

bupropion, [392](#), [498](#), [500](#), [1508](#), [1515](#)

citalopram, [436](#), [1513–1514](#), [1521](#), [1525](#), [1628](#)

duloxetine, [1514–1515](#)

escitalopram, [1513–1514](#)

fluoxetine, [392](#), [1512](#)

fluvoxamine, [420](#)

mirtazapine, [483](#), [487](#), [488](#), [1506](#), [1515](#)

paroxetine, [391–392](#), [500](#), [1508](#), [1513](#)

sertraline, [361](#), [364](#), [368–369](#), [1512–1513](#)

TCAs, [313–314](#), [315](#), [318](#), [321](#), [322](#), [391](#), [392](#), [1507](#), [1510–1511](#)

trazodone, [457](#), [1626](#)

- venlafaxine, 1508, 1514
- vortioxetine, 469
- antipsychotics, 1515-1531, 1624, 1625, 1626
  - aripiprazole, 744, 1523
  - for behavioral complications of dementia, 1517, 1518-1528, 1624-1626
  - cariprazine, 840, 848
  - classic antipsychotics, 610, 663, 1516, 1520-1521
  - clozapine, 1507-1508, 1516, 1521, 1525, 1528
  - for delirium, 1528
  - for delusional disorder, 1530
  - for diffuse Lewy body disease, 1528
  - iloperidone, 810, 818
  - lurasidone, 825
  - for mania, 1530-1531
  - monitoring blood levels of, 1527
  - for OCD, 1531
  - olanzapine, 654, 660, 1516, 1522-1523, 1524, 1525, 1528, 1530
  - for Parkinson's disease dementia, 1528
  - pharmacodynamics of, 1517-1518
  - pharmacokinetics of, 1517
  - for psychotic depression, 1530
  - quetiapine, 687, 692, 1523, 1524, 1525, 1529-1530
  - risperidone, 715, 717, 1515, 1521-1522, 1521-1524, 1525, 1526, 1529, 1530
  - safety and side effects of, 663
  - for schizophrenia, 1528-1530
  - side effects of, 1515-1516, 1516-1517
  - stroke/mortality risk in dementia patients, 424, 663, 717, 774, 818, 825, 848, **1370**, 1517, 1520, 1612, 1625-1626
  - tardive dyskinesia and, 617, 663, 1257, 1516, 1518, 1626
  - use of concomitant psychotropics with, 1525-1526
  - ziprasidone, 772-773
- benzodiazepines, 564, 567, 572, 577, 1075-1076, 1196, 1285, 1520, 1524, 1526, 1627
- buspirone, 590, 593, 1524
- dextromethorphan-quinidine combination, 1628
- diphenhydramine, 862
- lithium, 900-901, 903, 1506, 1507, 1530
- melatonin, 1070, 1071, 1076
- mood stabilizers
  - carbamazepine, 1524, 1612, 1627
  - lithium, 900-901, 903, 1506, 1507



- valproate, 930–931, 934, 1075–1076, 1524, 1612, 1627
- sedative-hypnotics, 1075–1076
- tramadol, 1384
- ECT in, 1110, 1124, 1530
- exclusion from clinical trials, 1506
- generalized anxiety disorder in, 1204
- insomnia in, 1070, 1071, 1075–1076
- osteoarthritis in, 1407
- pharmacodynamics in, 1508, 1517–1518
- pharmacokinetics in, 313–314, 1505–1508, **1507**, 1517
  - CYP enzymes and, 1505, 1506–1507
  - physiological changes associated with, **1507**
  - TCAs, 313–314
- schizophrenia in, 1515, 1528–1530
- SIADH in, 1508
- suicide among, 1509, 1598
- suicide in, 1509
- treatment of agitation and aggression in, 1515, 1612, 1623–1628, 1624, 1625, 1628
  - anticonvulsants, 930–931, 1627
  - antipsychotics, 1518, 1521, 1522, 1523, 1525, 1526, 1623–1626, 1624–1626, 1625, 1626
  - ziprasidone, 772–773
- benzodiazepines, 1524, 1526, 1627
- citalopram, 1525, 1628
- dextromethorphan–quinidine combination, 1628
- ECT, 1112
- memantine combined with acetylcholinesterase inhibitor, 1043
- new approaches, 1628
- SSRI combined with cognitive enhancer, 1627–1628
- trazodone, 1626–1627
- valproate, 930–931
- ziprasidone, 772–773

Electrocardiogram (ECG) effects of drugs

- asenapine, 804
- carbamazepine, 958
- citalopram, 370, 431, 444, 446
- classic antipsychotics, 607, 612, **615**, 618, 780–781
- clonidine, 1500
- dofetilide, 233
- escitalopram, 446
- eslicarbazepine acetate, 960

- fluvoxamine, [425](#)
- iloperidone, [815](#), [818](#)
- lithium, [905](#)
- lurasidone, [825](#)
- methadone, [1289–1290](#), [1292](#), [1390](#)
- nefazodone, [462](#)
- olanzapine, [672](#)
- paroxetine, [401](#)
- pimozide, [608](#)
- quetiapine, [721](#)
- risperidone, [721](#), [722](#)
- sertraline, [369](#), [370](#)
- sotalol, [233](#)
- TCAs, [323](#), [370](#)
- venlafaxine, [522](#)
- vortioxetine, [473](#)
- ziprasidone, [755](#), [781–782](#)
- Electroconvulsive therapy (ECT), [260](#), [268](#), [1105–1129](#), [1107](#), [1134](#)
  - administration of, [1122–1123](#)
  - anesthesia for, [1106](#), [1114](#), [1121](#), [1122–1124](#), [1125](#), [1126](#), [1127](#)
  - deep brain stimulation and, [1133](#)
  - effects on GABA concentration, [1106–1107](#)
    - MRS studies of, [260](#), [1107](#)
  - effects on HPA axis, [1107](#)
  - in elderly persons, [1110](#), [1124](#), [1530](#)
  - history of, [1105–1106](#)
  - indications for, [1109–1113](#)
    - behavioral symptoms of dementia, [1112](#)
    - bipolar disorder
      - in children and adolescents, [1443](#)
      - depressive episodes, [1183](#)
      - maintenance treatment, [1186](#)
      - mania, [1110–1111](#), [1180–1181](#)
      - OCD, [1112](#)
      - pain syndromes, [1113](#)
      - Parkinson's disease, [1112–1113](#)
      - psychosis and depression in Huntington's disease, [1112](#)
      - PTSD, [1112](#), [1217–1218](#)
      - schizophrenia, [1111–1112](#)
      - status epilepticus, [1112](#)
    - catatonia, [1111](#), [1112](#), [1605](#)
    - clozapine augmentation, [634](#)

- depression, [1109–1110](#), [1162](#), [1163](#), [1166](#)
  - compared with rTMS, [1130–1131](#)
  - compared with vagus nerve stimulation, [1131](#)
  - with dysthymia, [1109](#)
  - ketamine and, [553–554](#)
  - predictors of response to, [1109–1110](#)
  - prophylactic treatment after acute response to ECT, [1127–1129](#)
  - with psychotic features, [1162](#), [1530](#)
  - relapse after ECT course, [1162](#)
  - in schizophrenia, [1260](#)
  - stimulus dosing for, [1113–1121](#)
  - treatment-resistant illness, [1162](#)
- depression and psychosis in autoimmune disorders, [1113](#)
- neuroleptic malignant syndrome, [1111](#), [1607](#), [1614](#)
- suicidality in schizophrenia, [1261](#)
- ketamine in, [553–554](#)
- lithium discontinuation for, [903](#), [1181](#)
- mechanism of action of, [1106–1108](#), [1162](#)
  - anticonvulsant hypothesis, [1106–1107](#)
  - antidepressants and ECT effects on mood disorders, [1107–1108](#)
- neurotrophic effects of, [1108](#)
- pretreatment medical evaluation for, [1121–1122](#)
- safety of, [1106](#)
- side effects of, [1123–1127](#)
  - cardiovascular effects, [1124–1125](#)
  - cognitive effects, [1115–1116](#), [1117](#), [1125–1127](#), [1162](#)
  - effect on cerebral physiology, [1127](#)
  - interictal delirium, [1124](#)
  - postictal agitation, [1123–1124](#)
  - studies to determine brain damage, [1127](#)
- stimulus dosing for treatment of depression, [1113–1121](#)
  - convulsive, subconvulsive, and sham stimulation, [1114](#)
  - electrode placement and, [1119](#)
    - alternatives to estimating convulsive threshold, [1120–1121](#)
    - choosing electrode placement and stimulus dose, [1121](#)
    - estimating convulsive threshold, [1119–1120](#)
  - magnitude of stimulus dose, [1116–1118](#)
  - seizure morphology, [1118–1119](#)
  - stimulus waveform, [1114–1116](#)
- trends in use of, [1106](#)
- upregulation of 5-HT<sub>2</sub> receptors by, [63](#)
- use in pregnancy, [1111](#), [1113](#)

Electroencephalography (EEG), 240, 263–265, 269  
    barbiturate effects on, 1067  
    combined with fMRI, 265  
    combined with PET, 265  
    in depression, 265  
    after ECT, 1107, 1127  
    neuropsychiatric applications of, 264–265  
    quantitative, 265  
    in schizophrenia, 264–265  
    technical aspects of, 263–264  
Electroshock therapy, 1106  
Elimination half-life of drug, 219  
    dosage regimen and, 220–221  
    drug formulation and, 213, 214  
    for specific drugs  
        alcohol-type hypnotics, 1069  
        amantadine, 862  
        amphetamine, 1086  
        aripiprazole, 221, 736  
        asenapine, 798  
        atomoxetine, 1453  
        benzodiazepines, 216, **566**, 567, 569–570, 572, 1060, 1064, **1064**, **1364**  
        brexpiprazole, 737  
        bupropion, 497  
        buspirone, 588  
        carbamazepine, 944  
        cariprazine, 838, 840–841  
        classic antipsychotics, 610  
        clozapine, 627  
        cyclic antidepressants, 310, **311**, 312, 313  
        desvenlafaxine, 516  
        diphenhydramine, 861  
        donepezil, 1040  
        duloxetine, 533  
        eszopiclone, **1064**  
        fluoxetine, 340, 348  
        fluphenazine decanoate, 610  
        fluvoxamine, 420  
        gabapentin, 984  
        galantamine, 1041  
        haloperidol decanoate, 610  
        iloperidone, 810

ketamine, [550](#)  
lamotrigine, [1002](#)  
levomilnacipran, [533–534](#)  
licarbazepine, [947](#)  
melatonin, [1070](#)  
methylphenidate, [1088](#)  
milnacipran, [533–534](#)  
mirtazapine, [480](#)  
modafinil, [1089](#)  
nefazodone, [460](#)  
olanzapine, [653–654](#), [1522](#)  
paliperidone, [710](#)  
paroxetine, [348](#)  
physostigmine, [1042](#)  
pregabalin, [991](#)  
quetiapine, [1523](#)  
risperidone, [709–710](#), [1521](#)  
rivastigmine, [1041](#)  
selegiline, [297](#)  
sertraline, [361](#)  
topiramate, [1019](#)  
trazodone, [456](#)  
trihexyphenidyl, [858](#)  
venlafaxine, [516](#)  
vortioxetine, [468](#)  
zaleplon, **[1064](#)**  
ziprasidone, [760](#)  
zolpidem, [1057](#), **[1064](#)**  
zopiclone, [1057](#), **[1064](#)**  
steady-state concentration and, [220](#)  
*ELP3* gene, [446](#)  
EMBOLDEN I and II (Efficacy of Monotherapy Seroquel in BipOLar DEpression) studies, [689](#), [694](#)  
Emergency situations. *See* [Psychiatric emergencies](#)  
Enantiomers, [226](#)  
Encephalopathy  
  hepatic, [1059](#)  
  hyperammonemic, valproate-induced, [1179](#)  
  lithium-induced, [903](#)  
  Wernicke, [1613](#)  
ENCyclopedia Of DNA Elements (ENCODE) project, [136](#), [144](#)  
Endocannabinoid system, in borderline personality disorder, [1326](#)

Endorphins, 99, **100**  
Endozepines, 1059  
Enkephalins, 76, 99, **100**  
Enuresis in children  
    drug-induced  
        lithium, 1472  
        risperidone, 1467  
    TCAs for, 319–320  
Environment–gene interaction studies, **118**, 121, 122, 123, 143–144, 145  
Ephedrine, for drug-induced sexual dysfunction, 399  
Epidemiologic Catchment Area study, 1259  
Epidemiology, genetic, 117–124. *See also* Genetics  
Epigenetics, 4, 8, 9, 119–120  
    definition of, 119  
    depression and, 1153, 1158  
        antidepressant effects, 1158  
    disorders of, 122  
    of oxytocin and vasopressin receptor binding, 99  
    response to childhood trauma and, 144  
    of response to drug treatment, 124  
Epilepsy. *See* Seizures  
Epinephrine, 65, 179  
Epoxide hydrolase, 944, **945**, 962, 963, 968  
EPS. *See* Extrapyrmidal side effects  
Epworth Sleepiness Scale, 1096  
Equetro. *See* Carbamazepine  
Erectile dysfunction, drug-induced. *See also* Sexual dysfunction  
    antipsychotics, 609, 618–619, 718  
    duloxetine, 540  
    opioids, 1385  
    trazodone, 458  
ERK (extracellular signal-regulated kinase), **11**, **49**, **82–83**, 101, 926  
Erythrohydrobupropion, 498  
Erythromycin–drug interactions  
    antipsychotics, 620  
    carbamazepine, **964**, 967, 969, 970  
    quetiapine, 686  
Escitalopram, 431–446  
    in children and adolescents, 439–440, 1434, 1444, 1470, **1498**  
    discontinuation syndrome with, 444–445  
    dosing of, 436, **1634**  
        in children and adolescents, **1498**

- drug interactions with, 446
  - carbamazepine, 965
  - esomeprazole, 373
- in elderly persons, 1513–1514
- generic, 431
- history and discovery of, 431–432
- indications for, 436–442, 446
  - autism spectrum disorder, 1470
  - depression, 436–439, 446
    - with anxiety, 442
  - in asthmatic patients, 437
  - with bupropion, 482
  - bupropion and, 499, 500
  - in children and adolescents, 439–440, 1434
  - vs. duloxetine, 536, 537
  - GENDEP study, 438–439
  - iSPOT-D trial, 437–438
  - lisdexamfetamine and, 1088
  - maintenance treatment, 437
  - neuroimaging to predict treatment outcome, 267, 438
  - vs. paroxetine, 390
- generalized anxiety disorder, 440, 446, 1206–1207
- OCD, 442
  - maintenance treatment/relapse prevention, 1211
- panic disorder, 441, 1195
- social anxiety disorder, 441
  - in children and adolescents, 1444
- specific phobia, 1204
- investigational use for stress-induced myocardial ischemia, 442–443
- mechanism of action of, 434–436
- pharmacokinetics and disposition of, 434
- pharmacological profile of, 226, 433
- side effects and toxicology of, 443–444, 1434
- structure–activity relations for, 337, 432, 433, 1084
- suicidality and, 445–446
- switching to vortioxetine from, 474

Eslicarbazepine acetate (ESL), 941–942

- for bipolar disorder, 969
  - maintenance treatment, 955
  - mania, 950, 951–952
  - seizures, 943, 949, 960
- dosing of, 947–948

- drug interactions with, 968–969
- formulations of, 947
- history and discovery of, 942–943
- mechanism of action of, 949
- pharmacokinetics of, 947, 948
- pharmacological profile of, 943
- side effects and toxicology of, 960
- structure–activity relations for, 943
- suicidality and, 958, 960
- switching from oxcarbazepine to, 947–948
- use in hepatic disease, 947
- use in pregnancy and lactation, 960

Esmolol, for ECT, 1124, 1125

Esomeprazole, 373

ESRS (Extrapyramidal Symptom Rating Scale), 719, 802, 817

Estazolam

- dosing of, 1642
- in elderly patients, 1076
- for insomnia, 1353
- pharmacokinetics of, 1064
- structure of, 565

Estrogen(s), 166–167

- drug interactions with (*See also* Hormonal contraceptive–drug interactions)
  - antipsychotics, 620
  - benzodiazepines, 567
  - eslicarbazepine acetate, 969
  - lamotrigine, 1012
  - oxcarbazepine, 968
  - topiramate, 1030
- perimenopausal depression and, 167
- in pregnancy, 167, 1002
- replacement therapy with, 482
- serotonin 5-HT<sub>4</sub> receptor regulation of release of, 64

Eszopiclone

- in adjustment disorders, 1602
- dosing of, 1642
- for insomnia, 1057, 1365
- interaction with carbamazepine and oxcarbazepine, 963, 966
- mechanism of action of, 1351
- pharmacokinetics of, 1064
- side effects of, 1365
- with SSRIs for generalized anxiety disorder, 1208



structure–activity relations for, [1057](#), [1058](#)

Etanercept, [191](#)

Ethanol. *See* [Alcohol](#)

Ethchlorvynol, [1068](#)

Ethosuximide, interaction with carbamazepine and oxcarbazepine, [963](#), [964](#)

Etodolac, [1413](#)

Etomidate, for ECT, [1122](#), [1123–1224](#)

EUFEST (European First Episode Schizophrenia Trial), [765–766](#)

European First Episode Schizophrenia Trial (EUFEST), [765–766](#)

European Surveillance of Congenital Anomalies (EUROCAT) study, [1559](#)

Euthyroid sick syndrome, [192](#)

Evoked (event-related) potentials, [264](#)

- in depression, [93](#)
- in schizophrenia, [81](#), [264](#)
- in suicidal patients, [55](#)

Excessive daytime sleepiness benzodiazepine-induced, [569](#)

- in narcolepsy, [1068](#)
  - armodafinil for, [1084](#), [1090](#)
  - modafinil for, [1084](#), [1089](#), [1094](#)

Excitatory amino acid transporters (EAATs), [84](#)

Executive function

- central executive network, [259](#)
- deficits in schizophrenia, [1243](#), [1249](#)

Exercise

- in bulimia nervosa, [1338](#)
- in depression, [1165](#)
- for pain, [1395](#), [1396](#), [1398](#), [1399](#)
  - fibromyalgia, [1403](#), [1404](#)
  - low back pain, [1406](#)
  - osteoarthritis, [1407](#)
- in schizophrenia, [1252](#)

Exfoliative dermatitis, carbamazepine-induced, [1179](#)

Exposure therapy

- for acute stress disorder, [1219](#)
- for OCD, [1212](#)
- for panic disorder, fluvoxamine and, [421](#)
- for PTSD, [1218](#)
  - drug-enhanced exposure, [1218](#)
  - paroxetine and, [397](#)
- for social anxiety disorder
  - fluoxetine and, [1200](#)
  - sertraline and, [365](#)

for specific phobia, 1203

D-cycloserine and, 1204

Extracellular signal-regulated kinase (ERK), 11, 49, 82-83, 101, 926

Extrapyramidal side effects (EPS) of antipsychotics, 855-878, 1255-1256, 1316, 1624

acute-onset EPS, 614, 617

atypical antipsychotics, 651, 731-732, 871-874, 1242, 1247, 1500, 1518

aripiprazole, 746, 747, 871, 873, 1463

asenapine, 801-802, 804, 805, 873, 1180, 1464

brexpiprazole, 732, 748, 874

cariprazine, 848, 874, 1180

clozapine, 623, 628-629, 872

iloperidone, 816, 817, 873-874

lurasidone, 825, 873, 1255

olanzapine, 651, 655, 657, 668-669, 674, 720, 776, 805, 872, 1255

paliperidone, 712, 873, 1255, 1463

quetiapine, 669, 688, 693, 697, 720, 872-873, 1255, 1523

risperidone, 669, 693, 712, 713, 718-720, 719, 722, 816, 817, 872, 1179-1180, 1255, 1457, 1458, 1463, 1522

ziprasidone, 669, 756, 774, 776-777, 873, 1180, 1255, 1464

belief that EPS were necessary for antipsychotic efficacy, 604, 609, 623, 628, 855

in CATIE study, 871, 1255

classic antipsychotics, 424, 604, 609, 611, 614, 615, 617, 649, 650, 719, 720, 731, 816, 877, 1247, 1255, 1465, 1516, 1520

D<sub>2</sub> receptor blockade and, 72, 609, 614, 732, 733, 737, 869-870, 1255

in elderly persons, 663, 1516, 1518

historical recognition of, 855

late-onset EPS, 617

vs. negative symptoms of schizophrenia, 1243

in neonates after prenatal drug exposure, 1565

in diffuse Lewy body disease, 1528

prophylactic use of antiparkinsonian agents for, 876-877, 1609

rating scales for, 746

of SSRIs, 1497

fluoxetine, 339, 346

sertraline, 372

treatment of, 856-869, 857, 1255-1256, 1614

for acute dystonic reactions, 870

amantadine, 862-864

benzodiazepines, 866-867

benztropine, 860-861

- biperiden, [861](#)
- $\beta$ -blockers, [864–866](#), [865](#)
- botulinum toxin, [867–868](#)
- clozapine, [871](#), [872](#)
- diphenhydramine, [861–862](#)
- for parkinsonism and akathisia, [870–874](#), [871](#)
- procyclidine, [861](#)
- for tardive dyskinesia and tardive dystonia, [874–876](#)
- trihexyphenidyl, [856–860](#)
- vitamin E, [868–869](#)
- types of, [855–856](#), [1255–1256](#)

Extrapyramidal Symptom Rating Scale (ESRS), [719](#), [802](#), [817](#)

Facial expression processing, fMRI studies of, [257](#)

Facial pain, atypical, MAOIs for, [289](#), [294](#)

Fainting, MAOI-induced, [290](#)

Falls

- drug-related, [1508](#)
  - antipsychotics, [617](#), [1521](#)
  - benzodiazepines, [577](#), [1062](#), [1076](#), [1196](#), [1627](#)
  - SSRIs, [1508](#)
  - TCAs, [322](#), [1390](#)
- insomnia and, [1349](#)
- interictal delirium and, [1124](#)

Family studies, [117–119](#), [118](#)

- of response to drug treatment, [123–124](#)

Family therapy/interventions

- for anorexia nervosa, [1344](#)
- for bipolar disorder, [1186](#)
- for conversion disorder, [1605](#)
- for schizophrenia, [1245](#), [1251](#)

Fatal Toxicity Index, [522](#)

Fatigue

- chronic, [1401](#)
  - fluoxetine for, [345](#)
  - immune system in, [185](#)
- depression and, [1151](#)
- drug-induced
  - asenapine, [804](#), [806](#), [1439](#)
  - atomoxetine, [1472](#), [1473](#)
  - $\beta$ -blockers, [864](#), [866](#)
  - buspirone, [593](#), [594](#), [1474](#)

- carbamazepine, 1179
- clomipramine, 1449
- clozapine, 637
- eslicarbazepine acetate, 960
- guanfacine, 1472, 1501
- haloperidol, 816
- iloperidone, 816
- lithium, 1472
- olanzapine, 1316
- oxcarbazepine, 1440, 1502
- risperidone, 718, 816, 1439, 1457
- suvorexant, 1072, 1359, 1367
- topiramate, 1029, 1339
- ziprasidone, 1440
- psychostimulants for treatment of, 1094
- <sup>18</sup>FDG (<sup>18</sup>FDG fluorodeoxyglucose)-PET imaging, 240, 241–242, 242, 243, 244, 245
- Fear Questionnaire (FQ), 365, 1195, 1203, 1204
- FEAST (focal electrically administered seizure therapy), 1132
- Felbamate, interaction with carbamazepine and oxcarbazepine, 963, 964–965
- Felodipine, interaction with carbamazepine and oxcarbazepine, 963, 966, 968
- Fenfluramine, interaction with MAOIs, 293
- Fenproporex, 1254
- Fentanyl, 101, 1387
  - transdermal, 1387, 1388, 1388, 1408
- Fetal carbamazepine syndrome, 1559
- Fetal drug exposure. *See also* Pregnancy and lactation
  - acute and developmental effects of, 1546–1547, 1547
  - FDA reproductive safety ratings for, 1547–1548, 1548
  - fetal brain concentration and, 1550
  - guidelines for minimization of, 1543, 1544–1545
  - maternal dosage management for reduction of, 1548–1549, 1570
  - nonpsychotropic treatments for reduction of, 1569
  - placental drug transfer and, 1549
- Fetal valproate syndrome, 1557, 1558
- Fever
  - during alcohol or sedative-hypnotic withdrawal, 1613
  - in cholestatic jaundice, 618
  - drug-induced
    - amphetamine, 1086
    - bupropion, 504
    - haloperidol, 719

- risperidone, [719](#)
- ziprasidone, [775](#)
- in neuroleptic malignant syndrome, [1257](#), [1516](#), [1614](#)
- during opioid withdrawal, [1613](#)
- in serotonin syndrome, [346](#), [405](#)
- during sertraline discontinuation, [372](#)
- Fexofenadine, [227](#)
- FFM (Five-Factor Model) of personality, [1153–1154](#)
- FGAs (first-generation antipsychotics). *See* [Antipsychotics, classic](#)
- Fiber supplements, [1506](#)
- Fibromyalgia, [1379](#), [1380](#), [1401–1404](#)
  - anxiety, depression and, [992](#), [1402](#)
  - diagnostic criteria for, [1402](#)
  - immune system in, [185](#), [191](#)
  - mechanisms of pain in, [1402](#)
  - prevalence of, [992](#)
  - treatment of, [1401–1405](#)
    - algorithmic approach to, [1412](#), [1413–1415](#)
    - nonpharmacological, [1403](#), [1404](#)
      - cognitive-behavioral therapy, [1395](#)
      - ECT, [1113](#)
    - pharmacological, [1403](#), [1403–1404](#), [1408](#)
      - cyclobenzaprine, [1393](#)
      - duloxetine, [539](#), [1391](#)
      - exercise, [1398](#), [1399](#)
      - fluoxetine, [345](#)
      - ketamine, [552](#)
      - milnacipran, [534](#), [535](#), [1391](#)
      - modafinil for fatigue, [1094](#)
      - opioids, [1384](#)
      - pregabalin, [992–993](#), [1392](#)
      - TCAs, [319](#)
      - tramadol, [1384](#)
      - trazodone, [458](#)
      - venlafaxine, [1392](#)
- Fibromyalgia Relapse Evaluation and Efficacy for Durability of Meaningful Relief (FREEDOM) trial, [992](#)
- 15q11 copy deletion, [126](#)
- Fight-or-flight response, [179](#), [180](#)
- Filgrastim, [1615](#)
- Firearm access, [1598](#), [1599](#), [1600](#), [1601](#)
- First-pass effect, [214–215](#), [310](#), [1507](#)

FISH (fluorescent in situ hybridization), [125](#), [130](#)  
Five-Factor Model (FFM) of personality, [1153](#)  
*FKBP5* gene, [121](#), [144](#), [162](#), [439](#)  
Flakka, [1611](#)  
Flatulence, antipsychotic-induced, [816](#)  
Flecainide, interaction with fluoxetine, [350](#)  
Floppy infant syndrome, maternal drug use and  
    benzodiazepines, [576](#), [1567](#)  
    clozapine and, [1562](#)  
    lithium, [1556](#)  
Florinef. *See* [Fludrocortisone](#)  
Flu-like symptoms, drug-induced  
    citalopram, [1434](#)  
    topiramate, [1339](#)  
Fluconazole, interaction with carbamazepine, [964](#)  
Fludrocortisone, [290](#), [322](#)  
Flumazenil, [1018](#), [1059](#), [1059](#), [1060](#)  
Flunitrazepam, [566](#), [569](#), [1053](#)  
Fluorescence resonance energy transfer (FRET), [19](#)  
Fluorescent in situ hybridization (FISH), [125](#), [130](#)  
<sup>18</sup>Fluorodeoxyglucose (<sup>18</sup>FDG)-PET imaging, [240](#), [241–242](#), [242](#), [243](#), [244](#),  
    [245](#)  
Fluoxetine, [335–350](#)  
    antiviral effects of, [345](#)  
    aripiprazole augmentation of, [742](#)  
    in children and adolescents, [1211](#), [1433–1434](#), [1444](#), [1447–1448](#), [1498](#)  
    combined with olanzapine (*See* [Olanzapine–fluoxetine combination](#))  
    discontinuation syndrome with, [340](#), [348–349](#)  
    dosing of, [340](#), [342](#), [1635](#)  
        in children and adolescents, [1498](#)  
    drug interactions with, [340](#), [349–350](#), [1507](#)  
        antipsychotics, [620](#)  
            cariprazine, [840](#)  
            clozapine, [641](#)  
            olanzapine, [673](#)  
        benzodiazepines, [572](#)  
        carbamazepine, [964](#), [965](#)  
        risperidone, [722](#)  
        TCAs, [325](#)  
        vortioxetine, [473](#)  
        warfarin, [1508](#)  
    in elderly persons, [392](#), [1512](#)

- generic, 335
- history and discovery of, 335-336
- indications for, 340-345
  - alcohol use disorder, 344-345
  - anger and aggression, 343
  - anorexia nervosa, 343, 1345
  - autism spectrum disorder, 345, 1469-1470
  - avoidant personality disorder, 1328
  - borderline personality disorder, 343, 665, **1321-1322**
  - bulimia nervosa, 342-343, 1338, 1339
  - cognitive-behavioral therapy and, 1340
  - depression, 341-342
    - with anxious features, 341
    - vs. bupropion, 499
    - in children and adolescents, 1433- 1434
    - vs. duloxetine, 534, **536**
    - in elderly persons, 392, 1512
    - maintenance treatment, 341-342
    - vs. milnacipran, **538**
    - mirtazapine and, 481
    - vs. olanzapine-fluoxetine combination, 663
    - vs. paroxetine, 390
  - mixed anxiety disorders in children and adolescents, 1446
  - obesity, 345
  - OCD, 342, 1211
    - in children and adolescents, 1211, 1447-1448
    - olanzapine and, 668
  - other medical conditions, 345
  - pain syndromes, 319, 344, 345
  - panic disorder, 342, 1195, 1196
    - maintenance treatment, 1198
  - premature ejaculation, 344
  - premenstrual dysphoric disorder, 343
  - PTSD, 344
  - schizotypal personality disorder, 1329
  - social anxiety disorder, 1200
    - in children and adolescents, 1444
- mechanism of action of, 340
- once-weekly formulation of, 221, 341-342
- overdose of, 347, 349, 350
- pharmacokinetics and disposition of, 339-340, 1507
- pharmacological profile of, 336-339

- racemic, [226](#)
- side effects and toxicology of, [339](#), [345–346](#), [1470](#)
- structure–activity relations for, [336](#), [337](#)
- suicidality and, [346–347](#)
- switching to/from MAOI, [340](#), [346](#)
- switching to vortioxetine from, [473](#), [474](#)
- use in pregnancy and lactation, [347–348](#), [1549](#), [1550–1553](#)
- use in renal disease, [340](#)

Flupenthixol, for generalized anxiety disorder, [1209](#)

Flupenthixol decanoate, for borderline personality disorder, [1316](#), [1317](#)

Fluphenazine

- dosing of, [1643–1644](#)
- formulations of, [1249](#)
- interaction with carbamazepine and oxcarbazepine, [963](#), [966](#)
- for PTSD, [667](#)
- receptor affinities of, [613](#)
- side effects of, [615–616](#)
- structure–activity relations for, [605](#), [607](#)

Fluphenazine decanoate, [609–610](#), [620](#), [1644](#)

Flurazepam

- dosing of, [1642](#)
- for insomnia, [1052](#), [1064](#), [1351](#), [1353](#), [1364](#)
- pharmacokinetics of, [566](#), [1060](#), [1064](#)
- side effects of, [569](#), [1364](#)
- structure of, [565](#), [1053](#)

Fluvoxamine, [419–426](#)

- in children and adolescents, [421](#), [423](#), [1202](#), [1445–1446](#), [1448](#), [1470](#)
- discontinuation syndrome with, [420](#)
- dosing of, [1635](#)
- drug interactions with, [425](#)
  - antipsychotics, [620](#)
    - clozapine, [425](#), [641](#)
    - olanzapine, [673](#)
  - asenapine, [799](#)
  - carbamazepine, [964](#), [965](#)
  - warfarin, [425](#), [1508](#)
- in elderly persons, [420](#)
- familial aggregation of response to, [124](#)
- formulations of, [421](#), [422](#)
- history and discovery of, [419](#)
- indications for, [419](#), [421–424](#)
  - alcohol use disorder, [344](#)



- autism spectrum disorder, [1470](#)
- body dysmorphic disorder, [423](#)
- borderline personality disorder, [1322](#)
- bulimia nervosa, [1338](#)
- delirium, [424](#)
- depression, [421](#)
  - vs. milnacipran, [538](#)
- eating disorders, [423-424](#)
- impulse-control disorders, [423](#)
- mixed anxiety disorders in children and adolescents, [1445-1446](#)
- OCD, [422](#), [1211](#)
  - in children and adolescents, [423](#), [1448](#)
  - clomipramine and, [1211](#)
- pain syndromes, [424](#)
- panic disorder, [421](#), [1195](#)
- PTSD, [423](#)
- social anxiety disorder, [421-422](#), [1199](#)
  - in children and adolescents, [1202](#)
- trichotillomania, [423](#)
- mechanism of action of, [419-420](#)
- overdose of, [425](#)
- pharmacokinetics and disposition of, [420-421](#), [1507](#)
- pharmacological profile of, [420](#)
- side effects and toxicology of, [424-425](#), [1448](#)
- structure-activity relations for, [337](#), [419](#), [420](#)
- suicidality and, [425](#)
- use in hepatic or renal disease, [420](#)
- use in pregnancy and lactation, [425-426](#)
- fMRI. *See* [Functional magnetic resonance imaging](#)
- Focal electrically administered seizure therapy (FEAST), [1132](#)
- Focalin, Focalin XR. *See* [Dexmethylphenidate](#)
- Folate supplementation in pregnancy
  - with carbamazepine, [1560](#)
  - with valproate, [1558](#)
- Follicle-stimulating hormone (FSH), [166](#), [609](#), [722](#), [934](#)
- Foods. *See* [Diet](#)
- Forgetfulness, MAOI-induced, [290](#)
- Formulations of drugs. *See also specific drugs*
  - absorption and, [213-214](#), [214](#)
  - controlled-release forms, [213-214](#)
- FQ (Fear Questionnaire), [1195](#), [1203](#), [1204](#)
- Fractures, drug-related, [1508](#)

- benzodiazepines, [577](#)
- clozapine, [1521](#)
- SSRIs, [1508](#)
- TCAs, [322](#)
- Fragile X syndrome, [122](#)
- FREEDOM (Fibromyalgia Relapse Evaluation and Efficacy for Durability of Meaningful Relief) trial, [992](#)
- FRET (fluorescence resonance energy transfer), [19](#)
- FSH (follicle-stimulating hormone), [166](#), [609](#), [722](#)
- FSSs (functional somatic syndromes), [1401-1402](#)
- Functional magnetic resonance imaging (fMRI), [240](#), [251-260](#), [269](#)
  - of antidepressant effects, [269](#), [438](#)
  - BOLD signal in, [240](#), [251-255](#), [252](#), [255](#), [258-259](#)
  - combined with EEG, [265](#)
  - compared with PET imaging, [255](#), [256](#)
  - neural activation studies, [255-258](#)
    - cognitive “working memory” paradigms, [257-258](#)
    - facial-expression-processing paradigms, [257](#)
    - mood and self-referential paradigms, [256-257](#)
    - reward-processing paradigms, [258](#), [259](#)
  - resting-state studies, [256](#), [258-260](#)
    - central executive network, [259](#)
    - default mode network, [259-260](#)
    - salience network, [260](#)
  - in schizotypal personality disorder, [1328](#)
- Functional neurological symptom disorder, [1605](#)
- Functional somatic syndromes (FSSs), [1401-1402](#)
- Furazolidone, interaction with MAOIs, [293](#)
- Furosemide, for hyponatremia, [444](#)

G protein-coupled receptors (GPCRs), 25, 47, **48-49**, 50-53, **52**, 102  
  autoreceptors and heteroreceptors, 50-51  
  CRH activation of, 98  
  desensitization of, 51-53  
  downregulation of, 53  
  endocytosis of, 53  
  ligand-induced selective signaling of, 50  
  muscarinic, 80  
  number of, 50  
  opioid, 101  
  receptoromics, 34  
  regulation and trafficking of, 51-53  
  serotonin receptors, 59-64  
G proteins, 7, 25, 50, 61, **62**  
GABA. *See*  **$\gamma$ -Aminobutyric acid**  
GABA  $\alpha$ -oxoglutarate transaminase (GABA-T), 92, **94-95**  
Gabapentin, 983-990, 995  
  dosing of, 987, **1651**  
  drug interactions with, 989  
    lithium, 905  
  history and discovery of, 983  
  indications for, 984-990  
    alcohol dependence, 988-989  
    alcohol withdrawal, 988, 1286  
    bipolar disorder, 987-988  
      mania, 893  
    cannabis dependence, 989  
    clozapine-induced seizures, 638  
    generalized anxiety disorder, 986  
    migraine prophylaxis, 986  
    movement disorders, 985-986  
    OCD, 1212  
    pain syndromes, **1414**  
      fibromyalgia, 1403, **1403**  
      with morphine, 1398  
      neuropathic pain, 983, 985, 1392, 1400, 1401  
  panic disorder, 986, 987  
  seizures, 983, 984-985, 989  
  social anxiety disorder, 986-987, 1200-1201  
  mechanism of action of, 983  
  overdose of, 989

- pharmacokinetics and disposition of, 984
- pharmacological profile of, 983–984
- side effects and toxicology of, 989, 1401, 1404
- structure–activity relations for, 983, 984
- use in renal disease, 984, 989

Gabaxadol, 96

*GABRA6* gene, 1288

GAD. *See* Generalized anxiety disorder

GAD (glutamic acid decarboxylase), 92, 94–95

GAF (Global Assessment of Functioning Scale), 764, 1096

Galactorrhea, 1257

- antipsychotic-induced, 609, 616, 618, 1258
  - clozapine, 629
  - risperidone, 720, 721
- SSRI-induced
  - fluoxetine, 346
  - sertraline, 372

Galanin, 73, 100, 1350, 1351

Galantamine, 1040, 1041–1042

- for Alzheimer’s disease, 1041
  - antipsychotics and, 1521
- with antipsychotics for schizophrenia, 1042
- dosing of, 1041–1042, 1658
- mechanism of action of, 1041
- for vascular cognitive impairment, 1044

Gambling disorder, topiramate for, 1026

Gastric bypass surgery, sertraline plasma concentration after, 361

Gastrointestinal effects of drugs acetylcholinesterase inhibitors, 1040

- N*-acetylcysteine, 1473
- during alcohol or sedative-hypnotic withdrawal, 1613
- anticholinergic agents, 858, 859
- antipsychotics, 1516
- aripiprazole, 737, 746, 747, 1180, 1461
- asenapine, 804
- atomoxetine, 1473, 1498, 1499
- brexpiprazole, 737
- bupropion, 504, 1436, 1498
- buspirone, 593
- cancer chemotherapy, 484–485
- carbamazepine, 958, 1179, 1440
- cariprazine, 848, 848, 1180
- chloral hydrate, 1069

classic antipsychotics, 612, 618, **719**, **816**  
clomipramine, 1448, 1449  
clozapine, 626, 639, 1521  
desvenlafaxine, 521  
diphenhydramine, **1368**  
doxepin, **1367**  
doxylamine, **1368**  
duloxetine, 540, 1404, 1436, 1443, 1498  
iloperidone, 816, **816**  
ketamine, 555  
lamotrigine, 1011, 1182, 1502  
levomilnacipran, 541  
lithium, 216, 1178, 1438, 1439, 1458, 1459, 1472, 1501  
MAOIs, 290, 296, 297  
milnacipran, 541, 1404  
mirtazapine, 487, **1369**, 1498  
modafinil, 1090  
muscarinic receptor antagonists, 80  
nefazodone, 462, 1436  
NSAIDs, 1382  
olanzapine, 1179, **1370**  
opioids, 1385  
oxcarbazepine, 960, 1440, 1502  
paroxetine, 386, 398, 1435  
physostigmine, 1042  
quetiapine, **693**, 1180  
risperidone, **693**, 718, **719**, **816**, 1180, 1458  
selegiline transdermal system, 298, 1436  
sertraline, 1447  
SSRIs, 216, 345, 371, 398, 421, 424, 443, 444, 467, 1434, 1435, 1445, 1447, 1448, 1449, 1451, 1470, 1497  
TCAs, 321, **1368**, **1369**  
topiramate, 1021, 1029, 1440, 1502  
treatment of, 639  
valproate, 933, 1178, 1440, 1501  
venlafaxine, 521, 1208, 1404, 1471  
vortioxetine, 472, 474  
ziprasidone, 774, 1440  
*GATA4* gene, 1288  
*GDA* gene, 445  
Gemfibrozil, interaction with carbamazepine, **964**, 967

GENDEP (Genome-Based Therapeutic Drugs for Depression) study, [312](#), [438–439](#), [445](#)

## Gender

- depression and, [1152](#)
- eating disorders and, [1337](#), [1342](#)
- metabolic syndrome and, [1254](#)
- schizophrenia and, [1244](#)
  - substance use disorders and, [1258](#)
- suicide and, [1155](#), [1509](#), [1598](#)
- tardive dyskinesia and, [1257](#)

Gene × environment interaction studies, [118](#), [121](#), [122](#), [123](#), [143–144](#), [145](#)

## Gene expression, [3](#)

- disorders associated with changes in, [14](#)
- ectopic, identification of, [18–19](#)
- experimental approaches to determination and manipulation of, [13–19](#)
  - cloning of DNA, [14–16](#), [15](#)
    - polymerase chain reaction, [14–16](#)
    - positional cloning, [16](#)
  - differential display, [16–17](#)
  - gene delivery into mammalian cells, [17–19](#)
    - identification of ectopic gene expression, [18–19](#)
    - vectors and delivery, [17–18](#)
    - viral vectors, [18](#)

## inhibition of, [19–22](#)

- chromatin immunoprecipitation, [21–22](#)
- RNA interference, [19–20](#), [20](#)
- RNAi applications, [21](#)
- RNAi knockdown of gene expression, [20–21](#)

## principles of, [5–7](#)

- DNA replication, [6](#)
- genes and DNA, [5–6](#)
- transcription, [6](#)
- translation, [7](#)

## regulation of, [7–13](#)

- chromatin and DNA methylation, [7–9](#)
- cis*-regulation, [6](#)
- modification of nascent polypeptide chain, [13](#)
- non-coding RNAs, [13](#)
- posttranscriptional modification of RNA, [10–11](#), [12](#)
- RNA editing, [11–13](#)
- RNA polymerases, [9](#), [9–10](#)
- transcription factors, [10](#), [11](#)

- role in learning and memory, [13-14](#)
- variety in brain, [4](#)
- Gene transfer, [17-18](#)
- Generalized anxiety disorder (GAD), [1204](#)
  - in children and adolescents, [1443](#)
  - depression and, [1204](#)
  - in elderly persons, [1204](#)
  - genetics of, [121](#)
  - prevalence of, [1204](#)
  - rating scales for, [1205](#)
- Generalized anxiety disorder treatment
  - agomelatine, [1209](#)
  - antidepressants, [1206-1208](#)
    - bupropion, [1208](#)
    - duloxetine, [1208](#), [1443](#)
    - MAOIs, [289](#)
    - mirtazapine, [483](#), [1208](#)
    - SSRIs, [1206-1207](#)
      - citalopram, [440](#)
      - escitalopram, [440](#), [1206-1207](#)
      - nonbenzodiazepine hypnotics and, [1208](#)
      - paroxetine, [396](#), [1206](#)
      - sertraline, [371](#), [372](#), [1207](#), [1444](#)
  - TCAs, [1206](#)
    - imipramine, [396](#), [569](#)
  - trazodone, [457](#)
  - venlafaxine, [519](#), [1207-1208](#), [1443-1444](#)
  - vortioxetine, [468](#)
- antipsychotics, [1209](#)
  - quetiapine, [691](#), [1209](#)
  - risperidone, [717](#)
- benzodiazepines, [396](#), [569](#), [589](#), [1205](#)
- buspirone, [589-591](#), [1205-1206](#), [1444](#)
- in children and adolescents, [1443-1444](#)
  - buspirone, [1444](#)
  - duloxetine, [1443](#)
  - sertraline, [1444](#)
  - venlafaxine, [1443-1444](#)
- cognitive-behavioral therapy, [1210](#)
- complementary and alternative medicine approaches, [1209-1210](#)
- gabapentin, [986](#)
- hydroxyzine, [1208](#)

pregabalin, 993–994, 1208–1209

riluzole, 1209

## Genes

activation in response to drug treatment, 17

amplification of, 14–16

candidate, 16, 63, **118**, 131, 132, 138

for depression, 1158

chromosomal distribution of, 6

cloning of, 14, **15**

delivery into mammalian cells, 17–19

identification of ectopic gene expression, 18–19

vectors and, 17–18

viral vectors for, 18

DNA and, 5–6

gene–environment interaction studies, **118**, 121, 122, 123, 143–144, 145

gene–gene interactions, 123

mapping of, 14, 16

number in human genome, 3, 6, 136

transgenic and gene-targeting techniques, 25–26, **27**

optogenetics, 4, 30–33, **31–32**

tissue-specific gene manipulation, 30

use of mutant mice in studies of brain disease, 27–30

Genetic architecture, 142, 143

Genetics, 117–145

epidemiological basis for genetic contributions to neurobehavioral disorders, 117–124

adoption and twin studies, 117–122, **120**, **121**

gene–environment interactions, 121, 122, 123, 143–144, 145

genetic modifiers of response to drug treatment, 123–124

genetic risk factors, 120–121

heritability scores, 119, **121**

psychiatric disorders as complex genetic disorders, 122–123

epigenetics, 4, 8, 9, 119–120, 122

gender-specific predisposing genes for psychiatric disorders, 123

human genetic variation, 124–130

chromosomal variations, 124–126

molecular variation in genome, 126–130

identification of risk loci for psychiatric disorders, 130–144

association studies, 132–135

cross-disorder studies, 142–143

cytogenetic studies, 130–131

gene × environment interaction studies, **118**, 143–144, 145



- genomewide association studies, 135–142, **139**
  - linkage studies, 131–132
- imprinted disorders, 122–123
- Mendelian disorders, 122, 131
- methods for psychiatric research, 117, **118**
- mitochondrial inheritance, 122
- molecular, 3–35 (*See also* **Molecular biology**)
- polygenic inheritance, 122, 123
- polygenic risk score, 127, 141, 142
- reverse, 16
- sequencing of human genome, 3, 6, 117
- of specific disorders
  - ADHD, 127, 128
  - agoraphobia, **121**
  - alcohol use disorder, **121**
  - Alzheimer’s disease, 14
  - Angelman syndrome, 122, 126
  - anorexia nervosa, **121**
  - antisocial personality disorder, **121**
  - anxiety, 141
  - autism spectrum disorder, **121**, 123, 126, 127
  - bipolar disorder, **121**, 123, 125, 128, 140–141, 143
  - bulimia nervosa, **121**
  - conduct disorder, 125
  - depression, 14, 120, **121**, 123, 125, 128, 140, 141, 1158
  - fragile X syndrome, 122
  - generalized anxiety disorder, **121**
  - Huntington’s disease, 14, 28, 122
  - nicotine addiction, **121**
  - obsessive-compulsive disorder, **121**
  - panic disorder, **121**
  - Prader-Willi syndrome, 122, 126
  - schizophrenia, 14, **121**, 122, 123, 125, 127, 130, 138–140, **139**, 143
  - social anxiety disorder, **121**
  - specific phobia, **121**
- Genome, 5, 117, 131. *See also* **Molecular biology**
- editing technologies, 4, 22–25, **24**
  - human genome sequencing, 3–4, 16, 22, 127
    - cost of, 136–137
    - ENCODE project, 136
    - HapMap and 1,000 Genomes projects, 134, 136
    - Human Genome Project, 135–136

- molecular variation in, 126–130
- Genome-Based Therapeutic Drugs for Depression (GENDEP) study, 312, 438–439, 445
- Genomewide association studies (GWAS), 135–142
  - in anxiety, 141
  - in bipolar disorder, 140–141
  - of copy number variants, 130, 141
  - in depression, 140, 141
  - of escitalopram-related suicidality, 445–446
  - new possibilities from Human Genome Project, 135–136
  - in schizophrenia, 138–140, 139, 141, 142
  - of single nucleotide polymorphisms, 136–141
    - methodology for, 136–138
    - results of, 138–141
  - use of data from, 141–142
    - pathway analysis, 141
    - polygenic analysis, 141–142
- Genomic control method of population stratification, 135
- Genomics, 3–35, 117, 136, 142, 145. *See also* Molecular biology
  - pharmacogenomics, 225, 226–230, 229
    - of acamprosate, 1288
    - of fluvoxamine, 420
    - of naltrexone, 227, 1287
    - of paroxetine, 388–389, 1508
- Genotype, 16, 63, 126
  - of drug-metabolizing enzymes and transporters, 210, 229
  - genotype–phenotype correlations, 64
  - haploid, 126
  - homozygous vs. heterozygous, 126
  - 5-HTTLPR, 59, 128, 134, 143, 388
  - microsatellite markers, 131
  - population stratification and, 134
  - single nucleotide polymorphisms and, 129–130
    - ABCB1* and antidepressant outcomes, 227
    - genomewide association studies, 138
- Gepirone, 586
- German Society for Bipolar Disorder, 1005
- German Society of Psychiatry, 1005
- GFP (green fluorescent protein), 19
- GFRA2* gene, 815
- GGT ( $\gamma$ -glutamyl transferase), 1023, 1288
- GH. *See* Growth hormone

GHB ( $\gamma$ -hydroxybutyrate), 1069, 1611

Ghrelin, 667

*Ginkgo biloba*, 1044, 1210

Glaucoma

- ocular crisis in, 321
- psychotropic drug use in
  - antipsychotics, 612, 619
  - TCAs, 321, 322
  - trazodone, 458
- topiramate-induced, 1029

Glial cells

- cell biology of, 4-5
- 5-HT<sub>1A</sub> receptor expression on, 60
- microglial PET imaging, 247, 248-249

Global Assessment of Functioning Scale (GAF), 764, 1096

Glucocorticoid receptor (GR), 49, 60, 158, 159

- cytokine effects on, 193-194
- in depression, 160-161
- dexamethasone binding to, 160
- drug effects on, antidepressants, 315
- citalopram, 435
- in PTSD, 164

Glucocorticoids, 49, 53

- adrenocortical synthesis of, 157
- decreased sensitivity to, in depression, 160, 184, 193
- in depression, 99, 158, 160-162, 181, 184, 193, 1156
- 5-HT<sub>1A</sub> receptor downregulation by, 60
- immune system effects of, 158, 184, 187-188
- pulsatile secretion of, 158

Glucosamine, for osteoarthritis, 1408, 1409

10-*N*-Glucuronide, 653

Glutamate, 81-85, 82-83

- adenosine inhibition of, 97
- in depression, 1156
- drug effects on
  - carbamazepine, 948
  - gabapentin, 984
  - ketamine, 550
  - lamotrigine, 1002-1003, 1006
  - lithium, 890
  - memantine, 1043
  - oxcarbazepine, 949

- topiramate, 1018, 1019
- excitatory action in brain, 83, 84, 242, 1042
- inflammatory cytokine effects on, 1157
- metabolic PET studies of, 242
- MRS studies of, 260–261, **261**, 1108
- in schizophrenia, 84, 655–656
- synthesis of, 83
- Glutamate dehydrogenase, 984
- Glutamate receptors, 47, 85–91, 1042. *See also specific receptors*
  - classification of, **82**
  - ionotropic, **82**, 85–90
    - AMPA receptors, **82**, 88–89
    - kainate receptors, **82**, 89–90
    - NMDA receptors, **82**, 85–88
  - metabotropic, **82**, 90–91, **247**
- Glutamate transporter, 83–84
- Glutamic acid decarboxylase (GAD), 92, **94–95**, 984
- Glutamine, **82–83**, 83
  - in huntingtin, 28, 29
  - MRS imaging of, 260, **261**
- γ-Glutamyl transferase (GGT), 1023, 1288
- Glycine, 91–92
- Glycine receptors, 91–92
- Glycine transporter (GlyT1), 58, 92
- Glycogen synthase kinase 3 (GSK-3), 891, 926
- Glycopyrrolate, for ECT, 1122–1123, 1125
- Glycosylation, 13, 34, 136
- GlyT1, 58, 92
- GnRH (gonadotropin-releasing hormone), 166, 168
- Go/No-Go task, 257, 438
- Gonadal steroids, **49**, 53, 166, 186. *See also Estrogen(s); Hypothalamic-pituitary-gonadal axis; Progesterone; Testosterone*
  - depression and, 166
  - perimenopausal, 167
  - in pregnancy and postpartum, 167
  - premenstrual syndrome and, 166–167
- Gonadotropin-releasing hormone (GnRH), 166, 168
- GPCRs. *See G protein-coupled receptors*
- GR. *See Glucocorticoid receptor*
- GR205171, for social anxiety disorder, 1202
- Grapefruit juice–drug interactions, 215, 1507
  - carbamazepine, **964**

- cariprazine, [840](#)
- ketamine, [556](#)
- Green fluorescent protein (GFP), [19](#)
- GRIA4* gene, [815](#)
- GRIK1* gene, [1024](#)
- GRIK3* gene, [1158](#)
- Group therapy, for schizophrenia, [1245](#)
- Growth effects of psychostimulants in children, [1504](#)
- Growth hormone (GH), [165](#)
  - in depression, [165](#)
  - drug effects on, buspirone, [588](#)
  - in schizophrenia, [165](#)
- Growth hormone-releasing hormone (GHRH), [165](#)
- GSK-3 (glycogen synthase kinase 3), [891](#), [926](#)
- GTP (guanosine triphosphate), [7](#), [587](#)
- GTPases (guanosine triphosphatases), [11](#), [52](#)
- Guanethidine, interaction with TCAs, [325](#)
- Guanfacine
  - in children and adolescents, [1500–1501](#)
    - for ADHD, [76](#), [1455](#), [1456](#), [1657](#)
    - for autism spectrum disorder, [1472](#)
    - for PTSD, [1451](#)
    - for Tourette syndrome, [1460–1461](#)
  - discontinuation of, [1500](#)
  - for PTSD, [1217](#), [1451](#)
  - for schizotypal personality disorder, [1329](#)
  - side effects of, [1472](#), [1501](#)
- Guanosine triphosphatases (GTPases), [11](#), [52](#)
- Guanosine triphosphate (GTP), [7](#), [587](#)
- GWAS. *See* [Genomewide association studies](#)
- Gynecomastia, drug-induced
  - classic antipsychotics, [609](#), [618](#)
  - fluoxetine, [346](#)
  - risperidone, [720](#)
- H<sub>1</sub> receptors. *See* [Histamine H<sub>1</sub> receptors](#)
- Habit reversal training, for Tourette syndrome, [1461–1462](#)
- HADS (Hospital Anxiety and Depression Scale), [1205](#), [1207](#)
- Hair loss, valproate-induced, [935](#), [1502](#)
- Halazepam, [572](#)
- Halcion. *See* [Triazolam](#)
- Hallucinations

- during alcohol withdrawal, [1613](#)
- in Alzheimer's disease, [1518-1519](#)
  - olanzapine for, [663](#)
- antipsychotics for, [611](#)
- during benzodiazepine withdrawal, [573](#)
- during cocaine intoxication, [1611](#)
- drug-induced
  - amantadine, [863](#)
  - amphetamines, [1086](#), [1087](#), [1611](#)
  - anticholinergic agents, [859](#)
  - ketamine, [555](#)
- in Parkinson's disease, clozapine for, [633](#)
- in schizophrenia, [1242](#), [1243](#)
- Haloperidol, [603](#)
  - in children and adolescents, [659](#), [1464](#), [1465](#), [1469](#)
  - dosing of, [1644](#)
  - drug interactions with
    - buspirone, [594](#)
    - carbamazepine and oxcarbazepine, [963](#), [965-966](#)
    - paroxetine, [404](#)
  - formulations of, [1249](#), [1608-1609](#), [1610](#), [1612](#)
  - indications for
    - agitation and aggression, [569](#), [1606](#), [1607](#), [1608-1609](#), [1610](#)
    - autism spectrum disorder, [1469](#)
      - vs. clomipramine, [1470-1471](#)
    - behavioral complications of dementia, [1521](#), [1624](#)
      - vs. risperidone, [1523-1524](#)
      - switching to risperidone from, [1525](#)
      - therapeutic blood level monitoring of, [1527](#)
    - borderline personality disorder, [1316](#), [1317-1318](#)
    - conduct disorder and aggression, [1458](#)
    - delirium, [1612](#)
    - delirium tremens, [1613](#)
    - ketamine-induced psychosis, [84](#)
    - mania, [1179](#)
      - vs. lithium, [892](#)
    - OCD, [1212](#)
    - schizophrenia and schizoaffective disorder, [630](#)
      - behavioral emergencies, [1610](#)
      - in children and adolescents, [659](#), [1464](#), [1465](#)
      - vs. iloperidone, [811](#), [812](#), [813](#)
      - maintenance treatment, [634-635](#)

- mirtazapine and, 486
  - vs. olanzapine, 658
  - vs. risperidone, 712–715, 714
- schizotypal personality disorder, 1329
- Tourette syndrome, 1461, 1462
- receptor-binding affinity of, 613, 706, 707, 708, 709
- side effects of, 612, 615–616, 719, 816, 1458, 1469
  - extrapyramidal side effects, 614, 719, 871, 872, 877, 1521, 1525
  - prophylaxis for, 1609
  - hyperprolactinemia, 720
  - weight gain, 718, 1253
- structure–activity relations for, 606, 607
- use in pregnancy and lactation, 1565, 1566
- Haloperidol decanoate, 609–610, 620, 1644
- Hamilton Anxiety Scale (Ham-A), 396, 442, 481, 483, 569, 589, 591, 691, 744, 772, 927, 993–994, 1205, 1206, 1207, 1208, 1209, 1444
- Hamilton Rating Scale for Depression (Ham-D), 298, 341, 363, 390, 436, 481, 499, 521, 535, 591, 689, 744, 745, 746, 772, 927, 1004, 1020, 1021, 1096, 1207, 1435, 1510, 1511, 1512, 1513, 1514, 1515
- Haplotype, 126–127
  - haplotype block, 134
  - linkage disequilibrium and, 133–134
  - of P-gp single nucleotide polymorphisms, 227
- Haplotype–relative risk (HRR) method of population stratification, 134–135
- HapMap project, 134, 136
- HDAC (histone deacetylase), 8, 926, 935
- Head injury
  - amnesia after, 1604
  - due to drug-related falls, 1196
  - psychostimulants after, 1092–1093
- Headache. *See also* Migraine
  - during alcohol withdrawal, 1285
  - chronic daily, 1411
  - drug-induced
    - aripiprazole, 746, 747, 1180
    - asenapine, 1439
    - benzodiazepines, 1065
    - brexpiprazole, 748
    - bupropion, 504, 1436, 1498
    - buspirone, 593
    - cariprazine, 847, 847, 848
    - clomipramine, 1449

- duloxetine, [540](#), [1436](#), [1498](#)
- eslicarbazepine acetate, [960](#)
- fluoxetine, [1434](#)
- gabapentin, [987](#)
- guanfacine, [1501](#)
- haloperidol, [719](#), [816](#)
- iloperidone, [816](#), [817](#)
- lamotrigine, [1182](#)
- lithium, [1438](#), [1458](#)
- MAOIs, [290](#), [291](#)
- modafinil, [1090](#), [1092](#)
- nefazodone, [1436](#)
- paliperidone, [1463](#)
- psychostimulants, [1502](#)
- quetiapine, [693](#), [1180](#), [1440](#), [1463](#)
- risperidone, [693](#), [718](#), [719](#), [816](#), [1439](#), [1457](#), [1463](#)
- selegiline transdermal system, [1436](#)
- sertraline, [1435](#)
- SSRIs, [345](#), [371](#), [398](#), [443](#), [1434](#), [1435](#), [1445](#), [1447](#), [1449](#), [1451](#), [1497](#)
- suvorexant, [1359](#), [1367](#)
- trazodone, [1369](#)
- ziprasidone, [774](#), [1180](#)
- medication overuse, [1411](#)
- neuroimaging for, [1411](#)
- tension-type, [1408](#)
  - vs. migraine, [1411](#)
- treatment of, [1411](#)
  - fluoxetine, [344](#), [345](#)
  - mirtazapine, [484](#)
  - in pregnancy, [1544](#)
  - sertraline, [368](#)
  - stepped-care approach, [1411](#)
- TCAs, [319](#)

Health Information Portability and Accountability Act (HIPAA), [1594](#)

Heat stroke, [859](#), [1029](#)

Hematological effects of drugs

- benzodiazepines, [1065](#)
- carbamazepine, [957](#), [969](#), [1179](#), [1440](#)
- cariprazine, [848](#)
- classic antipsychotics, [616](#), [619](#)
- clozapine, [604](#), [623](#), [628](#), [630](#), [631](#), [635–636](#), [875](#), [1248](#), [1464](#), [1500](#), [1521](#), [1561](#), [1615](#)



- fluoxetine, [346](#)
- lurasidone, [825](#)
- mirtazapine, [965](#)
- olanzapine, [672](#)
- sertraline, [372](#)
- TCAs, [324](#)
- valproate, [933](#), [1179](#), [1502](#)
- venlafaxine, [522](#)
- Heparin, interaction with benzodiazepines, [572](#)
- Hepatic drug metabolism, [213](#), [225](#). *See also* [Pharmacokinetics](#)
- Hepatitis B, schizophrenia and, [1258](#)
- Hepatitis C
  - opioid use and, [1289](#)
  - schizophrenia and, [1258](#)
- Heroin, [101](#), [1289](#), [1291](#), [1613](#)
- Herpes simplex virus vectors for gene transfer, [18](#)
- Heteroreceptors, [50](#), [90](#)
- 5-HIAA (5-hydroxyindoleacetic acid), [309](#), [347](#)
- Hiccups, chlorpromazine for, [612](#)
- Hip fracture, drug-related, [1508](#)
  - benzodiazepines, [577](#)
  - SSRIs, [1508](#)
  - TCAs, [322](#)
- HIPAA (Health Information Portability and Accountability Act), [1594](#)
- Hippocampus
  - AMPA receptors in, [85](#), [88](#), [89](#)
  - antidepressant and ECT effects on function of, [1108](#)
  - in depression, [1156](#)
  - GABA receptors in, [93](#), [95](#)
  - HPA axis and, [158](#), [159](#)
  - kainate receptors in, [89](#), [90](#)
  - in learning and memory, [30](#)
    - studies in patients at risk of developing Alzheimer's disease, [258](#)
  - lithium effects on volume of, [891](#)
  - muscarinic receptors in, [80](#)
  - NMDA receptors in, [86](#)
  - norepinephrine transporter in, [73](#)
  - receptors for proinflammatory cytokines in, [189](#)
  - in schizophrenia, in utero infections and, [185](#)
  - serotonin receptors in, [59](#), [60](#), [64](#), [262](#)
  - serotonin transporter in, [58](#)
  - volume loss in depression, [183](#)

MRI studies of, 261–262

Hippuric acid, 295

Histamine H<sub>1</sub> receptors, 34, 63

- drug affinity for antihistamines, 861
- aripiprazole, 734, 735, 738, 834, 836
- asenapine, 797
- brexpiprazole, 734, 735, 738, 834, 836
- cariprazine, 833, 834, 834, 836
- classic antipsychotics, 607, 612
- clozapine, 626
- cyclic antidepressants, 308, 309–310, 320, 322, 336, 1070
  - doxepin, 1351, 1352, 1356
- fluoxetine, 336
- hydroxyzine, 1208
- mirtazapine, 480, 487
- olanzapine, 650, 652, 1522
- paliperidone, 707
- quetiapine, 686, 1523
- risperidone, 706, 707, 708, 1521
- trazodone, 456
- ziprasidone, 757

weight gain and antagonist activity at, 757

Histone acetyltransferase, 8, 10

Histone deacetylase (HDAC), 8, 926, 935

Histone methylation, 7–9, 22, 141

Histrionic personality disorder treatment, 1327

HIV. See [Human immunodeficiency virus disease](#)

*HLA-A\*3101* genetic testing, for carbamazepine use, 958

*HLA-B\*1502* genetic testing, for carbamazepine use, 957

HNK (hydroxynorketamine), 550, 552

Home Situation Questionnaire (HSQ), 1467

Homelessness, 1253, 1258, 1601

Homeopathy, for generalized anxiety disorder, 1209, 1210

Homicidal state, 1595, 1596, 1600–1601

Homovanillic acid, 1315

Hopelessness, 1155, 1260, 1597, 1597, 1600

Hormonal contraceptive–drug interactions

- benzodiazepines, 572
- carbamazepine, 231, 963, 967
- eslicarbazepine acetate, 969
- lamotrigine, 1012
- oxcarbazepine, 960, 963, 968

- topiramate, [1030](#)
- Hormone-responsive elements, [49](#), [54](#)
- Hospital Anxiety and Depression Scale (HADS), [1205](#), [1207](#)
- Hospitalization, psychiatric
  - for acute psychosis, [1245](#)
  - for anorexia nervosa, [1345](#)
  - for bulimia nervosa, [1340](#)
  - involuntary, in psychiatric emergencies, [1595–1596](#)
    - grave disability and inability to care for self, [1601](#)
    - homicidal state, [1600](#)
    - suicidal state, [1599](#)
  - for postpartum psychopathology, [1545](#)
  - suicide during or after, [1596–1597](#)
- Hot flashes
  - fluoxetine for, [345](#)
  - mirtazapine for, [485](#)
  - paroxetine for, [385](#), [398](#)
  - sertraline for, [370](#)
  - venlafaxine for, [520](#)
- Housing support, for schizophrenia patients, [1252–1253](#)
- HPA axis. *See* [Hypothalamic-pituitary-adrenal axis](#)
- HPG axis. *See* [Hypothalamic-pituitary-gonadal axis](#)
- HPT axis. *See* [Hypothalamic-pituitary-thyroid axis](#)
- HRR (haplotype-relative risk) method of population stratification, [134–135](#)
- HSDD (hypoactive sexual desire disorder), bupropion for, [495](#), [503–504](#)
- HSQ (Home Situation Questionnaire), [1467](#)
- 5-HT (5-hydroxytryptamine). *See* [Serotonin](#)
- 5HTR2A* gene, [388](#)
- HTR7* gene, [815](#)
- 5-HTT. *See* [Serotonin transporter](#)
- 5-HTTLPR (serotonin-transporter-linked polymorphic region), [59](#), [127–128](#), [134](#), [388](#)
- Human chorionic gonadotropin, [166](#)
- Human genome sequencing, [3–4](#), [16](#), [22](#), [127](#)
  - cost of, [136–137](#)
  - ENCODE project, [136](#)
  - HapMap and 1,000 Genomes projects, [134](#), [136](#)
  - Human Genome Project, [135–136](#)
- Human immunodeficiency virus (HIV) disease, [1155](#)
  - depression and, [1154](#)
  - neuropathy and, [1400](#), [1401](#)
  - opioid use and, [1289](#), [1292](#)

- psychostimulants for fatigue in, 1094
- schizophrenia and, 1258

Huntingtin, 28–29

Huntington's disease

- genetics of, 14, 28, 122
- prevalence of, 28
- sertraline for aggression in, 371
- transgenic mouse models of, 28–30
- treatment of, 612, 1112

Hyaluronic acid, for osteoarthritis, 1408, **1410**

Hydrocodone, 1387, **1388**, 1398, **1414**

Hydrocortisone

- for acute stress disorder, 1219
- drug-enhanced exposure therapy for PTSD, 1218

Hydromorphone, **1388**

Hydroxyamitriptyline, 311

7-Hydroxyamoxapine, 306, 311, 321

8-Hydroxyamoxapine, 311

Hydroxybupropion, 497, 498, 506

5-Hydroxybuspirone, 588

6-Hydroxybuspirone, 588

8-Hydroxybuspirone, 588

γ-Hydroxybutyrate (GHB), 1069, 1611

- receptors for, 1069

2-Hydroxydesipramine, 311, 314

Hydroxyimipramine, 311

5-Hydroxyindoleacetic acid (5-HIAA), 309, 347

Hydroxylation, 13

Hydroxynefazodone, 460

Hydroxynorketamine (HNK), 550, 552

Hydroxynortriptyline, 311, 313

*p*-Hydroxyphenylacetic acid, 294

9-Hydroxyrisperidone, 706, 709–710, 721, 722. *See also* **Paliperidone**

5-Hydroxytryptamine (5-HT). *See* **Serotonin**

Hydroxyzine

- in adjustment disorders, 1602
- for generalized anxiety disorder, 1208, 1210
- for opioid withdrawal, 1614

Hyperactivity

- in ADHD, 1452
- in autism spectrum disorder, 1466, 1472
- drug-induced

- lamotrigine, 1471
- SSRIs, 1470
- Hyperalgesia, 1379
  - in fibromyalgia, 1402
  - opioid-induced, 1383, 1387, 1390
  - prostaglandin-induced, 1382
- Hyperammonemic encephalopathy, valproate-induced, 1179
- Hypercalcemia, lithium-induced, 904
- Hyperemesis gravidarum, 485, 1565
- Hyperexcitability, drug-induced
  - benzodiazepines, 570
  - buspirone, 594
- Hyperglycemia. *See also* Diabetes mellitus
  - antipsychotic-induced, 695, 1253
    - clozapine, 638
    - olanzapine, 670, 671, 672, 695
    - quetiapine, 695, 696
    - risperidone, 695, 696, 717, 718
    - ziprasidone, 695, 777, 779–780
- Hyperhedonia, 65, 90
- Hyperhomocysteinemia, 1043
- Hypericum perforatum*. *See* St. John's wort
- Hyperkinesia, drug-induced
  - paliperidone, 1463
  - SSRIs, 1447, 1448, 1449
- Hyperparathyroidism, lithium-induced, 904
- Hyperprolactinemia, 618–619, 1257
  - antipsychotic-induced, 609, 612, 618–619, 733, 1257–1258, 1499–1500
    - brexpiprazole, 748
    - iloperidone, 810, 818
    - lurasidone, 825, 1257
    - olanzapine, 672, 1439, 1462
    - paliperidone, 720, 721, 722, 1247, 1257, 1463
    - quetiapine, 696
    - risperidone, 718, 720–721, 722, 1180, 1247, 1257, 1441, 1457, 1458
  - fluoxetine-induced, 346
  - management of, 1258
  - psychosis and, 166
- Hyperpyrexia
  - amphetamine-induced, 1086
  - in neuroleptic malignant syndrome, 1257, 1516, 1614
- Hypersalivation, antipsychotic-induced, 856

- clozapine, 639
- Hypersensitivity reactions to drugs
  - antipsychotics, 1516
  - asenapine, 804–805
  - bupropion, 504
  - carbamazepine, 958
  - ketamine, 555
  - lamotrigine, 1008, **1010**
  - modafinil, 1090
  - pregabalin, 995
  - TCAs, 324
- Hypertension, 122
  - during alcohol or sedative-hypnotic withdrawal, 1613
  - drug-induced
    - bupropion, 505
    - desipramine, 322
    - desvenlafaxine, 521
    - duloxetine, 540
    - ketamine, 555
    - levomilnacipran, 541
    - modafinil, 1090
    - venlafaxine, 322, 521, 1498
  - ECT-induced, 1124
  - insomnia and, 1349
  - in metabolic syndrome, 1254
  - during opioid withdrawal, 1613
  - rebound
    - after clonidine discontinuation, 1500
    - after guanfacine discontinuation, 1501
  - in serotonin syndrome, 346
  - vascular cognitive impairment and, 1043
- Hypertensive crisis, MAOI-induced, 283, 291–292, 325, 1555, **1607**, 1615
- Hyperthyroidism, 165
  - use of MAOIs in, 290
- Hypertonia, risperidone-induced, 1463
- Hypnosis, for pain, **1396**, 1397
- Hypoactive sexual desire disorder (HSDD), bupropion for, 495, 503–504
- Hypocretin. *See* Orexin (hypocretin)
- Hypoglycemia, 73, 87
  - $\beta$ -blockers and, 864, 866
  - fluoxetine and, 346
  - MAOIs and, 290

- in neonates after prenatal valproate exposure, [1558](#)
- Hypogonadism, [1257](#)
  - opioid-induced, [1385](#)
- Hypokalemia, topiramate-induced, [1029](#), [1030](#)
- Hypokinesia, antipsychotic-induced, [609](#)
- Hypomania. *See also* [Mania](#)
  - gabapentin-induced, [989](#)
  - treatment of
    - gabapentin, [987](#)
    - lamotrigine, [895-896](#), [1003](#), [1012](#)
    - lithium, [895-896](#), [1003](#)
    - quetiapine, [1180](#)
    - risperidone, [1441](#)
    - valproate, [927](#)
- Hyponatremia
  - clozapine for polydipsia-hyponatremia syndrome, [635](#)
  - drug-induced
    - carbamazepine, [957](#), [959](#), [962](#), [1179](#)
    - citalopram, [444](#)
    - escitalopram, [444](#)
    - eslicarbazepine acetate, [960](#)
    - oxcarbazepine, [960](#), [1501](#), [1502](#)
    - paroxetine, [401](#)
    - sertraline, [371-372](#)
- Hypotension
  - dialysis-induced, [370](#)
  - drug-induced
    - aripiprazole, [737](#)
    - brexpiprazole, [737](#)
    - classic antipsychotics, [612](#), [615](#), [1516](#)
    - clonidine, [871](#), [1500](#), [1614](#)
    - clozapine, [626](#), [636](#), [637](#), [1516](#), [1521](#)
    - concurrent antihypertensive medications and, [322](#), [459](#)
    - fludrocortisone for, [290](#), [322](#)
    - iloperidone, [809](#), [810](#), [817](#)
    - ketamine, [555](#)
    - lurasidone, [822](#)
    - MAOIs, [290](#), [295](#)
    - nefazodone, [462](#)
    - olanzapine, [1179](#), [1370](#), [1516](#), [1525](#)
    - paroxetine, [398](#), [459](#)
    - prazosin, [1368](#)

- quetiapine, 693, **1370**, 1516
- risperidone, 718, 721, 1516, 1525
- TCAs, 320, 322, **1368**, **1369**, 1390
- trazodone, 456, 457, 458, 459, 463, **1369**
- ECT-induced, 1125
- Hypothalamic-pituitary-adrenal (HPA) axis, 157–164, **159**
  - in anorexia nervosa, 168
  - circadian pattern of activity of, 158
  - corticotropin-releasing hormone, 98–99
  - drug effects on
    - buspirone, 588–589
    - citalopram, 435–436
    - mirtazapine, 480
    - paroxetine, 389
  - effects on HPG axis, 168
  - immune system and, 158, 187–188, 192–194, 1157
  - in pregnancy, 167
  - in specific disorders depression, 99, 158–162, 181, 184, 389, 1153, 1156–1157
  - ECT effects on, 1107
  - psychosis, 162–163
  - PTSD, 163–164
  - in stress response, 99, 157–158, 179, 187
- Hypothalamic-pituitary-gonadal (HPG) axis, 166–168
  - in anorexia nervosa, 168
  - effects of HPA axis on, 168
- Hypothalamic-pituitary-somatotrophic axis, 165
- Hypothalamic-pituitary-thyroid (HPT) axis, 164–165
  - in mood disorders, 165
  - in PTSD, 165
- Hypothyroidism, 165
  - lithium-induced, 903–904, 1501
- Hysteresis curves, clockwise and counterclockwise, **224**, 224–225



IASP (International Association for the Study of Pain), [1378](#), [1401](#)  
Ibuprofen, [1381](#), [1382](#), [1413](#), [1507](#)  
    combined with acetaminophen, [1398](#)  
    for opioid withdrawal, [1614](#)  
    topical, [1394](#)  
IC-SOHO (Intercontinental Schizophrenia Outpatient Health Outcomes) study, [631](#)  
ICSD (*International Classification of Sleep Disorders*), [1073](#), [1074](#)  
Idazoxan, [712](#)  
IDO (indoleamine 2,3-dioxygenase), [192](#)  
IDS-C30 (30-Item Inventory of Depressive Symptomatology—Clinician-Rated), [1096](#)  
IL. *See* [Interleukins](#)  
Ileus, drug-induced  
    antipsychotics, [612](#), [618](#)  
    clozapine, [626](#)  
    TCAs, [321](#)  
Illness management and recovery (IMR), for schizophrenia, [1252](#)  
Iloperidone, [809–819](#)  
    in children and adolescents, [810](#)  
    contraindications to, [818](#)  
    dosing of, [809](#), [810](#), [817](#), [1647](#)  
    drug interactions with, [810](#), [818](#)  
    in elderly persons, [810](#), [818](#)  
    formulations of, [810](#), [1249](#)  
    history and discovery of, [809](#)  
    indications for, [811–815](#)  
        schizophrenia and schizoaffective disorder, [809](#), [811–815](#), [812–813](#)  
        pharmacogenetic studies, [814–815](#)  
    pharmacokinetics and disposition of, [810](#)  
    pharmacological profile of, [809–810](#)  
    side effects and toxicology of, [809](#), [810](#), [815–818](#), [816](#)  
        extrapyramidal side effects, [817](#), [873–874](#)  
        orthostatic hypotension, [817](#)  
        QTc prolongation, [815](#), [818](#), [1248](#)  
        weight gain/metabolic effects, [817–818](#), [1253](#)  
    structure-activity relations for, [809](#), [810](#)  
    use in pregnancy and lactation, [810](#)  
Iminodibenzyl antipsychotics, [608](#)  
Imipramine  
    dosing of, [311](#), [1633](#)

- drug interactions with
  - carbamazepine, [965](#)
  - olanzapine, [673](#)
  - SSRIs, [405](#), [425](#)
- history and discovery of, [305–306](#), [1106](#)
- indications for
  - acute stress disorder, [1219](#)
  - bulimia nervosa, [1338](#)
  - cocaine use disorder in schizophrenia, [1259](#)
  - depression, [306](#), [316](#)
    - with anxiety, [317](#), [591](#)
    - with atypical features, [317](#)
    - in bipolar disorder, [317](#)
    - vs. milnacipran, [535](#)
    - vs. paroxetine, [390](#)
    - persistent depressive disorder (dysthymia), [318](#)
    - vs. sertraline, [363](#)
  - generalized anxiety disorder, [396](#), [1206](#)
  - nocturnal enuresis in children, [319–320](#)
  - pain syndromes, [1401](#)
  - panic disorder, [318](#), [421](#), [1196](#), [1197](#)
    - vs. buspirone, [590–591](#)
- pharmacokinetics of, [311](#), [311](#), [313](#), [314](#)
- pharmacological profile of, [89](#), [306](#), [308](#)
- side effects of, [314](#), [320](#), [321](#), [323](#)
- structure–activity relations for, [306](#), [307](#)

IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials), [1417](#)

Immune system, [177–197](#)

- adaptive immunity, [22](#), [158](#), [178](#), [180](#)
- effects of stress on, [179–181](#)
- effects on brain and behavior, [189–196](#)
  - anti-inflammatory agents for depression, [194](#)
  - antidepressant effects, [194–196](#)
  - antipsychotic effects, [196](#)
  - immune system-to-brain signaling pathways, [189](#), [189–190](#)
  - pathways by which cytokines produce neuropsychiatric disturbance, [191](#), [191–194](#)
  - sickness behavior and development of depression in medically ill persons, [190–191](#)
- immune triad, [177–179](#)
- innate immunity, [158](#), [178](#), [180](#), [186](#), [191](#)

- mediating pathways for CNS effects on, 185–188
  - autonomic nervous system, 186–187
  - HPA axis, 158, 187–188
- in specific disorders
  - chronic fatigue syndrome, 185
  - depression, 178, 181–184, **182**, 1153, 1157
  - postpartum psychosis, 167–168
  - psychophysical disorders, 185, 191
  - PTSD, 185
  - schizophrenia, 185
  - seasonal affective disorder, 185
- types of immune responses, 178–179
  - immunopathological responses, 178
  - immunoprotective responses, 178
  - immunoregulatory responses, 178
- Immunosuppressant-drug interactions
  - buspirone, 594
  - carbamazepine and oxcarbazepine, **963**, 967
  - nefazodone, 462
- Imovane. *See* Zopiclone
- Impulse-control disorders
  - fluvoxamine for, 423
  - sertraline for, 371
- Impulsivity
  - in ADHD, 1452
  - in autism spectrum disorder
    - atomoxetine for, 1473
    - levetiracetam for, 1472
    - methylphenidate for, 1472
  - in personality disorders, 1314, 1315, 1330
    - antisocial personality disorder, 1328
    - borderline personality disorder, 1315
      - antidepressants for, 1320, **1321–1322**
      - antipsychotics for, 1316, **1317–1319**
      - endocannabinoids for, 1326
      - glutamatergic drugs for, 1326
      - mood stabilizers for, 1320, 1323, **1324–1325**
      - treatment guidelines for, 1327, **1327**
    - schizotypal personality disorder, 1329
  - serotonin and, 55
- IMR (illness management and recovery), for schizophrenia, 1252
- Incontinence

- antipsychotic-induced, [612](#)
- duloxetine for, [539–540](#)
- in neuroleptic malignant syndrome, [1614](#)
- Inderal. See [Propranolol](#)
- Indinavir–drug interactions
  - benzodiazepines, [572](#)
  - suvorexant, [1072](#)
- Indoleamine 2,3-dioxygenase (IDO), [192](#)
- Indomethacin, [1382](#)
- Infection
  - drug-induced
    - doxepin, [1367](#)
    - gabapentin, [987](#), [989](#)
    - lamotrigine, [1182](#)
    - sertraline, [1435](#)
  - immune response to, [178](#)
  - schizophrenia and, [185](#)
- Inflammation, [178–179](#)
  - adenosine receptor activation in, [96](#)
  - autonomic nervous system and, [186–187](#)
  - cyclo-oxygenase and, [1382](#)
  - depression and, [160](#), [162](#), [182–184](#), [190](#), [1157](#)
    - anti-inflammatory agent effects on, [194](#)
    - antidepressant effects on, [162](#), [195–196](#)
    - in medically ill patients, [190](#)
  - HPA axis and, [157](#), [159](#), [187–188](#), [192–194](#)
  - microglial PET imaging of neuroinflammatory activation in psychiatric disorders, [248–249](#)
  - MRS profiling of brain response to, [260–261](#)
  - NSAIDs for treatment of, [1381–1382](#)
  - psychophysical disorders and, [185](#)
  - PTSD and, [185](#)
  - schizophrenia and, [196](#)
  - stress-induced, [180](#)
- Informed consent for pharmacotherapy
  - antipsychotic use in elderly patients, [1626](#)
  - in children and adolescents, [1432–1433](#)
  - in pregnancy, [1569](#)
- Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), [1417](#)
- Injuries
  - drug-related falls, [1508](#)

- antipsychotics, 617, 1521
- benzodiazepines, 577-578, 1062, 1076, 1196, 1627
- SSRIs, 1449, 1508
- TCAs, 322, 1390
- self-inflicted (*See* [Self-injurious behavior](#); [Suicide and suicidal behavior](#))

Inositol

- depletion of
  - depression and, 891
  - lithium-induced, 890-891
- for OCD, 1212

Inositol-1,4,5-triphosphate (IP<sub>3</sub>), 34, 56, 60, 61, 63, 74, 78, 90

Insomnia, 1073-1076. *See also* [Sleep disturbances](#)

- during alcohol withdrawal, 1285
- after barbiturate discontinuation, 1067
- chronic, 1074
- classification of, 1073
  - based on clinical features, 1075
  - based on duration, 1073-1075
- criteria for clinical significance of, 1349
- definition of, 1073
- drug-induced (*See* [Sleep effects of drugs](#))
- idiopathic, 1074
- medical illness and, 1349-1350
- nonpharmacological treatment of, 1350
- pharmacological treatment of, 1074, 1350, 1353-1372, **1364-1370** (*See also* [Sedative-hypnotics](#))
  - alcohol-type hypnotics, 1068-1069
  - antidepressants, 1362-1363, **1368-1369**
    - doxepin, 320, 1070, 1351-1352, 1356-1358, **1367**
    - trazodone, 290, 457-458
  - antihistamines, 1069-1070, 1361-1362, **1368**
  - antipsychotics, 1363, **1370**, 1371-1372
  - barbiturates, 1065-1068
  - benzodiazepines, 1053-1065, 1351, 1353-1354, **1364**
  - in elderly persons, 1075-1076
  - γ-hydroxybutyrate/sodium oxybate, 1069
  - mechanism of action, pharmacokinetics, and dosage as determinants of drug effects, 1350-1352
  - melatonin receptor agonists, 1071-1072, 1355-1356, **1366**
    - melatonin, 1070-1071
  - nonbenzodiazepine hypnotics, 1051, 1057, **1058**, 1060, 1064, **1064**, 1351, 1354-1355, **1365**

- prazosin, 1359–1361, **1368**
- suvorexant, 1051, 1072–1073, 1358–1359, **1367**
- prevalence of, 1073, 1349
- psychiatric disorders and, 1349–1350
- psychophysiological, 1075
- rebound, after benzodiazepine discontinuation, 570, 1057, 1062, **1063**
- short-term, 1074–1075
- suicide risk and, 1597
- transient, 1074
- Insulin, interaction with MAOIs, 290, **293**
- Insulin-like growth factor, 165
- Insulin resistance, antipsychotic-induced, 1254, 1499
  - olanzapine, 670
  - quetiapine, 696
  - risperidone, 718
  - ziprasidone, 777, 779
- Insulin shock therapy, 1106
- Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study, 631
- Interferon- $\alpha$ , 192, 260
  - depression induced by, 192, 1157
  - paroxetine for prevention of, 393, **394**
- Interferon- $\gamma$ , 180
- Interleukins (IL). *See also* Cytokines
  - CRH effects on production of, 187–188
  - in depression, 162, 182–184, 1157
  - immunoregulatory functions of, 179
  - proinflammatory, 178
  - in psychophysical disorders, 185
  - in PTSD, 185
  - in seasonal affective disorder, 185
- Intermittent explosive disorder, valproate for, 931
- International Association for the Study of Pain (IASP), 1378, 1401
- International Classification of Sleep Disorders* (ICSD), 1073, 1074
- International Society for Bipolar Disorders, 1005
- International Study to Predict Optimized Treatment in Depression (iSPOT-D), 437–438
- International Union of Basic and Clinical Pharmacology/British Pharmacological Society Guide to Pharmacology, 47
- Interpersonal and social rhythm therapy, for bipolar disorder, 1186
- Interpersonal therapy (IPT)
  - for binge-eating disorder, 1344

- for bipolar disorder, 1183, 1186
- for depression, 1164–1165, 1166
- Intestinal drug metabolism, 215
- Intramuscular drugs, 212–213, 221
- Intravenous drugs, 212, 213, **214**, **217**
- Invega. *See* **Paliperidone**
- Invega Trinza. *See* **Paliperidone palmitate, 3-month injection formulation**
- Involuntary hospitalization, 1595–1596
  - for grave disability and inability to care for self, 1601
  - for homicidal state, 1600
  - for suicidal state, 1599
- Involuntary psychotropic medications, 1608
- Ion channels, 21, 47, **211**
  - calcium, 51, **62**, 71, 76, 80, 86, 87, 95, **95**
    - drug effects on
      - carbamazepine, 949
      - gabapentin, 984
      - lamotrigine, 1002
      - opioids, 101
      - oxcarbazepine, 949
      - pregabalin, 990
      - topiramate, 1018
  - chloride, 33, 47, **49**, 1054, 1055
  - glutamatergic, 85–86, 90
  - muscarinic receptor, 80
  - optogenetics and, 30, 33
  - potassium, 47, **49**, 51, 58, 60, **62**, 71, 76, 80, **95**
    - drug effects on
      - lamotrigine, 1002
      - opioids, 101
  - serotonin receptor, 61, 64
  - sodium, 33, 47, **49**, 58, 85, 97
    - drug effects on
      - carbamazepine, 949
      - eslicarbazepine acetate, 949
      - lamotrigine, 1001, 1002
      - topiramate, 1017, 1018
  - voltage-gated, 140, 141
- Ionotropic receptors, 47–50, **48–49**. *See also specific receptors*
  - adenosine, 97
  - classification of, **82**
  - GABA<sub>A</sub>, 47, **94–95**

- glutamate, [47](#), [82](#), [82-83](#), [85-90](#)
  - AMPA receptors, [82](#), [88-89](#)
  - kainate receptors, [82](#), [89-90](#)
  - NMDA receptors, [82](#), [85-88](#)
- 5-HT<sub>3</sub>, [47](#), [59](#)
- nicotinic, [47](#), [79](#), [80](#), [97](#)
- IP<sub>3</sub> (inositol-1,4,5-triphosphate), [34](#), [56](#), [60](#), [61](#), [63](#), [74](#), [78](#), [90](#)
- Iproniazid, [283](#), [286](#), [290](#), [1106](#)
  - for panic disorder, [288](#)
- IPT. See [Interpersonal therapy](#)
- Irritability
  - in antisocial personality disorder, [1328](#)
  - in autism spectrum disorder, [1466](#)
    - N*-acetylcysteine for, [1473](#), [1475](#)
    - aripiprazole for, [735](#), [738](#), [743](#), [750](#), [1468](#), [1475](#)
    - brexpiprazole for, [749](#)
    - buspirone for, [593](#)
    - clonidine for, [1473](#)
    - escitalopram for, [1470](#)
    - haloperidol for, [1469](#), [1470](#)
    - mirtazapine for, [485](#), [1471](#)
    - olanzapine for, [1468](#)
    - oxcarbazepine for, [1472](#)
    - risperidone for, [712](#), [717](#), [1466](#), [1467](#), [1475](#)
      - N*-acetylcysteine and, [1475](#)
      - buspirone and, [593](#), [1474](#)
      - celecoxib and, [1474](#)
      - memantine and, [1474](#)
      - pentoxifylline and, [1475](#)
      - riluzole and, [1474](#)
    - valproate for, [931](#), [1471](#)
  - in borderline personality disorder
    - antidepressants for, [1320](#), [1321](#), [1322](#)
    - antipsychotics for, [1318](#), [1319](#)
    - valproate for, [1323](#), [1325](#)
  - in children with generalized anxiety disorder, [1443](#)
  - in dementia, [1518](#)
  - drug-induced
    - amantadine, [863](#)
    - anticholinergic agents, [859](#)
    - bupropion, [1436](#), [1498](#)
    - clonidine, [1500](#)



- clozapine, [1464](#)
- haloperidol, [1469](#)
- lithium, [1472](#)
- mirtazapine, [1471](#)
- psychostimulants, [1453](#), [1502](#)
- reboxetine, [1471](#)
- kainate receptor abnormalities and, [90](#)
- in neonates exposed to drugs in utero
  - benzodiazepines, [576](#)
  - olanzapine, [1563](#)
  - paroxetine, [403](#)
  - TCAs, [324](#), [1554](#)
  - valproate, [1558](#)
- in obsessive-compulsive personality disorder, [1330](#)
- in premenstrual dysphoric disorder, [397](#)
- in serotonin syndrome, [346](#)
- during substance withdrawal
  - alcohol, [1285](#)
  - benzodiazepines, [573](#)
  - opiates, [1613](#)
  - SSRIs, [348](#)
- Irritable bowel syndrome, [393](#), [1401](#)
- Isocarboxazid, [283](#), [284](#), [294–295](#)
  - contraindications to, [295](#)
  - dosing of, [1639](#)
  - indications for, [294–295](#)
    - bulimia nervosa, [289](#)
  - pharmacokinetics of, [294–295](#)
  - pharmacological profile of, [286](#)
  - side effects of, [290](#), [295](#)
  - structure of, [287](#)
- Isoniazid, interaction with carbamazepine, [964](#), [965](#), [967](#)
- iSPOT-D (International Study to Predict Optimized Treatment in Depression), [437–438](#)
- ITIH3* gene, [143](#)
- Itraconazole–drug interactions carbamazepine, [964](#)
  - suvorexant, [1072](#)
- JAL (Janus tyrosine kinase), [95](#)
- Janus tyrosine kinase (JAK), [95](#)
- Jaundice
  - cholestatic, antipsychotic-induced, [618](#)

in neonates after prenatal antipsychotic exposure, 1565

Jet lag, 1070, 1072, 1074

Joint Commission on Accreditation of Healthcare Organizations, 1416–1417

Kainate (KA) receptors, 82, 89–90, 1042

topiramate effects on, 1018

Karyotype analysis, 124–125

Kava, 1209–1210

*KCNIP4* gene, 446

Kemadrin. *See* Procyclidine

Kerlone. *See* Betaxolol

Ketamine, 49, 549–557

abuse of, 549, 555–556

antidepressant effects of, 85, 86, 89, 553, 1156

neuroimaging studies of mechanism of, 267–268

antinociceptive effects of, 551

dependence on, 555

drug interactions with, 556

history and discovery of, 549

indications for, 549–555

anesthesia, 540, 550–551, 552, 554, 555

depression, 85, 267–268, 553–554, 1156, 1162, 1640

ECT and, 553–554

investigative applications, 554–555

pain syndromes, 552

postoperative pain, nausea, and vomiting, 552–553

PTSD, 554, 1218

sedation, 552

suicidality, 86, 553, 1600

mechanism of action of, 550–552, 556

overdose of, 550

pharmacokinetics and disposition of, 550

pharmacological profile of, 550

side effects and toxicology of, 555–556

psychosis, 84, 86, 656

structure–activity relations for, 549–550, 550

Ketanserin, 308

Ketoconazole–drug interactions aripiprazole, 749

brexpiprazole, 749

carbamazepine, 964, 967

cariprazine, 840

classic antipsychotics, 620

- lurasidone, 822
- quetiapine, 686
- suvorexant, 1072
- ziprasidone, 782
- $\alpha$ -Ketoglutarate, 83, 83, 92, 94-95
- Ketorolac, 1381
- Kiddie-SADS-L (Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Lifetime Version), 1435
- Kiddie-SADS-P (Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present Episode Version), 1434
- Kuhn, Roland, 305
  
- Labetalol, for ECT, 1124
- Lacrimation, during opioid withdrawal, 1613
- Lactulose, interaction with lithium, 907
- Lamotrigine, 1001-1012
  - in children and adolescents, 1440-1441, 1471, 1501
  - cognitive effects in children exposed in utero to, 935, 1011-1012
  - dosing of, 1007-1008, 1008, 1009, 1651
    - in children and adolescents, 1501
    - in pregnancy and postpartum, 1561
  - drug interactions with, 1012
    - carbamazepine, 963
    - lithium, 905
    - oxcarbazepine, 963, 968
    - valproate, 936
  - effects on brain AMPA receptors, 89
  - history and discovery of, 1001
  - indications for, 1003-1007
    - autism spectrum disorder, 1471
    - behavioral complications of dementia, 1627
    - bipolar disorder
      - in children and adolescents, 1440-1441
      - depressive episodes, 662, 942, 943, 1003, 1004-1006, 1012, 1182
      - maintenance treatment, 896, 928, 929, 1003-1004, 1006, 1012, 1184
      - mania, 1007
      - with menstrual cycle-related mood variability, 1006-1007
      - with rapid cycling, 1006
  - borderline personality disorder, 1007, 1323, 1324-1325
  - clozapine augmentation, 634
  - depression, 1007
  - PTSD, 1216

- schizophrenia, [1007](#)
- seizures, [1001](#), [1003](#)
- mechanism of action of, [1002–1003](#)
- overdose of, [1011](#)
- pharmacokinetics and disposition of, [1001–1002](#)
- side effects and toxicology of, [1008–1009](#), [1012](#), [1182](#), [1471](#), [1502](#)
  - skin reactions, [1008–1009](#), [1010](#), [1441](#), [1502](#)
  - teratogenic effects, [1011](#), [1561](#)
- structure–activity relations for, [1001](#), [1002](#)
- use in pregnancy and lactation, [1002](#), [1011–1012](#), [1549](#), [1560–1562](#)
- use in renal or hepatic disease, [1002](#)
- Largactil. *See* [Chlorpromazine](#)
- Laryngeal dystonia, antipsychotic-induced, [614](#), [872](#), [1256](#)
  - botulinum toxin for, [868](#)
- Laryngospasm, ketamine-induced, [555](#)
- Latrepiridine, [1045](#)
- Latuda. *See* [Lurasidone](#)
- Lavender oil extract, [1210](#)
- Laxatives, [1398](#)
  - use in bulimia nervosa, [1338](#)
- LC. *See* [Locus coeruleus](#)
- LD (linkage disequilibrium), [132–134](#), [136](#), [139](#)
- Leg spasm, sertraline-induced, [1444](#)
- Lennox-Gastaut syndrome, [1003](#), [1019](#)
- Lenticular pigmentation, antipsychotic-induced, [616](#), [619](#)
- Leptin, [100](#), [667](#), [670](#)
- Leukopenia, drug-induced carbamazepine, [957](#), [969](#), [1179](#), [1440](#)
  - cariprazine, [848](#)
  - classic antipsychotics, [619](#)
  - clozapine, [635–636](#)
  - olanzapine, [672](#)
  - valproate, [933](#)
- Levetiracetam
  - indications for
    - autism spectrum disorder, [1472](#)
    - panic disorder, [1197](#)
    - social anxiety disorder, [1201](#)
  - interaction with carbamazepine and oxcarbazepine, [963](#), [968](#)
- Levoamphetamine, [297](#), [1084–1085](#)
- Levobupivacaine, interaction with carbamazepine and oxcarbazepine, [963](#)
- Levodopa, interaction with bupropion, [506](#)
- Levomilnacipran

- for depression, 534, 535, **539**, 1391
- dosing of, 535, **1637**
- drug interactions with, 542
- history and discovery of, 529
- pharmacokinetics and disposition of, 533–534
- pharmacological profile of, 530–533, **531**
- side effects and toxicology of, 541–542
- structure–activity relations for, 529, **530**

Lexapro. *See* [Escitalopram](#)

LH (luteinizing hormone), 166, 168, 609, 722

*LHPP* gene, 140

Licarbazepine, 941, 942, 943, 947

- for mania, 942
- S*-enantiomer of (*See* [Eslicarbazepine acetate](#))
- Lichen simplex chronicus, doxepin for, 320

Lidocaine, 1393–1394, 1506

- pharmacokinetics in elderly persons, 1506
- topical, 1393, 1400, **1415**

Liebowitz Social Anxiety Scale (LSAS), 365, 441, 987, 994, 1199, 1200

Light-headedness

- drug-induced
  - alcohol-type hypnotics, 1069
  - benzodiazepines, 1627
  - buspirone, 593
  - desvenlafaxine, 521
  - selegiline, 297
  - TCAs, 320
  - venlafaxine, 521, 1208
- in panic disorder, 1604

Lilly Worldwide Pharmacovigilance Safety Database, 1563

Linear dose range, 220, **221**

Linkage disequilibrium (LD), 132–134, 136, **139**

Linkage studies, 3, 16, **118**, 128, 130, 131–132, 141, 144

- LOD scores, 131–132
- of population stratification, 135

Lipid profile, drug effects on

- antipsychotics, 618, **695**, 1254, 1499
  - aripiprazole, 696, 747
  - asenapine, 805
  - clozapine, 638, 1254
  - iloperidone, 818
  - lurasidone, 825

- monitoring for, 1499
- olanzapine, 669, 670, **695**, 747, 931, 1254, 1462
- quetiapine, **695**, 696, 1254
- risperidone, **695**, 696, 718, 931, 1458
- ziprasidone, **695**, 696, 779–780
- β-blockers, 864
- carbamazepine, 959
- valproate, 934
- Lipophilic drugs, 213, 225
  - amphetamine, 1086
  - benzodiazepines, 216, 564, 567, 1060
  - β-blockers, 864, **865**
  - bupropion, 496
  - classic antipsychotics, 610
  - cyclic antidepressants, 310
  - distribution in elderly persons, 1506
  - ketamine, 550
  - paroxetine, 387
  - pregabalin, 991
- Lipophilic hormones, 47, 53–54
- Lisdexamfetamine, 1087–1088, 1453
  - dosing of, **1503**, **1655**
  - FDA classification of, **1084**
  - indications for
    - ADHD, **1084**, 1087
    - binge-eating disorder, 1087–1088, 1343, 1346
    - depression, 1088, 1095
  - pharmacokinetics and disposition of, 1087
- Lithium, 889–907
  - antidepressant augmentation of, 393
  - in children and adolescents, 899–900, 1438–1439, 1441–1442, 1458–1459, 1472, 1501, **1501**
  - discontinuation before ECT, 903, 1123, 1181
  - dosing of, 220–221, 942, **1652**
    - in children and adolescents, **1501**, **1652**
  - drug interactions with, 905–907
    - ACE inhibitors, 907
    - angiotensin receptor 1 blockers, 907
    - antidepressants, 906
    - antipsychotics, 903, 905–906
    - caffeine, 907
    - calcium channel blockers, 906–907

- carbamazepine, [905](#), [961](#)
- diuretics, [900](#), [906](#)
- gabapentin, [905](#), [989](#)
- lactulose, [907](#)
- lamotrigine, [905](#)
- NSAIDs, [906](#), [1507](#)
- paroxetine, [404](#), [405](#)
- theophylline, [907](#)
- topiramate, [905](#), [1030](#)
- valproate, [905](#)
- ziprasidone, [782](#)
- effect on brain glutamate, [88](#)
- in elderly persons, [900-901](#), [903](#), [1506](#), [1507](#), [1530](#)
- familial aggregation of response to, [123-124](#)
- formulations of, [215-216](#), [890](#)
- history and discovery of, [889](#), [1106](#)
- indications for, [891-899](#), [907](#)
  - antisocial personality disorder, [1328](#)
  - autism spectrum disorder, [1472](#)
  - bipolar disorder, [891-897](#), [942](#)
    - in children and adolescents, [899-900](#), [1438-1439](#), [1441-1442](#)
    - depressive episodes, [689-690](#), [893-894](#), [1181](#)
    - mania, [891-893](#), [1178](#)
    - prophylaxis and maintenance treatment, [662](#), [895-897](#), [927-929](#), [953-955](#), [954](#), [1003-1004](#), [1183-1184](#)
    - psychotic mania, [893](#)
    - with rapid cycling, [894-895](#)
    - reduced stroke risk and, [900-901](#)
  - borderline personality disorder, [1320](#), [1324](#), [1327](#)
  - conduct disorder and aggression, [1458-1459](#)
  - depression, [897-898](#)
    - antidepressants and, [898](#), [1160](#), [1162](#)
    - in children and adolescents, [1438](#)
  - disruptive mood dysregulation syndrome, [1459](#)
  - OCD, [1212](#)
  - suicidality, [898-899](#)
- mechanism of action of, [890-891](#)
  - glycogen synthase kinase inhibition, [891](#)
  - inositol depletion, [890-891](#)
  - neurotransmitter effects, [890](#)
  - neurotrophic and neuroprotective effects, [890](#), [891](#), [900](#)
- MRI studies of brain effects of, [262](#)

- pharmacogenomics of, [226](#)
- pharmacokinetics and disposition of, [890](#)
  - in elderly persons, [1506](#), [1507](#)
- pharmacological profile of, [889-890](#)
- side effects and toxicology of, [902-905](#), [1178](#), [1438](#), [1439](#), [1458](#), [1472](#), [1501](#)
  - cardiac effects, [905](#)
    - Ebstein's anomaly after prenatal exposure, [901](#), [1555](#)
  - cognitive effects, [902-903](#)
  - monitoring for, [902](#), [1501](#)
  - neurotoxicity, [903](#)
  - parathyroid abnormalities, [904](#)
  - renal effects, [900](#), [902](#), [904-905](#), [962](#)
  - thyroid abnormalities, [903-904](#), [1178](#)
  - tremor, [903](#), [905](#), [1458](#), [1472](#), [1501](#)
  - weight gain, [902-903](#), [1178](#), [1501](#)
- structure-activity relations for, [889](#)
- use in pregnancy and lactation, [901-902](#), [1555-1556](#)
  - monitoring of nursing infants, [1570](#)
- use in renal disease, [900](#), [903](#), [904-905](#), [1178](#)

Lithium Treatment Moderate-dose Use Study (LiTMUS), [894](#)

Livedo reticularis, amantadine-induced, [863-864](#)

Liver disease patients, drug use in

- acetaminophen, [1381-1382](#)
- asenapine, [799](#)
- barbiturates, [1067-1068](#)
- benzodiazepines, [567](#), [572](#), [1285](#)
- bupropion, [498](#)
- buspirone, [588](#)
- cariprazine, [837](#)
- eslicarbazepine acetate, [947](#)
- fluvoxamine, [420](#)
- gabapentin, [990](#)
- lamotrigine, [1002](#)
- lurasidone, [822](#)
- MAOIs, [294](#)
- mirtazapine, [480](#)
- nefazodone, [460](#)
- olanzapine, [654](#)
- paroxetine, [387](#), [393](#)
- pregabalin, [995](#)
- sertraline, [362](#)



- suvorexant, [1072](#)
- topiramate, [1019](#)
- tramadol, [1383](#), [1384](#)
- venlafaxine, [516](#)
- vortioxetine, [468](#)
- ziprasidone, [760](#)
- Liver effects of drugs
  - acetaminophen, [1381](#)
  - atomoxetine, [1499](#)
  - atypical antipsychotics, [1500](#)
  - clozapine, [639–640](#)
  - bupropion, [505](#)
  - carbamazepine, [957](#), [958](#), [1179](#)
    - in nursing infants, [1560](#)
  - classic antipsychotics, [616](#), [650](#)
  - disulfiram, [1286](#)
  - iproniazid, [283](#), [290](#)
  - kava, [1209](#)
  - MAOIs, [290](#)
    - iproniazid, [283](#), [290](#)
    - phenelzine, [294](#)
    - tranylcypromine, [295](#)
  - metformin, [670](#)
  - mirtazapine, [487](#)
  - nefazodone, [459](#), [462](#), [463](#), [1215](#)
  - TCAs, [323–324](#)
  - valproate, [933–934](#), [1179](#), [1502](#)
    - in neonates after in utero exposure, [1558](#)
- Locus coeruleus (LC), [1060](#), [1061](#)
  - $\alpha_2$ -adrenergic receptors in, [76](#)
  - antidepressant effects in, [195](#)
  - glutamate receptors in, in suicidal patients, [91](#)
  - norepinephrine in, [72–73](#), [75](#)
    - in suicidal patients, [59](#)
  - norepinephrine transporter in, [73](#), [76](#)
  - physiological roles of, [72–73](#)
  - serotonin in, in suicidal patients, [59](#)
- Logarithm of odds (LOD) score, [131–132](#)
- Long-term depression (LTD), [86](#)
- Long-term potentiation (LTP), [58](#), [86](#)
  - AMPA receptors in, [88](#)
  - NMDA receptors in, [86–87](#)

Loperamide, for opioid withdrawal, [1614](#)

Lopinavir/ritonavir-drug interactions

- bupropion, [506](#)
- suvorexant, [1072](#)

Lopressor. See [Metoprolol](#)

Loratadine, interaction with nefazodone, [462](#)

Lorazepam, [572](#)

- dosing of, [1642](#)
- drug interactions with
  - olanzapine, [1610](#)
  - pregabalin, [995](#)
- indications for
  - acute psychosis, [1245](#)
  - agitation and aggression in elderly patients, [1627](#)
  - alcohol withdrawal, [1285](#)
  - behavioral emergencies, [1606](#), [1607](#), [1608](#)
    - PCP intoxication, [1611](#)
  - catatonia, [1605](#)
  - extrapyramidal side effects, [866](#), [867](#)
  - generalized anxiety disorder, [993](#)
  - insomnia, [1064](#), [1353](#), [1364](#)
  - mania, [1610](#)
  - panic disorder, [568](#)
- intramuscular, [1608](#), [1611](#), [1642](#)
- pharmacokinetics of, [564](#), [566](#), [567](#), [572](#)
- side effects of, [569](#), [570](#), [1364](#)
- structure of, [565](#)
- use in pregnancy and lactation, [1562](#), [1567](#), [1568](#)

Lorcaserin, for obesity, [64](#), [503](#)

Loxapine, [306](#)

- dosing of, [1645](#)
- indications for
  - borderline personality disorder, [1317](#)
  - schizophrenia in children and adolescents, [1465](#)
- inhaled form of, [1608](#), [1645](#)
- interaction with carbamazepine, [966](#)
- receptor affinities of, [613](#)
- side effects of, [607](#), [615](#)–[616](#)
- structure-activity relations for, [606](#), [607](#)–[608](#), [624](#), [625](#)

LSAS (Liebowitz Social Anxiety Scale), [365](#), [441](#), [987](#), [994](#), [1199](#), [1200](#)

LSD (lysergic acid diethylamide), [54](#), [57](#), [62](#), [705](#), [708](#)

LTD (long-term depression), [86](#)

LTP. See [Long-term potentiation](#)

Lu AA21004. See [Vortioxetine](#)

Lunesta. See [Eszopiclone](#)

Lurasidone, [821–828](#)

- dosing of, [822](#), [823](#), [1647](#)
- drug interactions with, [822](#)
  - carbamazepine, [966](#)
- in elderly persons, [825](#)
- formulations of, [822](#), [1249](#)
- history and discovery of, [821](#)
- indications for, [821](#)
  - bipolar depression, [824](#), [825](#), [1005](#), [1182](#)
  - risk-benefit evaluation, [824–825](#)
  - schizophrenia, [823](#), [825](#)
- mechanism of action of, [64](#)
- pharmacokinetics of, [922](#)
- pharmacological profile of, [821–822](#)
- promising features of, [825–827](#)
  - favorable metabolic profile, [825](#)
  - potential cognitive benefits of, [826](#)
    - studies in schizophrenia, [826–827](#)
- side effects and toxicology of, [825](#), [1253](#)
  - extrapyramidal side effects, [825](#), [873](#), [1247](#)
- structure-activity relations for, [821](#), [822](#)
- use in renal or hepatic disease, [822](#)

Luteinizing hormone (LH), [166](#), [168](#), [609](#), [722](#), [934](#)

Lymphadenopathy, fluoxetine-induced, [346](#)

Lymphocytes, [182](#)

- in depression, [182](#)
- stress effects on, [180](#)

Lysergic acid diethylamide (LSD), [54](#), [57](#), [62](#), [705](#), [708](#)

M receptors. *See* [Muscarinic receptors](#)

M100907, [710](#)

Machine learning, [253](#), [263](#)

to profile risk of bipolar disorder, [265–266](#)

MADRS (Montgomery-Åsberg Depression Rating Scale), [390](#), [481](#), [663](#), [665](#), [741](#), [742](#), [743](#), [745–746](#), [824](#), [846](#), [894](#), [1004](#), [1006](#), [1007](#), [1434](#), [1435](#), [1514](#)

Magnetic resonance imaging (MRI), [239](#), [240](#), [249–251](#), [261–263](#), [269](#)

arterial spin labeling, [262–263](#)

diffusion-weighted and diffusion tensor imaging, [240](#), [252](#), [259](#), [262](#)

after ECT, [1127](#)

functional (*See* [Functional magnetic resonance imaging](#))

machine learning, [253](#), [263](#)

to profile risk of bipolar disorder, [265–266](#)

multimodal approaches, [253](#), [263](#)

perfusion-weighted, [240](#), [243](#), [252](#), [262–263](#)

research applications of, [252–253](#)

in specific disorders

autism spectrum disorder, [262](#)

depression, [163](#), [261–262](#), [263](#)

epilepsy, [242](#)

low back pain, [1405](#), [1406](#)

schizophrenia, [262](#)

T1- and T2-weighted, [250–251](#)

technical aspects of, [249–251](#)

volumetric methods, [261–262](#)

Magnetic resonance spectroscopy (MRS), [240](#), [247](#), [252](#), [260–261](#), [261](#), [269](#)

in depression, [260–261](#)

antidepressant effect of ketamine, [268](#)

GABA imaging, [260](#), [984](#)

of ECT effects, [1107](#)

glutamate imaging, [260–261](#), [261](#), [1108](#)

of ketamine effects in OCD, [554](#)

technical aspects of, [260](#)

Magnetic seizure therapy (MST), [268](#), [1132](#), [1163](#)

Magnetoencephalography (MEG), [240](#), [253](#), [263–264](#), [268](#), [269](#)

of antidepressant effect of ketamine, [268](#)

technical aspects of, [263–264](#)

Maintenance of Wakefulness Test, [1091](#)

Major depressive disorder (MDD). *See* [Depression](#)

Malignant melanoma, [181](#), [196](#)

Mammalian target of rapamycin (mTOR), [551](#), [556](#)

Mammary hypertrophy, fluoxetine-induced, [346](#)

Mania. *See also* [Bipolar disorder](#)

dopamine in, [68](#)

drug-induced in, [68](#)

antidepressants, [317](#), [662](#)

venlafaxine, [501](#)

benzodiazepines, [570](#)

gabapentin, [989](#)

medical evaluation of, [1605](#)

in schizophrenia, [1244](#)

Mania Rating Scale (MRS), [770](#), [771](#), [772](#), [1007](#)

Mania treatment

atypical antipsychotics, [1179–1180](#), [1610](#)

aripiprazole, [738](#), [741](#), [1180](#), [1439](#), [1610](#)

asenapine, [799](#), [802–803](#), [1180](#), [1439](#)

cariprazine, [71](#), [844](#), [845](#), [1180](#)

in children and adolescents, [663](#), [773](#), [899–900](#), [1438–1440](#), [1441–1443](#)

clozapine, [632](#)

in elderly persons, [1530–1531](#)

olanzapine, [661–662](#), [663](#), [1179](#), [1439](#), [1610](#)

paliperidone, [1181](#)

quetiapine, [892](#), [1180](#), [1439–1440](#), [1610](#)

risperidone, [716](#), [899–900](#), [1179–1180](#), [1439](#), [1610](#)

ziprasidone, [770](#), [770–771](#), [773](#), [892–893](#), [1180](#), [1440](#), [1610](#)

benzodiazepines, [1620](#)

carbamazepine, [893](#), [941](#), [942](#), [950](#), [951–952](#), [1179](#)

in children and adolescents, [1440](#), [1441](#)

in children and adolescents, [1438–1443](#)

classic antipsychotics, [1179](#)

ECT, [1110–1111](#), [1180–1181](#)

in children and adolescents, [1443](#)

emergency management, [1610](#)

eslicarbazepine acetate, [950](#), [951–952](#)

gabapentin, [987](#)

goal of, [1177](#)

lamotrigine, [1007](#)

in children and adolescents, [1440–1441](#)

lithium, [891–893](#), [1178](#), [1610](#)

vs. antipsychotics, [892–893](#)

vs. carbamazepine, [893](#), [950](#)

in children and adolescents, [899–900](#), [1438–1439](#), [1441–1442](#)

- in elderly persons, [900–901](#)
- with gabapentin, [893](#)
- for psychotic mania, [893](#)
- vs. valproate, [893](#)
- oxcarbazepine, [941](#), [942](#), [947](#), [950](#), [951–952](#), [1179](#)
  - in children and adolescents, [1440](#)
- tamoxifen, [1181](#)
- valproate, [738](#), [741](#), [803](#), [923](#), [926–927](#), [1178–1179](#), [1610](#)
  - in children and adolescents, [899–900](#), [1440](#), [1441–1442](#)
  - vs. lithium, [893](#)
  - in patients with head trauma or neurodevelopmental/neurodegenerative disorders, [929–930](#)

MAOIs. *See* [Monoamine oxidase inhibitors](#)

MAPK (mitogen-activated protein kinase), [53](#), [101](#), [192](#), [194](#)

Maprotiline

- dosing of, [311](#), [1634](#)
- indications for
  - depression, [306](#)
    - with anxious distress, [317](#)
    - vs. paroxetine, [390](#)
  - pain syndromes, [319](#)
  - panic disorder, [1197](#)
- interaction with MAOIs, [293](#)
- pharmacokinetics of, [311](#)
- pharmacological profile of, [308](#)
- side effects of, [321](#)
- structure–activity relations for, [306](#), [307](#)

Marks-Mathews Fear Questionnaire (FQ), [365](#), [1195](#), [1203](#), [1204](#)

Marks-Sheehan Main Phobia Severity Scale (MSMPSS), [1203](#)

Masked facies, antipsychotic-induced, [614](#), [856](#), [1256](#)

Massage therapy, [1396](#), [1404](#)

MBCT (mindfulness-based cognitive therapy), [1164](#)

MCCB (Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery), [825](#)

McLean Study of Adult Development (MSAD), [1315](#)

mCPP (*m*-chlorophenylpiperazine), [456](#), [460](#), [463](#)

MDD (major depressive disorder). *See* [Depression](#)

MDMA. *See* [3,4-Methylenedioxy-N-methamphetamine](#)

*MDR1* gene, [388](#). *See also* [ABCB1](#) gene

Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), [825](#)

MEC (minimal effective concentration) of drug, 213, **214**, 216, 217, **217**, 220, **221**

Medazepam, 1060, **1061**

Medical illness. *See also specific illnesses*

depression and, 1153, **1154**

immune function and, 190–191

paroxetine for, 393

sertraline for, 369–370

ECT in, 1121–1122

insomnia and, 1349–1350

MAOI use in, 290, 294, 295

opioid-related disorders and, 1289

Medical marijuana, 1395

Medication overuse headache (MOH), 1411

Meduna, Lazlo, 1106

MEG. *See* [Magnetoencephalography](#)

Meiosis, 131, 132

Melanocyte-stimulating hormone, **100**

Melatonin, 1070–1071, 1355–1356

age-related decline in production of, 1070, 1071

attenuation of antipsychotic-induced weight gain by, 671

for circadian rhythm sleep disorders, 1070, 1356

dosing of, 1070, 1355, **1366**

for insomnia, 1355–1356, **1366**

in autism spectrum disorder and neurodevelopmental disorders, 1355–1356

in elderly persons, 1070, 1071, 1076

prolonged-release formulation of, 1071

in regulation of circadian rhythmicity, 1070, 1350, **1351**, 1355

Melatonin receptor agonists, 1071–1072, 1355–1356

Melatonin (MT) receptors, 1071, 1355, 1356

*Melissa officinalis*, 1045

Mellaril. *See* [Thioridazine](#)

Meloxicam, **1413**

Memantine, 1042–1043, 1045

combined with donepezil, 1043

dosing of, 1043, **1658**

formulations of, 1043, **1658**

indications for

Alzheimer's disease, 1043

anticholinesterase inhibitors and, 1040, 1042–1043

autism spectrum disorder, 1474

- schizophrenia, [1042](#)
- vascular cognitive impairment, [1044](#)
- use in renal disease, [1043](#)
- Memory
  - changes in gene expression and, [14](#)
  - working
    - fMRI studies of, [257–258](#)
    - N-back test of, [257](#)
- Memory impairment. *See also* [Cognitive impairment](#)
  - drug-induced
    - anticholinergic agents, [859](#)
    - antipsychotics, [614](#)
    - benzodiazepines, [570](#), [1627](#)
    - γ-hydroxybutyrate, [1069](#)
    - lithium, [903](#)
    - opioids, [1385](#)
    - topiramate, [1021](#), [1028](#), [1029](#)
  - ECT-induced, [1125–1126](#)
  - medical evaluation of, [1604](#)
  - role of CREB in, [10](#)
  - in schizophrenia, [1243](#), [1249](#)
  - in Wernicke-Korsakoff syndrome, [1613](#)
- Mendelian disorders, [122](#), [131](#)
- Meningitis, aseptic, lamotrigine-induced, [1010](#)
- Menopausal symptoms
  - depression, [167](#)
  - treatment of
    - desvenlafaxine, [520](#)
    - fluoxetine, [345](#)
    - mirtazapine, [485](#)
    - paroxetine, [385](#), [398](#)
    - sertraline, [370](#)
    - venlafaxine, [520](#)
- Menstrual cycle, [166](#). *See also* [Premenstrual dysphoric disorder](#); [Premenstrual syndrome](#)
  - bipolar disorder and, [934](#)
  - borderline personality disorder and, [1326](#)
  - drug-related irregularities of
    - antipsychotics, [618–619](#)
    - benzodiazepines, [1065](#)
    - valproate-induced polycystic ovarian syndrome, [934](#), [1185](#), [1501](#), [1502](#)
  - escitalopram-induced cramps, [1434](#)



- lamotrigine for bipolar disorder patients with mood variability related to, [1006–1007](#)
- weight loss and, [168](#)
- Meperidine, [1381](#), [1388](#), [1615](#)
  - interaction with MAOIs, [292](#), [293](#), [297](#), [1555](#), [1615](#)
- Meprobamate, [563](#), [1052](#)
- Mesocortical dopamine circuit
  - effect of antipsychotic D<sub>2</sub> receptor blockade of, [608](#), [611](#), [612](#), [732](#)
    - risperidone and paliperidone, [711](#), [712](#)
    - ziprasidone, [756](#)
  - in schizophrenia, [732](#)
- Mesolimbic dopamine circuit, [65](#), [66](#), [68](#)
  - effect of antipsychotic D<sub>2</sub> receptor blockade on, [608](#), [611](#), [612](#)
    - aripiprazole, [737](#)
    - brexpiprazole, [737](#)
    - clozapine, [628](#)
    - olanzapine, [651](#)
    - risperidone, [706](#), [712](#)
  - neurotensin receptor modulation of, [656](#)
  - in schizophrenia, [732](#)
- Mesoridazine, [605](#), [607](#), [615–616](#)
- Metabolic acidosis, topiramate-induced, [1029–1030](#)
- Metabolic effects of antipsychotics, [1246](#), [1247–1248](#), [1253–1254](#), [1499](#). *See also* [Diabetes mellitus](#); [Dyslipidemia](#); [Weight changes](#)
  - aripiprazole, [747](#)
  - asenapine, [804](#), [805](#)
  - cariprazine, [847](#), [847](#), [849](#), [850](#)
  - classic antipsychotics, [618](#)
  - clozapine, [626](#), [628](#), [637–638](#), [1248](#), [1516](#)
  - in elderly persons, [1516](#), [1525](#)
  - iloperidone, [817–818](#)
  - lurasidone, [825](#)
  - management of, [1253–1254](#)
  - monitoring for, [638](#), [1254](#), [1499](#)
  - olanzapine, [669–672](#), [674](#), [696](#), [1248](#), [1516](#), [1522](#)
  - paliperidone, [718](#)
  - quetiapine, [694–696](#), [695](#), [1463](#)
  - risperidone, [695](#), [696](#), [718](#), [1462](#)
  - ziprasidone, [695](#), [696](#), [757](#), [777–780](#), [779](#)
- Metabolic ratio (MR), [228–229](#), [229](#)
- Metabolism of drugs, [214–216](#). *See also* [Pharmacokinetics](#)

cytochrome P450 enzymes in, 215, 229–230, **231**, 1507–1508 (*See also*  
Cytochrome P450 enzymes)  
in elderly persons, 1506  
first-pass effect, 214–215, 310, 1507  
hepatic, 213, 225  
Metabolites of drugs, 209, 215, 225–226, 797  
  amitriptyline, 311  
  amoxapine, 306, 311–312  
  aripiprazole, 734, 735, 736, 749  
  barbiturates, 1067  
  brexpiprazole, 737  
  bupropion, 497, 498  
  buspirone, 588  
  carbamazepine, 944  
  cariprazine, 833, **835**, 837–838, 840  
  classic antipsychotics, 609  
  clozapine, 626, 630  
  desipramine, 311  
  diazepam, **566**, 572, 576, 1059, 1060  
  duloxetine, 534  
  fluoxetine, 340, 1507  
  flurazepam, **566**, 1060, **1064**  
  imipramine, 311  
  ketamine, 550  
  milnacipran, 534  
  mirtazapine, 480  
  moclobemide, 295, 296  
  nefazodone, 460  
  nortriptyline, 311  
  olanzapine, 653  
  oxcarbazepine, 941, 942  
  phenelzine, 294  
  risperidone, 706, 709, 722  
  selegiline, 215, 297  
  sertraline, 360, 361  
  trazodone, 456  
  venlafaxine, 515, 516, 523  
  ziprasidone, 760  
Metabotropic glutamate receptors, **82**, 90–91, **247**  
Metadate CD, Metadate ER. *See* Methylphenidate  
Metallic taste, eszopiclone-induced, **1365**  
Metaxolone, 1393

Metformin, [670–671](#), [1254](#)

Methadone

drug interactions with

carbamazepine and oxcarbazepine, [963](#), [967](#)

fluvoxamine, [425](#)

for opioid use disorder, [1289–1290](#)

detoxification, [1289](#), [1291](#)

maintenance treatment, [1284](#), [1290](#), [1291–1292](#), [1388](#)

vs. buprenorphine, [1292](#)

overdose of, [1289](#), [1388](#), [1390](#)

for pain, [1387](#), [1388](#), [1388–1390](#)

pharmacokinetics of, [1289](#)

racemic, [226](#)

side effects of, [1289–1290](#), [1292](#), [1390](#)

use in pregnancy, [1293–1294](#), [1390](#)

Methamphetamine, [297](#)

for cocaine dependence, [1301](#)

dosing of, [1655](#)

dependence on

bupropion for, [1301–1302](#)

buspirone for, [71](#)

topiramate for, [1025](#)

mortality from, [1086](#)

side effects of, [1086](#)

structure–activity relations for, [1083](#)

violent behavior during intoxication with, [1611](#)

Methocarbamol

for opioid withdrawal, [1614](#)

for pain, [1393](#), [1413](#)

Methohexital, for ECT, [1122](#), [1125](#)

postictal agitation, [1123](#)

3-Methoxy-4-hydroxyphenylglycol (MHPG), [309](#)

Methsuximide, interaction with carbamazepine, [965](#)

*N*-Methyl-D-aspartate (NMDA) receptor agonists

D-cycloserine, [86](#), [92](#), [553](#), [1202](#), [1204](#), [1451](#)

in schizophrenia, [86](#), [656](#)

*N*-Methyl-D-aspartate (NMDA) receptor antagonists, [85–86](#)

acamprosate, [87](#)

antidepressant effects of, [85](#), [1156](#)

dizocilpine (MK-801), [86](#), [710](#), [711](#), [826](#)

ketamine, [84–85](#), [550](#), [551](#), [656](#), [711](#), [1156](#), [1218](#)

memantine, [87](#), [1042–1043](#), [1045](#)

- phencyclidine, [84](#), [652](#), [656](#), [711](#)
- psychosis induced by, [84](#), [555](#)
- N-Methyl-D-aspartate (NMDA) receptors, [47](#), [48-49](#), [82-83](#), [85-88](#), [1042](#)
  - adenosine modulation of, [97](#)
  - anti-NMDA receptor encephalitis, [87](#), [1113](#)
  - autoimmune antibodies to, [87](#)
  - brain distribution of, [85](#)
  - Cftr-loxP recombination technology for deletion of, [30](#)
  - classification of, [82](#)
  - compared with AMPA receptors, [88](#)
  - compared with kainate receptors, [90](#)
  - drug effects on, clozapine, [626](#)
  - excessive activation of, [87](#)
  - glycine in activation of, [91](#), [92](#)
  - in habituation process, [1326](#)
  - in long-term potentiation, [86-87](#)
  - in mood disorders, [84](#), [91](#)
  - in mouse model of Huntington's disease, [28](#), [29](#)
  - psychosis due to hypofunction of, [87](#)
  - in regulation of synaptic plasticity, [30](#), [86-87](#)
  - in schizophrenia, [84](#)
- S-Methyl-dihydroziprasidone, [760](#)
- $\alpha$ -Methyl-*p*-tyrosine (AMPT), [66-67](#), [72](#), [74-75](#), [315](#)
- Methylation, [7-9](#), [141](#)
- Methylene blue, [1218](#)
- 3,4-Methylenedioxy-*N*-methamphetamine (MDMA, Ecstasy), [1086](#)
  - in PTSD, [1218](#)
- L-Methylfolate, for depression, [1165](#)
- Methylin, Methylin ER. *See* [Methylphenidate](#)
- Methylphenidate, [1088-1089](#)
  - discontinuation syndrome with, [1089](#)
  - dosing of, [1085](#), [1453](#), [1655-1657](#)
    - in children and adolescents, [1503](#)
  - drug interactions with, [1089](#)
    - barbiturates, [1068](#)
    - carbamazepine and oxcarbazepine, [963](#), [966](#)
    - clonidine, [1500](#)
    - MAOIs, [293](#), [1089](#)
  - FDA classification of, [1084](#)
  - indications for
    - ADHD, [1084](#), [1092](#), [1301](#), [1452-1453](#)
    - vs. atomoxetine, [1454](#)

- with autism spectrum disorder, 1472
- clonidine and, 1455, 1459–1460
- amphetamine dependence, 745
- autism spectrum disorder, 1472
- depression, 1095
  - antidepressant augmentation, 1160
- drug-induced sexual dysfunction, 399
- fatigue, 1094
- narcolepsy, 1084
- poststroke depression, 1093
- stimulant dependence, 1301
- mechanism of action of, 70, 71, 1088
- overdose of, 1089
- pharmacokinetics and disposition of, 1088
- preparations of, 214, 1085, 1503
- racemic, 226, 1088
- side effects and toxicology of, 1088–1089, 1472
  - growth effects in children, 1504
  - sudden death, 1504
- structure–activity relations for, 1088
- use in tic disorders, 1502

Methylxanthines, 97

Methysergide, for serotonin syndrome, 1615

Metoprolol, 864, 865, 1414

Metrifonate, 1042

METS (Use of Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia) study, 670

Mexiletine, 1393–1394, 1401

MHPG (3-methoxy-4-hydroxyphenylglycol), 309

Mianserin, 390, 457

- for depression, 390
- interaction with carbamazepine, 965
- mechanism of action of, 63
- for pain, 1391

Microarray technology, 22, 130, 228

Microsatellite markers, 128–129

- linkage studies of, 131

Midazolam

- for ECT, 1123
- interaction with carbamazepine and oxcarbazepine, 963, 966
- intravenous, 1060
- pharmacokinetics of, 215, 566, 1507

## Mifepristone

- for bipolar depression, [1183](#)
- for drug-enhanced exposure therapy for PTSD, [1218](#)
- interaction with carbamazepine and oxcarbazepine, [963](#), [967](#)

## Migraine, [1379](#), [1408](#)

- with aura, [1408](#), [1411](#)
- bipolar disorder and, [986](#)
- bupropion-induced, [504](#)
- prophylaxis for
  - gabapentin, [986](#)
  - topiramate, [1017](#), [1019](#)
- vs. tension-type headache, [1411](#)
- treatment of, [1414](#)–[1415](#)
  - buspirone, [593](#)
  - divalproex, [923](#)
  - fluoxetine, [344](#), [345](#)
  - stepped-care approach, [1411](#)
  - triptans, [1411](#), [1411](#), [1414](#)

## Milnacipran

- dosing of, [532](#), [535](#), [542](#), [1637](#)
- drug interactions with, [542](#)
- history and discovery of, [529](#)
- indications for, [534](#)
  - depression, [535](#), [538](#), [543](#)
    - vs. SSRIs, [391](#), [535](#), [538](#)
    - vs. TCAs, [535](#)
  - pain syndromes, [539](#), [1391](#), [1414](#)
    - fibromyalgia, [1403](#), [1403](#)–[1404](#)
- overdose of, [541](#), [543](#)
- pharmacokinetics and disposition of, [533](#)–[534](#)
- pharmacological profile of, [530](#)–[533](#), [531](#)
- side effects and toxicology of, [541](#), [1404](#)
- structure–activity relations for, [529](#), [530](#)

## Mindfulness-based cognitive therapy (MBCT), [1164](#)

## Mineralocorticoid receptor (MR), [158](#), [159](#)

- in depression, [160](#)–[161](#)

## Mineralocorticoids, downregulation of 5-HT<sub>1A</sub> receptor expression by, [60](#)

## Mini-Mental State Exam (MMSE), [485](#), [684](#), [1522](#), [1527](#)

## Minimal effective concentration (MEC) of drug, [213](#), [214](#), [216](#), [217](#), [217](#), [220](#), [221](#)

## Mirtazapine, [479](#)–[489](#)

- in children and adolescents, [1436](#), [1438](#), [1471](#), [1498](#), [1498](#)

dosing of, **1639**

drug interactions with, **488, 489**

- carbamazepine and oxcarbazepine, **963, 965**

in elderly persons, **483, 487, 488, 1506, 1515**

history and discovery of, **479**

indications for, **481–486, 489**

- akathisia, **486**
- alcohol use disorder, **484**
- autism spectrum disorder, **1471**
- depression, **481–483**
  - in Alzheimer's disease, **485–486**
  - with anxiety, **483**
  - augmentation of other antidepressants, **482, 1160**
  - in children and adolescents, **485, 1436, 1438**
  - in elderly persons, **483**
  - lithium and, **898**
  - vs. paroxetine, **391, 481**
  - persistent depressive disorder (dysthymia), **483**
  - with sexual dysfunction, **482–483**
  - vs. trazodone, **457**
  - treatment-resistant illness, **1162**
  - with venlafaxine, **288, 481–482**
- generalized anxiety disorder, **483, 1208**
- insomnia, **482, 1362, 1369**
  - in adjustment disorders, **1602**
- nausea, **484–485**
- obstructive sleep apnea, **484**
- OCD, **483–484**
- pain syndromes, **484, 1392**
- panic disorder, **1196, 1197**
- pervasive developmental disorders, **485**
- PTSD, **484**
- schizophrenia, **486**
- social anxiety disorder, **483, 1199, 1200**
- SSRI discontinuation symptoms, **1196**
- vasomotor menopausal symptoms, **485**

mechanism of action of, **63**

overdose of, **488, 489**

pharmacokinetics of, **480**

- in elderly persons, **1506**

pharmacological profile of, **310, 479–480, 489**

side effects and toxicology of, **486–487, 489, 1369, 1471, 1498**

- structure-activity relations for, 479, **480**
- use in hepatic or renal disease, 480
- use in pregnancy and lactation, 485, 487-488, 1553, 1554

Mitogen-activated protein kinase (MAPK), 53, 101, 192, 194

Mivacurium, interaction with carbamazepine and oxcarbazepine, **963**

Mixed amphetamine salts, **1085**, 1087, 1092, 1453, **1503**. *See also*  
[Amphetamines](#)

MK-801 (dizocilpine), 86, 710, 711, 826

ML398, 72

MMSE (Mini-Mental State Exam), 485, 684, 1522, 1527

MMT (methadone maintenance treatment), 1284, 1290, 1291-1292

- during pregnancy, 1293-1294

Moclobemide, 283, **284**, 295-297, 298

- dietary interactions with, 296-297
- drug interactions with, 297
  - cimetidine, 297
  - meperidine, 297
  - paroxetine, 405
- indications for, 296
  - depression, 296
    - psychotic depression, 296
  - social anxiety disorder, 289, 296, 1201
- overdose of, 296
- pharmacokinetics of, 296
- pharmacological profile of, 295-296
- side effects of, 296
- structure of, **287**

Modafinil, 1045, 1089-1090

- in children and adolescents, 1090
- dosing of, **1654**
- drug interactions with, 1090
  - carbamazepine and oxcarbazepine, **963**
  - triazolam, 1089
- FDA classification of, **1084**
- indications for, **1084**, 1089, 1092
  - ADHD, 1092
  - cocaine dependence, 1093, 1302
  - depression, 1096
    - antidepressant augmentation, 1160
  - in bipolar disorder, 1096
- fatigue, 1094
- narcolepsy, 1089, 1094



- obstructive sleep apnea/hypopnea syndrome, 1089, 1094–1095
- schizophrenia, 1096
- traumatic brain injury patients, 1093
- mechanism of action of, 1089–1090
- overdose of, 1090
- pharmacokinetics and disposition of, 1089, 1507
- side effects and toxicology of, 1090
- structure–activity relations for, 1089
- MOH (medication overuse headache), 1411
- Molecular biology, 3–35
  - cell biology of neurons and glia, 4–5, 5
  - experimental approaches to determining and manipulating gene expression, 13–19
    - cloning of DNA, 14–16, 15
    - differential display, 16–17
    - gene delivery into mammalian cells, 17–19
  - genome-editing technologies, 4, 22–25, 24
  - human genome sequencing, 3
  - inhibition of cellular gene expression, 19–22
    - chromatin immunoprecipitation, 21–22
    - RNA interference, 19–20, 20
    - RNAi applications, 21
    - RNAi knockdown of gene expression, 20–21
  - molecular variations in genome, 126–130
    - alleles, genotypes, and haplotypes, 126–127
    - copy number variants, 127
    - insertion/deletion polymorphisms, 127–128, 141
    - microsatellites, 128–129
    - single nucleotide polymorphisms, 129–130
  - optogenetics, 4, 30–33, 31–32
  - principles of gene expression, 5–7
    - DNA replication, 6
    - genes and DNA, 5–6
    - transcription, 6
    - translation, 7
  - proteomics and beyond, 25, 33–34, 136
  - regulation of gene expression, 7–13
    - chromatin and DNA methylation, 7–9
    - modification of nascent polypeptide chain, 13
    - non-coding RNAs, 13
    - posttranscriptional modification of RNA, 10–11, 12
    - RNA editing, 11–13

- RNA polymerases, [9](#), [9-10](#)
- transcription factors, [10](#), [11](#)
- tissue-specific gene manipulation, [30](#)
- transgenic and gene-targeting techniques, [25-26](#), [27](#)
- use of mutant mice in studies of brain disease, [27-30](#)
- Molindone, [603](#)
  - interaction with paroxetine, [404](#)
  - receptor affinities of, [613](#)
  - for schizophrenia in children and adolescents, [1465](#)
  - side effects of, [615-616](#)
  - structure-activity relations for, [606](#), [608](#)
- Monitoring of Oral Ziprasidone As Rescue Therapy (MOZART) study, [768](#)
- Monoamine oxidase (MAO), [284-285](#)
  - in depression, [69](#)
  - in dopamine metabolism, [67](#)
  - enzyme kinetics of, [285](#)
  - inherited disorders associated with, [284-285](#)
  - MAO-A and MAO-B, [284-285](#)
  - in norepinephrine metabolism, [75](#)
  - PET labeling studies of, [69](#), [265](#), [285](#)
  - in serotonin metabolism, [55](#), [57](#)
- Monoamine oxidase inhibitors (MAOIs), [283-299](#). *See also specific drugs*
  - dietary interactions with, [283](#), [291-292](#), [292](#), [296-297](#), [298](#), [1615](#)
  - drug interactions with, [292-294](#), [293](#), [1615](#)
    - barbiturates, [1068](#)
    - benzodiazepines, [567](#), [572](#)
    - bupropion, [1297](#)
    - buspirone, [594](#)
    - carbamazepine, [965](#)
    - desvenlafaxine, [523](#)
    - duloxetine, [542](#)
    - levomilnacipran, [542](#)
    - meperidine, [292](#), [297](#), [1555](#), [1615](#)
    - methylphenidate, [1089](#)
    - milnacipran, [542](#)
    - SSRIs, [230](#), [297](#), [346](#), [373](#), [404](#), [405](#), [425](#), [446](#)
    - St. John's wort, [1165](#)
    - TCAs, [325](#)
    - trazodone, [459](#)
    - venlafaxine, [523](#)
    - vortioxetine, [473](#)
  - history and discovery of, [283](#)

ID card/bracelet for patients receiving, 294

indications for, 286–289, **287**, 299

- borderline personality disorder, 1316, **1321**
- bulimia nervosa, 289, 1338
- chronic pain, 289
- depression, 286–288
  - with atypical features, 286–288, 317, 1159
  - in bipolar disorder, 317
  - lithium and, 898
  - maintenance treatment, 290
  - persistent depressive disorder (dysthymia), 288
  - psychotic, 296
  - treatment-resistant illness, 1162
  - generalized anxiety disorder, 289
  - neurological diseases, 289
  - obsessive-compulsive disorder, 289
  - panic disorder, 288–289, 1197
  - premenstrual dysphoria, 289
  - PTSD, 289
  - social anxiety disorder, 289, 296, 1201

irreversible, 283, **284**, 286–294

isocarboxazid, 294–295

mechanism of action of, 54, 55, 69

moclobemide, 295–297

overdose of, 1316

pharmacological profile of, 59, 286

phenelzine, 294

reversible, 283, **284**, 286, **287**

selectivity of, 283, **284**

selegiline hydrochloride, 215, 297–298

selegiline transdermal system, 298

side effects of, 289–290, 1159

- hypertensive crisis, 283, 291–292, 325, 1555, 1615

structure of, 283, **284**, 286, **287**

switching to/from

- SSRIs, 340, 346, 405
- venlafaxine, 523

tranylcypromine, 295

use in hepatic disease, 294

use in pregnancy and lactation, 1555

Monoamines, 46, 50, 54. *See also* Dopamine; Norepinephrine; Serotonin

Montgomery-Åsberg Depression Rating Scale (MADRS), 390, 481, 663, 665, 741, 742, 743, 745–746, 824, 846, 894, 1004, 1006, 1007, 1434, 1435, 1514

Mood stabilizers. *See also specific drugs*

antipsychotics and, 230, 611–612

in children and adolescents, 1501–1502

dosage and monitoring of, 1501, 1501

side effects of, 1501–1502

gabapentin, 983–990, 995

indications for

autism spectrum disorder, 1471–1472

borderline personality disorder, 1320, 1323, 1324–1325, 1327

mania, 1177–1181

in children and adolescents, 1440–1443

lamotrigine, 1001–1012

lithium, 889–907

pregabalin, 990–995

topiramate, 1017–1031

use in pregnancy and lactation, 1555–1562

valproate, 923–936

Morphine, 99, 101, 1381, 1384, 1387, 1394, 1414

for acute stress disorder, 1219

combined with acetaminophen, 1398

combined with gabapentin, 1398

dosing of, 1387, 1388, 1389

for lumbar root pain, 1401

for osteoarthritis, 1408

tolerance to, 101

Mortality

alcohol-related, 1284

in anorexia nervosa, 666, 1344

antipsychotic-related risk in elderly dementia patients, 424, 663, 717, 774, 818, 825, 848, 1370, 1517, 1520, 1612, 1625–1626

in delirium, 1612

in neuroleptic malignant syndrome, 1257

in schizophrenia, 618

in serotonin syndrome, 346

sudden cardiac death

psychostimulants and, 1503–1504

TCAs and, 319, 323, 324

from suicide, 1155, 1596 (*See also Suicide and suicidal behavior*)

Motion sickness, 861

## Motivation

- loss, in depression, [68](#)
- mesolimbic dopamine circuit and, [65](#), [68](#)
- reward-processing paradigms and, [258](#)

## Motivational interviewing

- for depression, [1164](#)
- for smoking cessation, [1299](#)

MOZART (Monitoring of Oral Ziprasidone As Rescue Therapy) study, [768](#)

MP-214. *See* [Cariprazine](#)

MR. *See* [Mineralocorticoid receptor](#)

MR (metabolic ratio), [228–229](#), [229](#)

MRI. *See* [Magnetic resonance imaging](#)

MRS. *See* [Magnetic resonance spectroscopy](#)

MRS (Mania Rating Scale), [770](#), [771](#), [772](#), [1007](#)

MSAD (McLean Study of Adult Development), [1315](#)

MSMPSS (Marks-Sheehan Main Phobia Severity Scale), [1203](#)

MST (magnetic seizure therapy), [268](#), [1132](#), [1163](#)

MTA (Multimodal Treatment of ADHD) study, [1504](#)

*MTHFR* gene, [1559](#)

mTOR (mammalian target of rapamycin), [551](#), [556](#)

Multimodal Treatment of ADHD (MTA) study, [1504](#)

Multiple sclerosis, [368](#), [1094](#), [1395](#), [1605](#)

Muscarinic (M) receptors, [62](#), [79](#), [80](#)

- antagonists of, [80](#)

- drug effects on

  - antihistamines, [861](#)

  - aripiprazole, [734](#), [735](#)

  - asenapine, [797](#)

  - brexpiprazole, [734](#), [735](#)

  - classic antipsychotics, [612](#), [618](#)

  - clozapine, [626](#), [636](#), [1521](#)

  - cyclic antidepressants, [308](#), [309](#), [321](#), [336](#)

  - fluoxetine, [336](#)

  - olanzapine, [650](#), [652](#), [1522](#)

  - paroxetine, [386](#)

  - trihexyphenidyl, [856](#), [858](#)

  - ziprasidone, [757](#)

Muscimol, [1054](#), [1055](#)

Muscle cramps, MAOI-induced, [290](#)

## Muscle rigidity

- antipsychotic-induced, [609](#), [614](#), [617](#), [816](#), [856](#), [1256](#)
- in neuroleptic malignant syndrome, [617](#), [639](#), [1257](#), [1614](#)

- in serotonin syndrome, [1615](#)
- Muscle tension, during benzodiazepine withdrawal, [573](#)
- Music therapy, [1396](#)
- Myalgias
  - drug-induced
    - sertraline, [371](#)
    - topiramate, [1029](#)
  - fibromyalgia, [1401-1404](#)
- Myasthenia gravis, use of benzodiazepines in, [1065](#)
- Mydriasis
  - drug-induced
    - classic antipsychotics, [612](#), [619](#)
    - olanzapine, [672](#)
    - trihexyphenidyl, [858](#)
  - during opioid withdrawal, [1613](#)
- Myocardial ischemia, stress-induced, escitalopram for, [442-443](#)
- Myocarditis, clozapine-induced, [636-637](#), [640](#), [1248](#), [1500](#)
- Myoclonus
  - drug-induced
    - MAOIs, [290](#)
    - SSRIs, [1497](#)
  - in serotonin syndrome, [346](#), [1615](#)
  - after SSRI discontinuation, [1615](#)
- Myotonic dystrophy, [1094](#)
  
- NAA. See [N-Acetylaspartate](#)
- Nabilone, [1394](#)
- NAC. See [N-Acetylcysteine](#)
- Nadolol, [864](#), [865](#)
- Nalmefene, [1287-1288](#)
- Naloxone, [1416](#)
  - combined with buprenorphine, [1390](#)
    - for opioid use disorder, [1290](#), [1292-1293](#)
    - for pain, [1390](#)
  - to prevent opioid overdose, [1295](#)
- Naltrexone
  - for alcohol use disorder, [1286-1287](#)
    - extended-release injectable formulation, [1287](#)
    - oral administration, [1287](#), [1660](#)
    - pharmacogenomics of, [227](#), [1287](#)
    - in schizophrenia, [1259](#)
  - for alcohol use disorder, [1286-1287](#)

- sertraline and, [369](#)
  - vs. topiramate, [1024](#)
- combined with bupropion, for obesity, [502–503](#)
- mechanism of action of, [1286–1287](#), [1290](#), [1294](#)
- for opioid use disorder
  - detoxification, [1290](#)
  - formulations of, [1290](#)
  - relapse prevention, [1290](#), [1294–1295](#)
    - extended-release injectable formulation, [1294–1295](#), [1661](#)
    - oral administration, [1294](#), [1660](#)
- Naproxen, [1382](#), [1413](#)
- Narcissistic personality disorder treatment, [1327](#)
- Narcolepsy, [1093–1094](#)
  - with cataplexy, [1051](#), [1072](#), [1094](#)
  - treatment of
    - armodafinil, [1084](#), [1090](#), [1091](#)
    - modafinil, [1084](#), [1089](#), [1094](#)
    - psychostimulants, [1084](#)
    - sodium oxybate, [1068](#)
- Nasal congestion, drug-induced
  - antipsychotics, [816](#)
  - prazosin, [1368](#)
- Nasopharyngitis, drug-induced
  - cariprazine, [848](#)
  - duloxetine, [1436](#), [1498](#)
  - paliperidone, [1463](#)
- NaSSA (noradrenergic and specific serotonergic antidepressant), [479](#). *See also* [Mirtazapine](#)
- National Comorbidity Survey Replication (NCS-R), [1210](#)
- National Fibromyalgia Association, [1404](#)
- National Health Interview Surveys, [1295](#)
- National Institute of Mental Health (NIMH)
  - CATIE study, [604](#), [620](#), [631](#), [637](#), [658](#), [661](#), [669](#), [688](#), [694](#), [695](#), [696](#), [697](#), [713](#), [714](#), [715](#), [718](#), [720](#), [721](#), [722](#), [764–765](#), [766](#), [767](#), [776](#), [778](#), [779–780](#), [871](#), [875](#), [1106](#), [1246–1247](#), [1250](#), [1253](#), [1254](#), [1255](#), [1524](#)
  - Combination Medication to Enhance Depression Outcomes study, [482](#)
  - Multimodal Treatment of ADHD study, [1504](#)
  - Preschool ADHD Treatment Study, [1453](#), [1505](#)
  - Treatment of SSRI-Resistant Depression in Adolescents trial, [1437](#)
- National Institute of Mental Health Global Obsessive-Compulsive Scale (NIMH-GOCS), [367](#), [1447](#)
- National Pain Care Policy Act of 2003, [1377](#)

National Survey on Drug Use and Health, 1155, 1299

Natural killer (NK) cells, 178, 182, **182**, 188

Nausea/vomiting

during alcohol withdrawal, 1285

during benzodiazepine withdrawal, 573

drug-induced

*N*-acetylcysteine, 1473

aripiprazole, 737, 746, 747, 1180, 1461

asenapine, 804

atomoxetine, 1473

brexpiprazole, 737

bupropion, 504, 1436, 1498

buspirone, 593

cancer chemotherapy, 484–485

carbamazepine, 958, 1179, 1440

cariprazine, **848**, 1180

chloral hydrate, 1069

classic antipsychotics, 618, **719**

desvenlafaxine, 521

doxepin, **1367**

duloxetine, 540, 1404, 1436, 1443, 1498

ketamine, 555

lamotrigine, 1011, 1182, 1502

levomilnacipran, 541

lithium, 1178, 1438, 1439, 1458, 1459, 1472, 1501

MAOIs, 290, 296, 297

milnacipran, 541, 1404

mirtazapine, 487

modafinil, 1090

nefazodone, 462, 1436

opioids, 1385

oxcarbazepine, 1440, 1502

physostigmine, 1042

quetiapine, **693**

risperidone, **693**, 718, **719**, 1180

selegiline transdermal system, 1436

SSRIs, 345, 371, 398, 421, 424, 443, 444, 467, 1434, 1435, 1445, 1447, 1448, 1449, 1451, 1497

topiramate, 1029, 1440, 1502

valproate, 933, 1178, 1501

venlafaxine, 521, 1208, 1404, 1471

vortioxetine, 472, 474



- ziprasidone, 774, 1440
- during opioid withdrawal, 1613
- self-induced, in bulimia nervosa, 1338
- after SSRI discontinuation, 1615
- treatment of
  - cannabinoids, 1394
  - classic antipsychotics, 607, 612
  - mirtazapine, 484–485
  - in pregnancy, 485, 1544, 1565
- Navane. *See* [Thiothixene](#)
- NBI-98854 (valbenazine), 875
- NCS-R (National Comorbidity Survey Replication (NCS-R), 1210
- NDMC (*N*-desmethyloclozapine), 626, 630
- NE. *See* [Norepinephrine](#)
- Nebivolol, interaction with paroxetine, 404
- Nefazodone, 455, 459–463
  - dosing of, 462, **1639**
  - drug interactions with, 462
    - antipsychotics, 620
    - benzodiazepines, 572
    - carbamazepine, **964**, 965
    - quetiapine, 686
  - generic, 459, 462, 463
  - history and discovery of, 459
  - indications for, 461–462
    - depression, 461
      - in alcohol-dependent patients, 461
      - in children and adolescents, 1436
      - maintenance treatment, 461
      - vs. paroxetine, 391
    - social anxiety disorder, 1199, 1200
    - SSRI discontinuation symptoms, 1196
  - mechanism of action of, 460–461
  - overdose of, 462
  - pharmacokinetics and disposition of, 460
  - pharmacological profile of, 459–460
  - side effects and toxicology of, 462, 1436
  - structure of, **459**
  - use in hepatic disease, 460
  - use in pregnancy and lactation, 1553
- Nelfinavir, interaction with carbamazepine, 967
- Nephrogenic diabetes insipidus, lithium-induced, 903, 904, 962

- in infants after prenatal exposure, [1556](#)
- Nephrolithiasis, topiramate-induced, [1029](#)
- Nervousness
  - drug-induced
    - amphetamine, [1086](#)
    - buspirone, [593](#)
    - haloperidol, [719](#)
    - methylphenidate, [1088](#)
    - risperidone, [719](#)
    - SSRIs, [1447](#), [1448](#)
    - topiramate, [1028](#)
    - venlafaxine, [1498](#)
  - after guanfacine discontinuation, [1501](#)
- NET. *See* [Norepinephrine transporter](#)
- Neupogen. *See* [Filgrastim](#)
- Neural tube defects, anticonvulsant-induced, [901](#), [935](#), [959](#), [1011](#), [1556](#)–[1557](#), [1559](#)
- Neuralgia
  - postherpetic, [1379](#), [1400](#)
    - gabapentin for, [983](#), [985](#), [1392](#)
    - lidocaine patch for, [1383](#)
    - opioids for, [1384](#)
    - pregabalin for, [990](#), [991](#), [1392](#)
  - trigeminal, [1400](#)
    - carbamazepine for, [943](#), [949](#), [1393](#)
    - oxcarbazepine for, [943](#)
- Neuregilin, [654](#), [656](#), [674](#)
- Neurofibrillary tangles, [247](#), [248](#)
- Neurogenesis
  - antidepressant effects on, [60](#), [419](#), [435](#)
  - in depression, [1158](#)
  - ECT effects on, [1108](#), [1127](#)
  - stress effects on, [1157](#)
- Neuroimaging, [239](#)–[269](#). *See also specific imaging modalities*
  - machine learning, [263](#)
  - MRI, [249](#)–[251](#), [252](#)–[253](#)
    - diffusion-weighted and diffusion tensor imaging, [262](#)
    - functional, [251](#)–[260](#)
    - perfusion-weighted and arterial spin labeling, [262](#)–[263](#)
    - structural, [261](#)–[262](#)
  - MRS, [260](#)–[261](#), [261](#)
  - multimodal approaches, [263](#)

- novel applications of, [265-269](#)
  - elucidating treatment mechanisms of actions, [267-269](#)
    - acute and delayed effects of deep brain stimulation, [268](#)
    - antidepressant effects of ketamine, [267-268](#)
    - for older medications, [269](#)
  - identifying persons at risk of developing psychopathology, [265-266](#)
    - machine learning to profile risk of bipolar disorder, [265-266](#)
    - MAO-PET labeling studies, [265](#)
  - neurochemical targeting in antipsychotic treatment, [266-267](#)
    - discriminating biological changes mediating antipsychotic effects and side effects, [266-267](#)
    - mechanisms of dopamine hyperresponsiveness in schizophrenia, [266](#)
  - profiling to guide treatment selection for depression, [267](#)
  - subtyping of clinical syndromes, [267](#)
- PET, [240-249](#)
- techniques for, [239-240](#)
- types of measurements provided by, [240](#)
- Neuroleptic-induced deficit syndrome, [607](#)
- Neuroleptic-induced parkinsonism (NIP). *See* [Parkinsonism, antipsychotic-induced](#)
- Neuroleptic malignant syndrome (NMS)
  - amoxapine-induced, [321](#)
  - antipsychotic-induced, [617](#), [1257](#), [1500](#), [1516](#), [1614](#)
    - cariprazine, [848](#)
    - clozapine, [639](#)
    - lurasidone, [825](#)
    - in neonates after prenatal drug exposure, [1565](#)
    - prevalence of, [1257](#)
    - risperidone, [717](#)
  - mortality from, [1257](#)
  - risk factors for, [1257](#)
    - extrapyramidal side effects, [870](#)
  - symptoms of, [1257](#)
  - treatment of, [1257](#), [1607](#), [1614](#)
    - ECT, [1111](#), [1614](#)
- Neuroleptics. *See* [Antipsychotics](#)
- Neurons
  - cell biology of, [4-5](#), [5](#)
  - dopaminergic, [65](#), [66](#)
  - firing rate of, [46](#)
  - GABAergic, [92-93](#)
  - 5-HT<sub>1A</sub> receptor expression on, [60](#)

- noradrenergic, 72–73, **74**
- orexin, 1072
- serotonergic, 54, **56**
- signal transduction mechanisms of, 46–47
- Neuropathic pain (NP) management, 101, 1378, 1379, 1380, 1400–1401
  - algorithmic approach to, 1412, **1413**–1415
  - botulinum toxin, 1400
  - cannabinoids, 1395
  - capsaicin, 1394, 1400
  - carbamazepine, 943, 949, 1393
  - combination therapy, 1398
  - in diabetes (*See Diabetic neuropathy*)
  - duloxetine, 344, 529, 534, 1391
  - fluoxetine, 344
  - fluvoxamine, 424
  - gabapentin, 983, 985, 990, 1392, 1400
  - guidelines for, 1400–1401
  - ketamine, 552
  - local anesthetics, 1393, 1400
  - milnacipran, 1391
  - opioids, 1384, 1385, 1400, 1401
  - oxcarbazepine, 943
  - pregabalin, 990, 991–992, 995, 1392, 1400
  - TCAs, 1401
  - tramadol, 1384
  - trazodone, 458
- Neuropeptide Y (NPY), 73, **101**, 186
  - in aggression, 63
  - in eating behaviors, 342
- Neuropeptides, 73, **100–101**
  - for borderline personality disorder, 1323
  - as neurotransmitters, 98–102
- Neuroprotective effects of drugs
  - huperzine A, 1042
  - lithium, 890, 891, 900
  - nicotine and cotinine analogues, 1042
  - valproate, 926
- Neuropsychiatric Inventory (NPI), 744, 1519, 1523, 1527
- Neuropsychiatric Inventory—Nursing Home edition (NPI/NH), 664, 774, 1519
- Neurotensin, **100**
  - olanzapine effects on, 656
  - receptors for, 654, 656

- in schizophrenia, 656
- Neuroticism, 1153
- Neurotransmitters, 45–102. *See also specific neurotransmitters*
  - adenosine, 96–98
  - amino acid (*See*  $\gamma$ -Aminobutyric acid; Glutamate)
  - cholinergic system, 77–81, 78–79
  - criteria for, 45–46
  - dopaminergic system, 65–72, 66–67
  - GABAergic system, 92–96, 94–95, 568
  - glutamatergic system, 81–91, 82–83
  - glycine, 91–92
  - noradrenergic system, 72–77, 74–75
  - number of endogenous substances functioning as, 46
  - peptidergic, 98–102, 100–101
    - CRH, 98–99
    - opioids, 99–102
    - oxytocin and vasopressin, 99
  - receptors for, 46–54 (*See also* Receptors)
  - serotonergic system, 54–64, 56–57, 335–336
  - in specific disorders
    - Alzheimer's disease with psychosis, 1519–1520
    - depression, 1155–1156
  - synthesis of, 46
- Neurotrophic hypothesis of depression, 1157–1158
- Neurovegetative symptoms
  - in adjustment disorders, 1602
  - in depression, 1151, 1155, 1259
- Neutropenia, antipsychotic-induced, 1500
  - cariprazine, 848
  - clozapine, 1464
- NF- $\kappa$ B (nuclear factor  $\kappa$ B), 10, 185, 186, 187, 188, 194
- Nicardipine, for ECT, 1124
- Nicotinamide, interaction with carbamazepine, 964, 967
- Nicotine replacement therapies (NRT), 1296–1297, 1298
  - in patients with psychiatric disorders, 1299–1300
    - schizophrenia, 1259
  - use in cardiac disease patients, 1297
- Nicotinic ligands for PET imaging, 81
- Nicotinic receptor agonists, as cognitive enhancers, 1042, 1045
  - in schizophrenia, 1262
- Nicotinic receptors, 47, 79, 80–81, 97
  - adenosine modulation of, 97

- drug effects on
  - biperiden, [861](#)
  - bupropion, [496–497](#), [1297](#)
  - galantamine, [1041](#)
  - ketamine, [552](#)
  - varenicline, [1297](#)
- in schizophrenia, [81](#)
- Nifedipine, [291](#)
- Night-eating syndrome
  - sertraline for, [371](#)
  - topiramate for, [1023](#)
- Nightmares
  - induced by alcohol-type hypnotics, [1069](#)
  - in PTSD
    - benzodiazepines for, [1215](#)
    - clonidine for, [1451](#)
    - prazosin for, [1217](#), [1360–1361](#)
- Nigrostriatal dopamine circuit, [65](#), [66](#), [245](#), [372](#)
  - effects of antipsychotic D<sub>2</sub> receptor blockade of, [607](#), [608](#), [609](#), [612](#), [614](#), [732](#)
  - clozapine, [628](#)
  - olanzapine, [651](#)
  - risperidone, [711](#)
  - ziprasidone, [756](#)
- NIMH. *See* [National Institute of Mental Health](#)
- NIMH-GOCS (National Institute of Mental Health Global Obsessive-Compulsive Scale), [367](#), [1447](#)
- Nimodipine, interaction with carbamazepine and oxcarbazepine, [963](#), [966](#)
- NIP (neuroleptic-induced parkinsonism). *See* [Parkinsonism, antipsychotic-induced](#)
- Nitrazepam, [566](#), [572](#), [1064](#)
- NK (natural killer) cells, [178](#), [182](#), [182](#), [188](#)
- NK<sub>1</sub> receptor antagonists, for depression, [391](#)
- NMDA receptors. *See* [N-Methyl-D-aspartate receptors](#)
- NMS. *See* [Neuroleptic malignant syndrome](#)
- Nociceptin, [100](#)
- Non-rapid eye movement (NREM) sleep, drug effects on
  - fluoxetine, [346](#)
  - trazodone, [458](#)
- Nonbenzodiazepine hypnotics. *See also specific drugs*
  - in elderly persons, [1076](#)
  - history of, [1052](#)

- for insomnia, 1354–1355, **1365**
- pharmacokinetics of, 1060, 1064, **1064**
- pharmacological profile of, 1057, 1076
- side effects of, **1365**
- with SSRIs for generalized anxiety disorder, 1208
- structure of, **1058**

Nonsteroidal anti-inflammatory drugs (NSAIDs), 1381–1382, **1413**, 1416

- abuse potential of, 1387
- combined with acetaminophen, 1398
- cyclo-oxygenase inhibition by, 1382
- indications for
  - fibromyalgia, 1403
  - headache, 1411, **1411**
  - low back pain, 1391, 1406, **1406**
  - osteoarthritis, 1407, 1408
  - vascular cognitive impairment, 1044
- interaction with lithium, 906, 1507
- side effects of, 1382
- topical, 1394, **1415**

Noradrenergic and specific serotonergic antidepressant (NaSSA), 479. *See also Mirtazapine*

Norclozapine, 626, 628, 630

Norepinephrine (NE), 72–73, **74–75**

- brain distribution of, 72, **74**
- cytokine effects on, 191–192
- drug effects on
  - amphetamine, 1086
  - bupropion, 495, 496
  - buspirone, 587
  - carbamazepine, 948
  - cyclic antidepressants, 305, 309, 315, 319
  - desvenlafaxine, 515, 517
  - duloxetine, 531, 542
  - fluoxetine, 338–339
  - levomilnacipran, 531
  - lithium, 890
  - milnacipran, 531, 533
  - mirtazapine, 479
  - moclobemide, 295
  - nefazodone, 460–461
  - norepinephrine reuptake inhibitors, 73
  - paroxetine, 385

- tramadol, [1383](#)
- venlafaxine, [515](#), [517](#)
- ECT effects on, [1107](#)
- receptors for, [76–77](#)
- in sleep–wake cycle, [1350](#), [1351](#)
- in specific disorders
  - Alzheimer’s disease with psychosis, [1519](#)
  - bipolar disorder, [55](#), [59](#)
  - depression, [73](#)
  - PTSD, [73](#)
  - suicidality, [55](#), [59](#)
- synthesis of, [72](#)
- Norepinephrine reuptake inhibitors, [73](#), [309](#), [315](#). *See also* [Serotonin–norepinephrine reuptake inhibitors](#)
  - amoxapine, [306](#)
  - antinociceptive effects of, [319](#)
  - atomoxetine, [532](#)
  - bupropion, [506](#)
  - cardiac effects of, [401](#), [541](#)
  - maprotiline, [397](#), [532](#)
  - paroxetine, [385](#), [391](#), [401](#)
  - reboxetine, [391](#), [532](#)
- Norepinephrine transporter (NET), [73–76](#)
  - brain distribution of, [73](#)
  - drug effects on amphetamine, [1086](#)
    - atomoxetine, [76](#)
    - BMS-820836, [69](#)
    - bupropion, [496](#), [498](#)
    - citalopram, [432](#), [434](#)
    - cyclic antidepressants, [306](#), [308](#), [309](#), [311](#), [315](#), [325](#), [532](#)
    - duloxetine, [529](#), [531](#), [532](#)
    - levomilnacipran, [529](#)
    - milnacipran, [529](#), [531](#), [532](#)
    - paroxetine, [386](#)
    - venlafaxine, [517](#)
    - ziprasidone, [757](#)
  - regulation of, [73](#)
  - structure of, [58](#)
- Norfluoxetine, [340](#), [1507](#)
- Norketamine, [550](#)
- Norrie’s disease, [285](#)
- North American Antiepileptic Drug Pregnancy Registry, [1011](#)



North American Pregnancy Registry, [1561](#)

Nortriptyline

dosing of, [311](#), [1632](#)

drug interactions with, [325–326](#)

bupropion, [497](#)

carbamazepine, [965](#)

indications for

alcohol abuse in antisocial personality disorder, [1328](#)

depression, [306](#)

in elderly persons, [318](#), [392](#)

vs. mirtazapine, [482](#)

vs. paroxetine, [390](#)

pain syndromes, [1413](#)

headache, [1411](#)

nocturnal enuresis in children, [319](#)

smoking cessation, [1298](#)

pharmacokinetics of, [311](#), [311–312](#), [313](#)

pharmacological profile of, [308](#)

plasma concentration of, [127](#), [311](#), [314](#)

side effects of, [322](#), [323](#)

structure–activity relations for, [306](#), [307](#)

NP. *See* [Neuropathic pain management](#)

*NPAS3* gene, [815](#)

NPI (Neuropsychiatric Inventory), [744](#), [1519](#), [1523](#), [1527](#)

NPI/NH (Neuropsychiatric Inventory— Nursing Home edition), [664](#), [774](#), [1519](#)

*NR3C1* gene, [1158](#)

*NRG1* gene, [656](#)

*NRG3* gene, [815](#)

NSAIDs. *See* [Nonsteroidal anti-inflammatory drugs](#)

*NUBPL* gene, [815](#)

Nuclear factor  $\kappa$ B (NF- $\kappa$ B), [10](#), [185](#), [186](#), [187](#), [188](#), [194](#)

Nuclear receptor coregulators, [54](#)

Nuclear receptors, [47](#), [48–49](#), [53–54](#)

Nutraceuticals, as cognitive enhancers, [1044](#), [1045](#)

Nystagmus

drug-induced

carbamazepine, [957](#)

ketamine, [555](#)

topiramate, [1029](#)

in serotonin syndrome, [1615](#)

OATP1A2 and OATP2B1 (organic anion transporting polypeptides), [212](#)

Obesity/overweight

- binge-eating disorder and, [1342](#)

- bipolar disorder and, [959](#)

- BMI in, [502–503](#)

- drug-induced (See [Weight changes, drug-induced](#))

- lithium use in, [903](#)

- schizophrenia and, [669](#), [1253–1254](#)

- treatment of

  - amphetamine, [1095](#)

  - bupropion/naltrexone, [502–503](#)

  - Class I BAT activators, [76](#)

  - fluoxetine, [345](#)

  - lorcaserin, [64](#), [503](#)

  - orlistat, [503](#), [1254](#), [1343](#)

  - phentermine-topiramate combination, [503](#), [1017](#), [1019](#), [1028](#)

  - topiramate, [1017](#), [1019](#), [1028](#)

OBRA (Omnibus Budget Reconciliation Act) of 1987, [1520](#)

Obsessive-compulsive disorder (OCD), [1210](#)

- bulimia nervosa and, [1338](#)

- in children and adolescents, [1447](#)

- genetics of, [121](#)

- postpartum, [1545](#)

- in pregnancy, [1545](#)

- prevalence of, [1210](#)

- rating scale for, [1210](#)

Obsessive-compulsive disorder treatment, [1210–1212](#)

- antidepressants

  - clomipramine, [306](#), [318](#), [342](#), [396](#), [1210–1211](#)

  - MAOIs, [289](#)

  - mirtazapine, [483–484](#)

  - SSRIs, [318](#), [1211](#)

    - citalopram, [442](#), [484](#)

    - escitalopram, [442](#)

    - fluoxetine, [342](#)

    - fluvoxamine, [422–423](#)

    - paroxetine, [396–397](#)

    - sertraline, [366–367](#)

  - venlafaxine, [519](#)

- antipsychotics, [1212](#)

  - olanzapine, [668](#)

- quetiapine, [692](#), [1211](#)
- risperidone, [717](#)
- augmentation strategies, [1211–1212](#)
- benzodiazepines, [569](#)
- in children and adolescents, [1447–1450](#)
  - N*-acetylcysteine, [1450](#)
  - atypical antipsychotic augmentation, [1449–1450](#)
  - citalopram, [1449](#)
  - clinical recommendations for, [1450](#)
  - clomipramine, [1211](#), [1448–1449](#)
  - D-cycloserine, [1450](#)
  - fluoxetine, [1211](#), [1447–1448](#)
  - fluvoxamine, [423](#), [1448](#)
  - paroxetine, [396](#), [1449](#)
  - riluzole, [1450](#)
  - sertraline, [367](#), [1211](#), [1447](#)
  - with Tourette syndrome, [1461](#)
- cognitive-behavioral therapy, [1211](#), [1212](#)
- gabapentin, [986](#), [1212](#)
- inositol, [1212](#)
- maintenance treatment/relapse prevention, [1211](#)
- in pregnancy, [1545](#)
- somatic therapies, [1212](#)
  - deep brain stimulation, [1133](#), [1163](#), [1212](#)
  - ECT, [1112](#)
  - neurosurgery, [1212](#)
  - rTMS, [1212](#)
- St. John's wort, [1212](#)
- topiramate, [1026–1027](#)
- Obsessive-compulsive personality disorder, [1329](#), [1330](#)
- Obsessive-compulsive spectrum disorders, [1330](#)
  - fluoxetine for, [342](#)
- Obsessive-compulsive symptoms
  - in autism spectrum disorder, [1466](#)
  - clozapine-induced, [640](#)
  - in schizophrenia, [1261](#)
- Obstipation, anticholinergic-induced, [859](#)
- Obstructive sleep apnea (OSA)
  - drug use
    - in benzodiazepines, [1064–1065](#)
    - ramelteon, [1356](#)
    - suvorexant, [1359](#)

HPA effects of, [158](#)  
treatment of  
    armodafinil, [1084](#), [1090–1091](#)  
    mirtazapine, [484](#)  
    modafinil, [1084](#), [1089](#), [1094–1095](#)  
    trazodone, [458](#)  
OCD. *See* [Obsessive-compulsive disorder](#)  
Ocular effects of drugs. *See also* [Visual disturbances](#)  
    antipsychotics, [616](#), [619](#), [1516](#)  
    carbamazepine, [957](#)  
    ketamine, [555](#)  
    quetiapine, [697](#)  
    topiramate, [1029](#)  
    trihexyphenidyl, [858](#), [859](#)  
Oculogyric crisis, antipsychotic-induced, [614](#), [1256](#), [1614](#)  
ODD. *See* [Oppositional defiant disorder](#)  
ODV (*O*-desmethylvenlafaxine), [515](#), [516](#), [523](#). *See also* [Desvenlafaxine](#)  
OFC. *See* [Olanzapine-fluoxetine combination](#)  
Okadaic acid, [73](#)  
Olanzapine, [649–674](#)  
    in children and adolescents, [634](#), [654](#), [659–660](#), [663](#), [672](#), [1438](#), [1439](#),  
        [1441](#), [1462](#), [1464–1465](#), [1468](#), [1499](#)  
    dosing of, [650](#), [657](#), [660–661](#), [1647](#)  
        in children and adolescents, [1499](#)  
        in elderly patients, [1522–1523](#), [1525](#)  
    drug interactions with, [673–674](#)  
        carbamazepine and oxcarbazepine, [963](#), [966](#)  
        lorazepam, [1610](#)  
    in elderly persons, [654](#), [660](#), [1522–1523](#), [1524](#), [1525](#), [1528](#), [1530](#)  
    formulations of, [652–653](#), [661](#), [1249](#), [1606](#), [1647–1648](#)  
        intramuscular, [653](#), [661](#), [1608](#), [1609](#), [1610](#)  
        long-acting injectable, [653](#), [659](#), [661](#), [1247](#)  
        oral disintegrating preparation, [652–653](#), [661](#)  
    history and discovery of, [649–650](#)  
    indications for, [657–668](#)  
        acute psychosis, [1245](#)  
        aggression and agitation, [1606](#), [1608](#), [1609](#), [1610](#)  
        aggression in children and adolescents, [1458](#)  
        anorexia nervosa, [666–667](#)  
        autism spectrum disorder, [1468](#)  
        behavioral complications of dementia, [663–665](#), [1522–1523](#), [1524](#), [1525](#),  
            [1624](#)

- bipolar disorder, 661–663
  - vs. asenapine, 802–803
  - in children and adolescents, 663, 1438, 1439, 1441
  - maintenance treatment, 662, 896–897, 929
  - mania, 892, 1179, 1609, 1610
- borderline personality disorder, 665–666, 1316, **1318–1319**, **1327**
  - comorbid with schizotypal personality disorder, 1329
- delirium, 1528
- ECT-induced postictal agitation, 1123
- insomnia, **1370**, 1371
- OCD, 668
- panic disorder, 1198
- psychotic depression, 1530
- PTSD, 667–668, 1216
- schizophrenia, 657–661, 1522
  - for behavioral emergencies, 1610
  - CATIE study, 620, 658, 661, 713, 1246–1247
  - in children and adolescents, 634, 659–660, 1462, 1464–1465
  - in elderly persons, 660
  - vs. lurasidone, 823
  - maintenance treatment, 801
  - vs. quetiapine, 659, 688–689
  - with substance use disorder, 1259
  - topiramate and, 1021
  - treatment-resistant illness, 631, 658, 1248
  - valproate and, 931
- social anxiety disorder, 1201
- treatment-resistant depression, 663
- mechanism of action of, 63, 654–657
- overdose of, 672
- pharmacokinetics and disposition of, 652–654, 1522
- pharmacological profile of, 650–652, 1522
- side effects and toxicology of, 668–672, 674, 1179, 1248, 1316, **1370**,  
1439, 1522–1523
  - cardiovascular effects, 672, 1248, 1516
  - extrapyramidal side effects, 651, 655, 657, 668–669, 674, 720, 776, 872,  
1255
  - hematological effects, 672
  - hyperprolactinemia, 672
  - neurological effects, 668
- sedation, 672, 1248, **1370**, 1439, 1522, 1523, 1525

- weight gain/metabolic effects, [34](#), [637](#), [666](#), [667](#), [669–672](#), [674](#), [695](#),  
[1253](#), [1254](#), [1468](#)
- topiramate for, [1027](#), [1028](#)
- smoking and, [673–674](#)
- structure–activity relations for, [625](#), [650](#), [651](#)
- use in pregnancy and lactation, [672–673](#), [1563](#)
- use in renal or hepatic disease, [654](#)
- Olanzapine–fluoxetine combination (OFC), [653](#), [1648](#)
  - for bipolar depression, [662](#), [1005](#), [1181–1182](#)
    - in adolescents, [663](#)
    - vs. lamotrigine, [1005–1006](#), [1182](#)
  - for borderline personality disorder, [665](#)
  - for treatment-resistant depression, [663](#)
- Oleptro. *See* [Trazodone](#)
- Omega-3 fatty acids
  - for borderline personality disorder, [1323](#)
  - for depression, [1165](#)
  - for prodromal schizophrenia, [1262](#)
- Omeprazole, interaction with carbamazepine, [964](#)
- Omnibus Budget Reconciliation Act (OBRA) of 1987, [1520](#)
- Ondansetron
  - indications for
    - alcohol use disorder, [1289](#)
    - OCD, [1212](#)
    - opioid withdrawal, [1614](#)
    - social anxiety disorder, [1201](#)
    - SSRI discontinuation syndrome, [1196](#)
  - mechanism of action of, [57](#), [64](#)
- 1,000 Genomes project, [134](#), [136](#)
- Opioid antagonists
  - for borderline personality disorder, [1323](#)
  - naloxone, [1292](#), [1390](#)
  - naltrexone, [1290](#), [1294](#), [1295](#)
- Opioid receptor like-1 (ORL1), [101](#)
- Opioid receptors, [76](#), [101](#)
  - drug effects on, [1262](#)
    - buprenorphine, [1290](#)
    - ketamine, [551](#), [555](#)
    - methadone, [1289](#)
    - tramadol, [1383](#)
  - PET imaging of, [247](#)
- Opioid-related disorders, [1289–1295](#)

- benzodiazepine abuse and, 574
- depression and, 1154
- incidence of, 1289
- laboratory screening for, 1611
- medical comorbidity with, 1289
- mortality from, 1289
- OPRM1* polymorphisms and, 101
- risk in chronic pain patients, 1386–1387
- smoking cessation in, 1300
- treatment of, 1289–1295
  - buprenorphine, 1290, 1291, 1292, 1390
  - for detoxification, 1290–1291
  - maintenance therapy, 1291–1294
    - buprenorphine, 1292
    - buprenorphine implants, 1293
    - buprenorphine–naloxone, 1290, 1292–1293
  - methadone, 1291–1292
  - during pregnancy, 1293–1294
  - methadone, 1289–1290, 1291
  - naloxone for overdose prevention, 1295
  - naltrexone, 1290
    - for relapse prevention, 1290, 1294–1295
- Opioid withdrawal, 1290–1291, 1613
  - neonatal, 1294
  - onset and duration of, 1290, 1613
  - protracted abstinence syndrome, 1290
  - rapid detoxification procedures, 1291
  - symptoms of, 1613
  - taper regimens for, 1290–1291
  - treatment of, 1290–1291, 1613–1614
    - buprenorphine, 1290, 1291
    - buspirone, 592
    - clonidine, 76, 1291, 1613–1614
    - methadone, 1289–1290, 1291
- Opioids
  - adverse effects of, 1385–1386
  - diversion of, 1386
  - drug interactions with
    - MAOIs, 292, **293**, 297
    - suvorexant, 1073
  - endogenous, 99–102, **100**
  - indications for

- borderline personality disorder, 1323
- ECT, 1122
- pain, 101, 1382–1390, **1414**
  - buprenorphine, 1390
  - combined with acetaminophen or aspirin, 1398, 1408
  - efficacy of, 1384–1385
  - equianalgesic doses of, 1387, **1388**
  - long-acting opioids, 1388
  - low back pain, 1406, **1406**
  - management strategy for chronic pain, 1388, **1389**
  - methadone, 1388–1390
  - migraine, **1411**
  - neuropathic pain, 1384, 1385, 1400, 1401
  - osteoarthritis, 1384, 1408
  - principles of use of, 1387–1388
  - tramadol, 1383–1384
- misuse of, 1386
- overdose of, 1289, 1290, 1294, 1295, 1383, 1386
- Schedule I–V drugs, 1383
- tolerance and addiction to, 1386–1387
- use in pregnancy and lactation, 1293–1294, 1390
- Opiorphin, 99
- Opisthotonos, antipsychotic-induced, 614
- Oppositional defiant disorder (ODD), 1456–1457
  - ADHD and, 1456
  - treatment of, 1456–1457
    - atomoxetine, 1456–1457
    - clinical recommendations for, 1460
    - psychostimulants, 1456
    - valproate, 930
- OPRM1* gene, 101, 1287
- Oral contraceptives. *See* Hormonal contraceptive–drug interactions
- Oral drugs, 212–214
- Oral hypoesthesia, asenapine-induced, 804, 805, 806, 1439
- Orexin (hypocretin), 73, **101**, 1072, 1358
  - in narcolepsy with cataplexy, 1051, 1072
  - receptors for, 1072, 1358
  - in sleep–wake cycle, 1350, **1351**, 1359
- Orexin (hypocretin) receptor antagonists, 1051, 1072–1073, 1358–1359
- ORG 3770. *See* Mirtazapine
- Organic anion transporting polypeptides (OATP1A2, OATP2B1), 212
- ORL-1 (opioid receptor like-1), 101



Orlistat, [503](#), [1254](#)  
for binge-eating disorder, [1343](#)  
Oropharyngeal pain, duloxetine-induced, [1443](#)  
Orphenadrine, [1393](#)  
Orthostatic hypotension, drug-induced  
aripiprazole, [737](#)  
brexpiprazole, [737](#)  
classic antipsychotics, [612](#), [615](#), [1516](#)  
clozapine, [626](#), [636](#), [637](#), [1516](#), [1521](#)  
concurrent antihypertensive medications and, [322](#), [459](#)  
fludrocortisone for, [290](#), [322](#)  
iloperidone, [809](#), [810](#), [817](#)  
lurasidone, [822](#)  
MAOIs, [290](#), [295](#)  
nefazodone, [462](#)  
olanzapine, [1179](#), [1370](#), [1516](#), [1525](#)  
paroxetine, [398](#), [459](#)  
prazosin, [1368](#)  
quetiapine, [693](#), [1370](#), [1516](#)  
risperidone, [718](#), [721](#), [1516](#), [1525](#)  
TCAs, [320](#), [322](#), [1368](#), [1369](#), [1390](#)  
trazodone, [456](#), [457](#), [458](#), [459](#), [463](#), [1369](#)  
OSA. See [Obstructive sleep apnea](#)  
Osteoarthritis, [1380](#), [1407](#)  
aging and, [1407](#)  
pain management for, [1377](#), [1380](#), [1407–1408](#), [1412](#)  
duloxetine, [1391](#), [1408](#)  
exercise, [1399](#), [1407](#)  
glucosamine, chondroitin, and hyaluronic acid, [1408](#), [1409–1410](#)  
nonopioid analgesics, [1381](#), [1407](#)  
opioids, [1384](#), [1408](#)  
placebo effect and, [1412](#), [1416](#)  
topical NSAIDs, [1394](#)  
tramadol, [1384](#)  
surgery for, [1407](#)  
Overdose of drug  
alcohol-type hypnotics, [1069](#)  
anticholinergic agents, [859](#)  
barbiturates, [1067](#), [1068](#)  
benzodiazepines, [1065](#)  
buprenorphine, [1290](#), [1292–1293](#)  
bupropion, [505](#)

buspirone, 594  
cariprazine, 849  
clonidine, 1500  
desvenlafaxine, 522  
duloxetine, 543  
gabapentin, 989  
ketamine, 550  
lamotrigine, 1011  
MAOIs, 1316  
methadone, 1289, 1388, 1390  
methylphenidate, 1089  
milnacipran, 541, 543  
mirtazapine, 488, 489  
moclobemide, 296  
modafinil, 1090  
nefazodone, 462  
olanzapine, 672  
opioids, 1289, 1290, 1294, 1295, 1383, 1386  
risperidone, 721–722  
SSRIs, 1159, 1497, 1514  
    fluoxetine, 347, 349, 350  
    fluvoxamine, 425  
    paroxetine, 401–402  
suicide and, 1599, 1600  
TCAs, 313, 314, 320, 321, 322, 323, 324, 326, 1316, 1390, 1511, 1615  
trazodone, 458  
valproate, 935  
venlafaxine, 522  
vortioxetine, 473  
ziprasidone, 781

Oxazepam  
    for agitation and aggression in elderly patients, 1627  
    for alcohol withdrawal, 1285  
    dosing of, 1642  
    pharmacokinetics of, 566, 567, 572, 1060, 1061, 1064  
    structure of, 565  
    use in pregnancy and lactation, 1568

Oxcarbazepine (OXC), 941–970  
    in children and adolescents, 1440, 1471–1472, 1501  
    dosing of, 947, 1652  
        in children and adolescents, 1501  
    drug interactions with, 947, 963, 967–968, 969

- lamotrigine, 1012
- formulations of, 946–947
- history and discovery of, 942
- indications for, 949–953
  - autism spectrum disorder, 1471–1472
  - bipolar disorder, 969
    - in children and adolescents, 1440
    - maintenance treatment, 953, 954
    - mania, 941, 942, 947, 950, 951–952, 1179
    - predictors of response to, 956
  - seizures, 942, 947, 949–950
  - trigeminal neuralgia, 943
- mechanism of action of, 949
- monohydroxy derivative of, 945, 947, 964, 967, 968, 969 (*See also* Licarbazepine)
- pharmacokinetics and disposition of, 945, 947, 948
- pharmacological profile of, 943
- side effects and toxicology of, 959–960, 1440, 1502
- structure–activity relations for, 943
- suicidality and, 958, 960
- switching to eslicarbazepine acetate from, 947–948
- use in pregnancy and lactation, 960

Oxtellar. *See* Oxcarbazepine

Oxycodone, 424, 1384, 1387, 1388, 1414, 1416

- combined with acetaminophen, 1398
- interaction with pregabalin, 995
- for neuropathic pain, 1401
- for osteoarthritis, 1408

Oxytocin, 99, 100, 1326

- for borderline personality disorder, 1323, 1326
- buspirone effects on, 588
- intranasal, for autism spectrum disorder, 1473

P-glycoprotein (P-gp), 212, 215, 227, 312, 388, 709

- placental, 1549

P2RX7 gene, 1158

PAAS (Panic and Anticipatory Anxiety Scale), 1195

Paclitaxel, interaction with carbamazepine and oxcarbazepine, 963

Padua Inventory, 666

Pain, 1377–1379

- acute, 1378, 1380
- allodynia, 1379

- assessment and monitoring of, 1416–1418, **1417**
- during benzodiazepine withdrawal, 573
- central sensitization and, 1379, 1402, 1403
- chronic, 1379, 1380
- classification of, 1378–1379
- definition of, 1378
- domains of, 1417
- drug-induced
  - carbamazepine, 958
  - citalopram, 1434
  - duloxetine, 1436, 1498
  - escitalopram, 1434
  - ketamine, 555
  - nefazodone, 1436
  - psychostimulants, 1502
  - quetiapine, **693**
  - risperidone, **693**
  - sertraline, 371
  - SSRIs, 1434, 1435, 1447, 1449, 1497
  - venlafaxine, 1436, 1498
  - ziprasidone, 774
- economic cost of, 1377
- as “fifth vital sign,” 1377, 1416, 1417
- hyperalgesia, 1379
- of musculoskeletal disorders, 1379, 1380
- neuropathic, 1378, 1379, 1380
- nociceptive, 1378–1379
- prevalence of, 1377
- psychiatric comorbidity with, 1377
- in serotonin syndrome, 346
- somatic, 1379
- visceral, 1379

Pain management, 1379–1418

- algorithmic approach to chronic pain, 1412, **1413–1415**
- anticonvulsants, 1392–1393
  - carbamazepine, 943, 949, 1393
  - gabapentin, 983, 985, 1392, 1400, 1401
  - oxcarbazepine, 943
  - pregabalin, 990, 991–992, 1392–1393, 1400, 1401
- antidepressants, 1390–1392
  - duloxetine, 344, 535, 539, 1391, 1399, 1401
  - MAOIs, 289

- maprotiline, 319
- milnacipran, 539, 1391–1392
- mirtazapine, 484, 1392
- SSRIs, 344, 345, 424, 1391
- TCAs, 310, 319, 1390–1391, 1401
- trazodone, 458
- venlafaxine, 1392
- cannabinoids, 1394–1395
- combination therapy, 1398–1400
- in comorbid depression or anxiety, 1412
- complementary and alternative medicine, 1378
- ECT, 1113
- gaps in knowledge base about treatment of chronic pain, 1418
- ketamine, 552
- mexiletine, 1393–1394, 1401
- nonopioid analgesics, 1381–1382
- nonpharmacological, 1380, 1395–1398, **1396–1397**
  - cognitive-behavioral therapy, 1395–1397
  - exercise, 1398, **1399**
  - other psychological interventions, 1397–1398
  - pain self-management programs, 1397
- opioid analgesics, 101, 1382–1390
  - adverse effects of, 1385–1386
  - buprenorphine, 1390
  - efficacy of, 1384–1385
  - equianalgesic doses of oral and transdermal drugs, 1387, **1388**
  - long-acting opioids, 1388
  - management strategy for chronic pain, 1388, **1389**
  - methadone, 1388–1390
  - principles of use of, 1387–1388
  - tolerance and addiction to, 1386–1387
  - tramadol, 1383–1384
- overview of, 1379–1380
- placebo effect and, 1412, 1416
- skeletal muscle relaxants, 1393
- for specific pain disorders, 1380, 1400–1411 (*See also specific disorders*)
  - fibromyalgia, 1401–1404, **1403**
  - headache, 1408, 1411, **1411**
  - low back pain, 1404–1407, **1406**
  - neuropathic pain, 1400–1401
  - osteoarthritis, 1407–1408, **1409–1410**
- strength of evidence for specific treatments, 1380–1381

- topical analgesics, 1393–1394
- Pain self-management (PSM), 1396, 1397
- Paliperidone, 705–723
  - in children and adolescents, 1462, 1463, 1465, 1499
  - dosing of, 709, 1648
    - in children and adolescents, 1499
  - drug interactions with, 722
  - formulations of, 1249
    - extended-release, 706, 709, 712, 715
  - history and discovery of, 706
  - indications for, 712
    - behavioral complications of dementia, 1522
    - bipolar disorder
      - maintenance treatment, 1185
      - mania, 1181
    - borderline personality disorder, 1319
    - schizoaffective disorder, 706
    - schizophrenia, 706, 712, 715–716, 1522
      - in children and adolescents, 1462, 1463, 1465
  - mechanism of action of, 710–712
  - pharmacokinetics and disposition of, 709–710
  - pharmacological profile of, 706–708, 708
  - side effects and toxicology of, 1247–1248, 1463
    - extrapyramidal side effects, 712, 873, 1247, 1463
    - hyperprolactinemia, 720, 721, 1247
    - metabolic effects, 718
  - structure of, 707
- Paliperidone palmitate, 706, 709, 716, 721, 723, 1247
  - dosing of, 709, 1648
  - indications for, 712
  - 3-month injection formulation, 706, 709, 712, 716, 722, 1261
  - use in pregnancy, 1564
- PALLD* gene, 815
- Palpitations, drug-induced
  - antidepressants, 1196
    - duloxetine, 1443
    - paroxetine, 1445
    - sertraline, 371
  - risperidone, 718, 722
- Pancreatitis, drug-induced
  - carbamazepine, 1179
  - valproate, 933, 1179, 1502

Pancuronium, interaction with carbamazepine and oxcarbazepine, [963](#), [967](#)  
Pancytopenia, antipsychotic-induced, [619](#)  
PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections), [185](#)  
Panic and Agoraphobia Scale (PAS), [987](#)  
Panic and Anticipatory Anxiety Scale (PAAS), [1195](#)  
Panic attacks, [1604](#)  
    methylxanthine-induced, [97](#)  
    in schizophrenia, [569](#)  
    suicide risk and, [1597](#)  
Panic disorder  
    acute tryptophan depletion and, [55](#)  
    binge-eating disorder and, [1342](#)  
    bulimia nervosa and, [1338](#)  
    in children and adolescents, [1445](#)  
    differential diagnosis of, [1604](#)  
    GABA in, [248](#)  
    genetics of, [121](#)  
    medical evaluation of, [1604](#)  
    in pregnancy, [1545](#), [1546](#)  
    rating scales for, [1195](#)  
Panic Disorder Severity Scale (PDSS), [1195](#)  
Panic disorder treatment, [1195-1199](#)  
    anticonvulsants, [1197-1198](#)  
    antidepressants  
        bupropion, [1197](#)  
        clomipramine, [1195](#)  
        MAOIs, [288-289](#), [294](#), [1197](#)  
        maprotiline, [1197](#)  
        mirtazapine, [1196](#), [1197](#)  
        nefazodone, [1196](#)  
        reboxetine, [1197](#)  
    SSRIs, [1195-1196](#)  
        in children and adolescents, [1445](#)  
        citalopram, [440-441](#), [1195](#), [1445](#)  
        escitalopram, [441](#), [1195](#)  
        fluoxetine, [342](#), [1195](#), [1196](#), [1445](#)  
        fluvoxamine, [395](#), [1195](#)  
        paroxetine, [395](#), [1195](#), [1197](#), [1445](#), [1604](#)  
        sertraline, [365-366](#), [1195](#), [1445](#), [1604](#)  
    TCAs, [318](#), [1196-1197](#)  
    trazodone, [1197](#)

- venlafaxine, 519, 1197, 1604
- atypical antipsychotics, 1198
- benzodiazepines, 563, 568–569, 1196, 1445, 1604
  - discontinuation of, 1198
- buspirone, 590–591, 1197
- in children and adolescents, 1445
  - benzodiazepines, 1445
  - citalopram, 1445
  - fluoxetine, 1445
  - paroxetine, 1445
  - sertraline, 1445
- cognitive-behavioral therapy, 1196, 1198–1199
- emergency management, 1603, 1604
- gabapentin, 986, 987
- maintenance treatment, 1198
- PANSS (Positive and Negative Syndrome Scale), 486, 631, 635, 658, 659, 667, 668, 671, 713, **714**, 722, 739, 740, 741, 742, 745, 763, 764, 765, 767.768.769, 800–801, 803, 811, **812–813**, 814, 823, 840, **841–843**, 843, 844, 846, 931, 1007, 1021, 1022, 1028, 1463, 1464, 1465
- Paralytic ileus, drug-induced
  - antipsychotics, 612, 618
  - TCAs, 321
- Parasympathetic nervous system, immune system and, 186
- Parent training, for ADHD, 1458
- Paresthesias
  - drug-induced
    - asenapine, 804, 805, 806, 1439
    - MAOIs, 290
    - topiramate, 1028, 1029, 1440, 1502
  - after SSRI discontinuation, 1615
- Pargyline, interaction with MAOIs, **293**
- Parkinsonism
  - antipsychotic-induced, 614, **615**, 719, 855, 856, 1255–1256
  - atypical antipsychotics, 871–874
    - aripiprazole, 746, 873
    - asenapine, 873
    - brexpiprazole, 874
    - cariprazine, 848, 849, 874
    - clozapine, 872
    - iloperidone, 873–874
    - lurasidone, 873
    - olanzapine, 668, 669, 872



- paliperidone, 873, 1463
- quetiapine, 872-873
- risk factors for, 871
- risperidone, 719, 872
- ziprasidone, 873
- methamphetamine-induced, 1086
- symptoms of, 856
- treatment of, 856-864, **857**, 870, **871**, 1256
  - amantadine, 862-864
  - benztropine, 860-861
  - biperiden, 861
  - diphenhydramine, 861-862
  - gabapentin, 986
  - procyclidine, 861
  - trihexyphenidyl, 856-860
- Parkinson's disease
  - depression in, 368, 1153, **1154**
  - differentiation from other causes of parkinsonism, 69
  - neuroimaging in, 69, 245
  - norepinephrine transporter in, 76
- Parkinson's disease treatment
  - adenosine A<sub>2A</sub> receptor antagonists, 97
  - amantadine, 862, 863
  - benztropine, 860
  - buspirone, 593
  - deep brain stimulation, 1134, 1163
  - for dementia
    - antipsychotics, 1528
    - rivastigmine, 1041
  - for depression
    - paroxetine, 393
    - sertraline, 368
  - L-dopa, 65
  - ECT, 1112-1113
  - modafinil, 1094
  - for psychosis, 1528
    - clozapine, 633, 1528
    - quetiapine, 692-693, 1528
  - selegiline, 289
  - trihexyphenidyl, 856
- Paroxetine, 385-406
  - augmentation of

- aripiprazole, 742
- pindolol, 389
- in children and adolescents, 393–395, 1435, 1444, 1445, 1449, **1498**
- discontinuation syndrome with, 348–349, 401, 1615
- dosing of, 392–393, **1635–1636**
  - in children and adolescents, **1498**
- drug interactions with, 403–405, **404**
  - antipsychotics, 620
  - asenapine, 799
  - benzodiazepines, 572
  - bupropion, 506
  - clozapine, 641
  - tamoxifen, 398, 404, 405
  - TCAs, 325
  - vortioxetine, 473
- effects on HPA axis, 389
- in elderly persons, 391–392, 500, 1508, 1513
- formulations of, 213, 215–216, 385, 387–388, 405
  - controlled-release, 385, 386, 387–388, 391, 392, 393, 395, 397, 398, 405
- generic, 388
- history and discovery of, 385–386
- indications for, 385, 386, 390–398, 405
  - bipolar depression, 393, 689–690, 927
  - depression, 390–391
    - vs. bupropion, 499
    - in children and adolescents, 393–395, 1435
    - comparative studies of, 390–391
    - vs. duloxetine, 534, **536**
    - in elderly persons, 391–392
    - maintenance treatment, 392–393
    - in medically ill patients, 393, **394**
    - vs. milnacipran, **538**
    - vs. mirtazapine, 481
    - postpartum depression, 406
- generalized anxiety disorder, 396, 1206
  - vs. quetiapine, 691, 1209
- OCD, 396–397
  - in children and adolescents, 1449
  - maintenance treatment/relapse prevention, 1211
- panic disorder, 395, 1195, 1604
  - in children and adolescents, 1445
  - maintenance treatment, 1198

- vs. reboxetine, [1197](#)
- vs. risperidone, [1198](#)
- vs. venlafaxine, [519](#)
- premenstrual dysphoric disorder, [397](#)
- PTSD, [397](#)
- social anxiety disorder, [395–396](#), [1200](#)
  - in children and adolescents, [1202](#), [1444](#)
  - maintenance treatment, [1203](#)
- specific phobia, [1203–1204](#)
- vasomotor menopausal symptoms, [385](#), [398](#)
- mechanism of action of, [389](#), [1108](#)
- overdose of, [401–402](#), [405](#)
- pharmacogenomics and response to, [388–389](#), [1508](#)
- pharmacokinetics and disposition of, [386–388](#)
- pharmacological profile of, [386](#)
- side effects and toxicology of, [398–401](#), [1435](#), [1445](#), [1449](#)
  - anticholinergic effects, [386](#), [392](#), [398](#)
  - medical safety, [400–401](#)
  - sexual dysfunction, [398–399](#)
  - teratogenic effects, [1549–1550](#)
- structure–activity relations for, [336](#), [337](#), [386](#), [386](#)
- suicidality and, [347](#), [393–395](#), [399–400](#), [405](#)
- use in hepatic or renal disease, [387](#), [393](#)
- use in pregnancy and lactation, [402–403](#), [406](#), [1549–1553](#)
- Paroxetine mesylate, [388](#), [398](#)
- PARS (Pediatric Anxiety Rating Scale), [1443](#), [1446](#)
- PAS (Panic and Agoraphobia Scale), [987](#)
- Pathological gambling, [423](#)
- Pathway analysis of genomewide association study data, [141](#)
- Patient Global Impression of Change scale, [1418](#)
- Patient Global Impression of Improvement (PGI-I) Scale, [667](#), [1026](#)
- PATS (Preschool ADHD Treatment Study), [1453](#), [1504](#)
- Pauling, Linus, [251](#)
- Paxil. *See* [Paroxetine](#)
- PCL (PTSD Checklist), [1213](#)
- PCOS (polycystic ovarian syndrome), valproate-induced, [934](#), [1185](#), [1501](#), [1502](#)
- PCP. *See* [Phencyclidine](#)
- pCPA (para-chlorophenylalanine), [585](#), [588](#), [589](#)
- PCR. *See* [Polymerase chain reaction](#)
- PDE9A* gene, [1158](#)
- PDE11A* gene, [1158](#)

PDSS (Panic Disorder Severity Scale), [1195](#)  
Pediatric Anxiety Rating Scale (PARS), [1443](#), [1446](#)  
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), [185](#)  
Pediatric OCD Treatment Study (POTS), [1447](#)  
Pedigree, [14](#), [119](#), [125](#), [132](#)  
PEG three-item pain scale, [1417](#), [1417](#)  
Pentoxifylline, for autism spectrum disorder, [1474](#)–[1474](#)  
Pergolide, [1329](#)  
Peripheral edema, drug-induced  
    MAOIs, [290](#)  
    pregabalin, [995](#), [1393](#)  
Peripheral neuropathy. *See also* [Neuropathic pain](#)  
    diabetic  
        duloxetine for, [529](#), [534](#)  
        fluoxetine for, [344](#)  
        fluvoxamine for, [424](#)  
        gabapentin for, [985](#), [990](#)  
        pregabalin for, [990](#), [991](#)–[992](#), [995](#)  
        trazodone for, [458](#)  
    MAOI-induced, [290](#)  
Perphenazine  
    dosing of, [1645](#)  
    formulations of, [1249](#)  
    indications for  
        behavioral complications of dementia, [1521](#)  
        psychotic depression, [317](#)  
        schizophrenia  
            CATIE study, [620](#), [688](#), [713](#), [1246](#)–[1247](#), [1250](#)  
            for cognitive deficits, [250](#)  
    interaction with paroxetine, [404](#)  
    poor metabolizers of, [228](#)  
    receptor affinities of, [613](#)  
    side effects of, [615](#)–[616](#)  
        extrapyramidal side effects, [720](#), [871](#)  
        ocular effects, [619](#)  
        weight gain/metabolic effects, [695](#), [1253](#)  
    structure–activity relations for, [605](#), [607](#)  
    use in pregnancy and lactation, [1565](#), [1566](#)  
Persistent depressive disorder (dysthymia)  
    disability due to, [1151](#)  
    gender and, [1152](#)

- prevalence of, [1152](#)
  - in adolescents, [1433](#)
- treatment of, [1159](#)
  - ECT, [1109](#)
  - MAOIs, [288](#)
  - mirtazapine, [483](#)
  - SSRIs, [1159](#)
  - TCAs, [318](#), [1159](#)
- Persistent pulmonary hypertension of the newborn (PPHN), maternal SSRI use and, [348](#), [403](#), [1552-1553](#)
- Personality
  - changes in dementia, [1518](#)
  - depression and, [1153](#)
  - Five-Factor Model of, [1153-1154](#)
  - models of, [1314](#)
  - traits and functions of, [1314](#)
- Personality disorders
  - antidepressant response in, [1161](#)
  - bulimia nervosa and, [1338](#)
  - classification of, [1314](#)
  - common dimensions of, [1314](#)
  - dimensional models of, [1314](#)
  - longitudinal studies of, [1315](#)
  - prognosis for, [1315](#)
  - suicide and, [1155](#)
- Personality disorders treatment, [1313-1330](#)
  - for Cluster A disorders: schizotypal personality disorder, [1328-1329](#)
  - for Cluster B disorders, [1315-1328](#)
    - antisocial personality disorder, [1328](#)
    - borderline personality disorder, [1315-1328](#)
    - histrionic personality disorder, [1327](#)
    - narcissistic personality disorder, [1327](#)
  - for Cluster C disorders, [1329-1330](#)
    - avoidant personality disorder, [1329-1330](#)
    - dependent personality disorder, [1329](#)
    - obsessive-compulsive personality disorder, [1329](#), [1330](#)
  - indications for pharmacotherapy, [1313](#)
- Pervasive developmental disorders. *See also* [Autism spectrum disorder](#)
  - treatment of ECT, [1112](#)
    - mirtazapine, [485](#)
    - risperidone, [717](#)
    - sertraline, [371](#)

PET. See Positron emission tomography Pexeva. See [Paroxetine](#)

PFC. See [Prefrontal cortex](#)

PGC (Psychiatric Genomics Consortium), [138](#), [140](#), [141](#), [143](#)

PGI-I (Patient Global Impression of Improvement) Scale, [667](#), [1026](#)

PGRS (polygenic risk score), [127](#), [141](#), [142](#)

Phantom boarder syndrome, [1518](#)

Phantom limb pain, [552](#), [1379](#), [1384](#), [1392](#), [1400](#)

Pharmacodynamics, [210](#), [221–225](#), [233](#)

- clockwise and counterclockwise hysteresis curves, [224](#), [224–225](#)
- definition of, [210](#)
- dose–effect relationship and, [210–211](#), [211](#), [222](#), [222–223](#)
- of drug interactions, [230](#)
- in elderly persons, [1508](#)
  - antipsychotics, [1517–1518](#)
- plasma drug concentration and intensity of effect, [223–224](#), [224](#)
- variability of, [210](#), [211](#), [221](#)

Pharmacogenetics, [226](#)

- of antidepressants, [63](#)
- of clozapine, [628](#)
- CYP2D6* copy number variations and, [127](#)
- dose–effect relationship and, [210](#), [211](#), [226–230](#), [229](#), [231](#)
- frequency histograms, [228](#), [229](#)
- of iloperidone, [814–815](#)

Pharmacogenomics, [225](#), [226–230](#), [229](#)

- of acamprosate, [1288](#)
- of fluvoxamine, [420](#)
- of naltrexone, [227](#), [1287](#)
- of paroxetine, [388–389](#), [1508](#)

Pharmacokinetics, [211–221](#), [233](#)

- definition of, [209](#)
- dose–effect relationship and, [210–211](#), [211](#)
- of drug interactions, [230–233](#)
- in elderly persons, [1505–1508](#), [1507](#)
  - antipsychotics, [1517](#)
  - TCAs, [313–314](#)
- of enantiomers, [226](#)
- genetic differences in, [227](#)
- mathematical models of, [211](#)
- multiple dosing to steady state, [219–221](#), [221](#)
- during pregnancy, [1544](#), [1548–1550](#)
- significance of drug transporters, [211–212](#), [227–228](#)
- single-dose drug disposition, [212–219](#)

- absorption, 212-214, **214**
- distribution, 216-218, **217**, **218**
- elimination, 218-219
- presystemic elimination, 214-216
- sleep-promoting effects of drugs related to mechanism of action, dose and, 1350-1351
- of specific drugs
  - amantadine, 862
  - amphetamine, 1086
  - aripiprazole, 734-736
  - armodafinil, 1091
  - asenapine, 798-799
  - barbiturates, 1067
  - benzodiazepines, 564-567, **566**, 1060, **1061**, **1064**
  - benztropine, 860
  - biperiden, 861
  - $\beta$ -blockers, 864, **865**
  - botulinum toxin, 867
  - brexpiprazole, 736-737
  - bupropion, 497-498
  - carbamazepine, 944-946, **945**
  - cariprazine, 837-838, **839**
  - citalopram, 433-434
  - classic antipsychotics, 609-610
  - clozapine, 627-628
  - desvenlafaxine, 516-517
  - diphenhydramine, 861
  - duloxetine, 533, 534
  - escitalopram, 434
  - eslicarbazepine acetate, 947, **948**
  - fluvoxamine, 420-421
  - gabapentin, 984
  - iloperidone, 810
  - isocarboxazid, 294-295
  - ketamine, 550
  - lamotrigine, 1001-1002
  - levomilnacipran, 533-534
  - licarbazepine, **945**, 947
  - lisdexamfetamine, 1087
  - lithium, 890
  - lurasidone, 922
  - methadone, 1289

- methylphenidate, 1088
- milnacipran, 533–534
- mirtazapine, 480
- moclobemide, 296
- modafinil, 1089
- nefazodone, 460
- nonbenzodiazepine hypnotics, 1060, **1064**
- oxcarbazepine, **945**, 947, **948**
- paliperidone, 709–710
- paroxetine, 386–388
- phenelzine, 294
- pregabalin, 990–991
- quetiapine, 686–687
- risperidone, 709–710
- selegiline, 297
- selegiline transdermal system, 298
- sertraline, 360–362
- suvorexant, 1072–1073
- topiramate, 1018–1019
- tranlycypromine, 295
- trazodone, 456
- trihexyphenidyl, 858
- valproate, 923–926, **925**, **926**
- venlafaxine, 516–517
- vortioxetine, 468
- ziprasidone, 759–761
- variability of, **210**, **211**
- Pharyngitis, antipsychotic-induced, **693**
- Phencyclidine (PCP), **49**, 86, 549, 1605
  - psychosis induced by, 84, 656
    - animal model of, 652
    - antipsychotics for, 611, 710
  - violent behavior during intoxication with, 1611
- Phenelzine, **284**, 294
  - contraindications to, 294
  - dietary interactions with, 291
  - dosing of, **1640**
  - drug interactions with
    - meperidine, 292
    - phenylephrine, 294
  - indications for, 294
    - avoidant personality disorder, 1329



- borderline personality disorder, [1321](#)
- bulimia nervosa, [289](#), [1338](#)
- depression, [288](#)
  - with atypical features, [288](#), [317](#)
- panic disorder, [288-289](#), [1197](#)
- PTSD, [289](#)
- social anxiety disorder, [289](#), [1201](#)
  - cognitive-behavioral therapy and, [1203](#)
- pharmacokinetics of, [294](#)
- pharmacological profile of, [286](#)
- side effects of, [290](#), [294](#)
- structure of, [287](#)

Phenobarbital, [1065](#)

- drug interactions with
  - carbamazepine, [965](#)
  - lamotrigine, [1012](#)
  - oxcarbazepine, [968](#)
  - propranolol, [866](#)

Phenocopies, [122](#)

Phenothiazines. *See also* [Antipsychotics](#)

- aliphatic, [605](#), [607](#)
- history and discovery of, [603](#)
- piperazine, [605](#), [607](#)
- piperidine, [605](#), [607](#)
- side effects of, [615-616](#), [619](#)
- structure-activity relations for, [604](#), [605](#), [607](#)
- use in pregnancy, [1565](#)

Phenotype, [9](#), [122](#), [144](#)

- chromosomal number variations and, [124-125](#)
- drug response as, [124](#)
- genetic phenotyping, [229](#)
- 5-HTTLPR and, [128](#)
- linkage analysis and, [130](#), [131](#)
- metabolic ratio as, [228](#), [229](#)
- polygenic risk score in relation to, [142](#)
- single nucleotide polymorphisms and, [130](#)
- variable number of tandem repeats and, [129](#)

Phentermine-topiramate combination, [503](#), [1017](#), [1019](#), [1028](#)

Phentolamine, [308](#)

- for MAOI-induced hypertensive crisis, [291](#)

Phenylacetic acid, [294](#)

Phenylephrine, interaction with MAOIs, [294](#)

Phenylethylamine, 1084  
Phenylhydrazine, 283  
Phenylketonuria, 122  
Phenytoin, 1066  
    cognitive effects in children exposed in utero to, 935, 1012  
    drug interactions with  
        antipsychotics, 619  
        carbamazepine and oxcarbazepine, 963, 964, 965, 968  
        eslicarbazepine acetate, 969  
        lamotrigine, 1009, 1012  
        paroxetine, 405  
        propranolol, 866  
        quetiapine, 686  
        topiramate, 1019, 1030  
        valproate, 934  
    indications for  
        antisocial personality disorder, 1328  
        mania, 942  
        seizures, 943  
    pharmacokinetics of, 1506, 1507  
Pheochromocytoma, use of MAOIs in, 294  
PHN. See Postherpetic neuralgia  
Phobia, specific, 1203–1204  
    age at onset of, 1203  
    genetics of, 121  
    prevalence of, 1203  
    rating scales for, 1203  
    treatment of, 1203–1204  
Phosphodiesterase inhibitors, for sexual dysfunction, 372, 399, 1160–1161  
Phospholipase C (PLC), 53, 56–57, 59, 61, 62, 63, 71, 74–75, 76, 78–79  
Phosphorylation, 13, 19, 34, 49, 136  
    CREB, 9, 10, 11  
    of G protein-coupled receptors, 50, 52–53  
    of GABA<sub>A</sub> receptors, 95  
    of glucocorticoid receptor, 194  
    of glutamate transporters/receptors, 84, 86–87, 88, 89  
    of norepinephrine transporter, 73  
    of opioid receptors, 101  
    of receptor tyrosine kinases, 53  
Photosensitivity reactions to drugs  
    classic antipsychotics, 616, 619  
    TCAs, 324

Physical restraint of patient, **1607**  
in delirium, **1612**  
alcohol-withdrawal, **1613**  
for involuntary administration of medications, **1608**  
rooms for, **1611**  
in schizophrenia, **1245, 1257**  
for substance intoxication/psychosis, **1611**

Physostigmine  
for anticholinergic delirium, **321**  
as cognitive enhancer, **1042**

[<sup>11</sup>C] PIB (Pittsburgh Compound-B), **248, 269**

Picrotoxin, **1066**

Pigmentary retinopathy, antipsychotic-induced, **616, 619, 1516**

Pilocarpine eye drops, **322**

Pimozide  
dosing of, **1645**  
drug interactions with  
fluvoxamine, **425**  
paroxetine, **404**  
side effects of, **615-616**  
structure-activity relations for, **606, 608**  
for Tourette syndrome, **608, 612, 1461, 1462**

Pindolol, **339, 865**  
for paroxetine augmentation, **389**

Pipercuronium, interaction with carbamazepine and oxcarbazepine, **963**

Piracetam, **1045**

Pittsburgh Compound-B ([<sup>11</sup>C] PIB), **248, 269**

PKA (protein kinase A), **11, 49, 53, 81**

PKC (protein kinase C), **53, 60, 61, 73, 81, 891**

Placental drug transfer, **227**. *See also* **Pregnancy and lactation**

Plasma drug concentration, **209-210**  
drug formulation and, **213, 214**  
drug interactions affecting, **231, 232**  
intensity of effect and, **223-224, 224**  
linearity and, **220, 221**  
minimal effective concentration, **213, 214, 216, 217, 217, 220, 221**  
of specific drugs  
amantadine, **862**  
aripiprazole, **735**  
armodafinil, **1091**  
asenapine, **798**  
brexpiprazole, **737**

bupropion, 497  
carbamazepine, 946  
cariprazine, 838, **839**  
citalopram, 433, 434  
classic antipsychotics, 609  
clozapine, 627-628  
cyclic antidepressants, 209, 305, **311**, 312  
    prospective dosing techniques and, 315  
    response and, 314  
    toxicity and, 314-315, 320  
desvenlafaxine, 516  
diphenhydramine, 861  
doxepin, 1351  
duloxetine, 533  
fluvoxamine, 421  
iloperidone, 810  
ketamine, 550  
lamotrigine, 1001-1002  
levomilnacipran, 534  
lithium, 890, 1178, 1184  
lurasidone, 922  
milnacipran, 534  
modafinil, 1091  
nefazodone, 460  
olanzapine, 653, 654  
paliperidone, 709-710  
paroxetine, 387  
pregabalin, 990  
quetiapine, 686  
risperidone, 709-710  
sertraline, 360-361  
suvorexant, 1072  
topiramate, 1018  
trazodone, 456  
trihexyphenidyl, 858  
valproate, 924, **925**, **926**, 1178, 1185  
venlafaxine, 516  
vortioxetine, 468  
ziprasidone, 759-760  
steady-state, **219**, 219-221, **221**, 225-226, 231  
time course of, 216  
tissue concentration and, 217, **217**

Plasma protein binding of drugs, 217–218, **218**

amphetamine, 1086

antidepressants

bupropion, 497

citalopram, 434

cyclic antidepressants, 310, 313

duloxetine, 533

fluvoxamine, 420

ketamine, 550

levomilnacipran, 533, 534

milnacipran, 533, 534

moclobemide, 296

nefazodone, 460

paroxetine, 387, 405

sertraline, 361, 373

antipsychotics, 610, 619

aripiprazole, 735

asenapine, 799

brexpiprazole, 737

cariprazine, 838

olanzapine, 653

paliperidone, 709

risperidone, 709

ziprasidone, 757, 760

carbamazepine, 944, 962

in elderly persons, 1506

eslicarbazepine acetate, 968

lamotrigine, 1002

licarbazepine, 947

methylphenidate, 1088

modafinil, 1089

oxcarbazepine, 947

topiramate, 1018

valproate, 924, **926**, 935–936

PLC (phospholipase C), 53, **56–57**, 59, 61, **62**, 63, 71, **74–75**, 76, **78–79**

PMDD. *See* Premenstrual dysphoric disorder

PMS. *See* Premenstrual syndrome

Polycystic ovarian syndrome (PCOS), valproate-induced, 934, 1185, 1501, **1502**

Polydipsia, lithium-induced, 1439, 1501

Polydrug abuse, 575

Polygenic analysis of genomewide association study data, 141–142

Polygenic risk score (PGRS), [127](#), [141](#), [142](#)

Polymerase chain reaction (PCR)

- for DNA cloning, [14-16](#)
- for microsatellite amplification, [128](#)
- quantitative (qPCR), [22](#)
- real-time, [16](#)
- reverse transcriptase (RT-PCR), [16-17](#)

Polymorphisms

- clozapine response and, [628](#)
- copy number variations, [127](#)
- insertion/deletion, [127-128](#), [141](#)
  - 5-HTTLPR, [59](#), [127-128](#), [134](#), [388](#)
- microsatellite markers, [128-129](#)
- pharmacogenomics and, [226](#), [227](#)
- pharmacokinetic/pharmacodynamic variability due to, [210](#), [211](#)
- positional cloning, [16](#)
- single nucleotide, [129-130](#)
- variable number tandem repeats, [69](#), [128-129](#)

Polyuria, drug-induced

- lithium, [1439](#), [1501](#)
- venlafaxine, [1471](#)

POMC (pro-opiomelanocortin), [64](#), [99](#), [158](#), [342](#)

POMS (Profile of Mood States), [988](#)

Poor metabolizers, [228-229](#), [229](#)

Population stratification, [134-135](#)

Porphyria, use of barbiturates in, [1067](#)

Positional cloning, [16](#)

Positive and Negative Syndrome Scale (PANSS), [486](#), [631](#), [635](#), [658](#), [659](#), [667](#), [668](#), [671](#), [713](#), [714](#), [722](#), [739](#), [740](#), [741](#), [742](#), [745](#), [763](#), [764](#), [765](#), [767](#), [768](#), [769](#), [800-801](#), [803](#), [811](#), [812-813](#), [814](#), [823](#), [840](#), [841-843](#), [843](#), [844](#), [846](#), [931](#), [1007](#), [1021](#), [1022](#), [1028](#), [1463](#), [1464](#), [1465](#)

Positron emission tomography (PET), [239](#), [240-249](#), [269](#)

- amyloid imaging, [247](#), [248](#)
- blood-flow studies, [242-243](#)
- combined with deep brain stimulation, [244](#)
- combined with EEG, [265](#)
- compared with fMRI, [255](#), [256](#)
- dopamine imaging, [69](#), [129](#), [245](#)
- to guide treatment selection, [267](#)
- MAO-labeling studies, [69](#), [265](#), [285](#)
- metabolic and blood-flow studies in neuropsychiatry, [243](#), [243-244](#)
- metabolic studies, [241-242](#), [242](#)

- microglial imaging, 248–249
- nicotinic ligands for, 81
- norepinephrine transporter, 76
- receptor-labeling studies, 244–245, 246–247
  - dopamine receptors, 71
    - asenapine affinity for, 798
    - cariprazine affinity for, 836–837
    - quetiapine affinity for, 685
    - risperidone affinity for, 707–708
    - studies of antipsychotic effects and side effects, 266–267
    - ziprasidone affinity for, 756, 757, 758
- GABA<sub>A</sub> receptor, 93
- serotonin receptors, 61, 63–64
  - olanzapine affinity for, 655
- serotonin imaging, 59, 245, 248
- serotonin transporter, 59, 245
  - duloxetine affinity for, 532
  - milnacipran affinity for, 532
  - venlafaxine affinity for, 532
  - vortioxetine affinity for, 467
- in specific disorders
  - ADHD, 244, 245
  - Alzheimer's disease, 244, 247, 248
  - bipolar disorder, 69, 244
  - depression/suicidality, 59, 61, 69, 243, 245, 248
  - epilepsy, 242
  - Parkinson's disease, 245
  - PTSD, 244, 248
  - schizophrenia, 93, 244, 267
  - substance use disorders, 244
- technical aspects of, 240–241
- venlafaxine receptor binding affinity, 59, 517
- Postherpetic neuralgia (PHN), 1379, 1400
  - gabapentin for, 983, 985, 1392
  - lidocaine patch for, 1383
  - opioids for, 1384
  - pregabalin for, 990, 991, 1392
- Postpartum hemorrhage, venlafaxine and, 522
- Postpartum psychopathology, 1545
  - bipolar disorder, 1545
  - blues, 166
  - depression, 166, 167, 1544, 1545

- CBT for, 363
- effects on infant development, 1546
- paroxetine for, 406
- prevalence of, 1545
- sertraline for, 363, 364
- hospitalization for, 1545
- neuroendocrinology of, 157, 166–169
- OCD, 1545
- psychosis, 1545
  - immune system in, 167–168
- Poststroke depression, 345, 1093
- Posttraumatic stress disorder (PTSD), 1212–1213
  - behavioral indicators of risk for, 1603
  - borderline personality disorder and, 1326
  - childhood abuse history and, 163–164, 185
    - FKBP5* gene polymorphism and, 121, 144
  - in children and adolescents, 1450–1451
  - GABA in, 248
  - ICU-induced, 76
  - immune system in, 185
  - neurobiology of
    - HPA axis, 99, 163–164
    - HPT axis, 165
    - vasopressin, 99
  - norepinephrine in, 73
  - PET studies in, 244, 248
  - in pregnancy, 1545, 1546
  - prevalence of, 1213
  - rating scales for, 1213
  - treatment immediately after trauma for prevention of, 1218–1219, 1602–1604
- Posttraumatic stress disorder treatment, 1213–1218
  - anticonvulsants, 1216
    - carbamazepine, 1216
    - lamotrigine, 1216
    - tiagabine, 1216
    - topiramate, 1026, 1216
    - valproate, 931, 1216
  - antidepressants, 1213–1215
    - MAOIs, 289, 1213
    - mirtazapine, 484, 1215
    - nefazodone, 1215



- SSRIs, 569, 1214–1215
  - fluoxetine, 344, 1214
  - fluvoxamine, 423, 1214–1215
  - paroxetine, 397, 1214
  - sertraline, 367–368, 1214
  - thyroid hormone and, 1217
- TCAs, 1213
- trazodone, 457–458
- venlafaxine, 519, 1215
- antipsychotics, 1216–1217
  - olanzapine, 667–668, 1216
  - quetiapine, 692, 1217
  - risperidone, 1216–1217
- benzodiazepines, 569, 1215–1216
- in children and adolescents, 1451–1452
  - carbamazepine, 1451
  - citalopram, 1451
  - clinical recommendations for, 1452
  - clonidine, 1451
  - D-cycloserine, 1452
  - guanfacine, 1451
  - prazosin, 1452
  - propranolol, 1452
  - quetiapine, 1452
  - risperidone, 1452
  - sertraline, 1451
- cognitive-behavioral therapy, 1218
- drug-enhanced exposure therapy, 1218
- guanfacine, 1217
- innovative treatments, 1217–1218
- ketamine, 554, 1218
- prazosin, 1217
- propranolol, 76
- somatic treatments, 1217–1218
  - ECT, 1112, 1217–1218
  - rTMS, 1217
  - stellate ganglion block, 1218
- Potassium ion channels, 47, 49, 51, 58, 60, 62, 71, 76, 80, 95
  - drug effects on
    - lamotrigine, 1002
    - opioids, 101
- POTS (Pediatric OCD Treatment Study), 1447

1-PP (1-(2-pyrimidinyl)piperazine), 588, 594  
PP3M. See [Paliperidone, 3-month formulation of](#)  
PPHN (persistent pulmonary hypertension of the newborn), maternal SSRI use and, 348, 403, 1552–1553  
Prader-Willi syndrome, 122, 126  
Pramipexole, for bipolar depression, 1183  
Prazepam, 564, 566, 572, 1061  
Praziquantel, interaction with carbamazepine and oxcarbazepine, 963  
Prazosin, 626, 692, 712  
    for insomnia, 1359–1361, 1368  
    for PTSD, 1217  
    in children and adolescents, 1452  
    side effects of, 1368  
Prednisolone  
    challenge in depression, 161  
    interaction with carbamazepine and oxcarbazepine, 963  
Prefrontal cortex (PFC)  
    dorsolateral, in executive function, 259  
    GABAergic neurons in, in depressed patients, 92  
    glutamate receptors in, in suicidal patients, 87, 91  
    5-HT<sub>2A</sub> receptors in, 64  
    kainate receptors in, 89  
    in mood disorders, 68, 1156  
    in stress response, 54, 73, 80  
Pregabalin, 990–995  
    abuse potential of, 995  
    dosing of, 1393, 1652  
    drug interactions with, 995  
    indications for, 990, 991–995  
        alcohol use disorder, 994–995  
        benzodiazepine discontinuation, 995  
        generalized anxiety disorder, 993–994, 1208–1209, 1210  
        pain syndromes, 1414  
            fibromyalgia, 992–993, 1403, 1403–1404  
            neuropathic pain, 990, 991–992, 1392–1393, 1400, 1401  
        seizures, 991, 1393  
        social anxiety disorder, 994, 1201  
    mechanism of action of, 990  
    pharmacokinetics and disposition of, 990–991  
    pharmacological profile of, 990  
    side effects and toxicology of, 995, 1393, 1401, 1404  
    structure–activity relations for, 990, 990

use in renal or hepatic disease, [991](#), [995](#)

Pregnancy and lactation. *See also* [Breast milk](#); [Postpartum psychopathology](#)

anxiety in, [1545–1546](#)

bipolar disorder in, [1544](#)

depression in, [167](#), [1544–1546](#)

    bright light therapy for, [1163](#)

ECT in, [1111](#), [1113](#)

effects of maternal psychiatric disorders on offspring, [1545–1546](#)

fetal drug exposure

    acute and developmental effects of, [1546–1547](#), [1547](#)

    FDA reproductive safety ratings for drugs, [1547–1548](#), [1548](#)

    fetal brain concentration and, [1550](#)

    guidelines for minimization of, [1543](#), [1544–1545](#)

    maternal dosage management for reduction of, [1548–1549](#), [1570](#)

    nonpsychotropic treatments for reduction of, [1569](#)

    placental drug transfer and, [1549](#)

OCD in, [1545](#)

panic disorder in, [1545](#), [1546](#)

pharmacokinetics during, [1544](#), [1548–1550](#)

prevalence of drug use in, [1544](#)

psychosis in, [1545](#)

psychotropic drug use during, [1543–1570](#)

    amantadine, [864](#), [1566](#)

    antidepressants, [1544–1545](#), [1550–1555](#)

        bupropion, [498](#), [505–506](#), [1553](#)

        desvenlafaxine, [522](#), [1554](#)

        duloxetine, [541](#), [1553](#), [1554](#)

        MAOIs, [1555](#)

        mirtazapine, [485](#), [487–488](#), [1553](#), [1554](#)

        SSRIs, [347–348](#), [364](#), [373](#), [402–403](#), [425–426](#), [1549](#), [1550–1553](#)

        TCAs, [324–325](#), [348](#), [1549](#), [1551](#), [1554–1555](#)

        venlafaxine, [522](#), [1553](#), [1554](#)

    antipsychotics, [610](#), [1562–1566](#)

        aripiprazole, [1564](#)

        cariprazine, [849–850](#)

        classic antipsychotics, [1565–1566](#)

        clozapine, [1562–1563](#)

        iloperidone, [810](#)

        olanzapine, [672–673](#), [1563](#)

        paliperidone, [1564](#)

        quetiapine, [697](#), [1564](#)

        risperidone, [1563–1564](#)

- ziprasidone, [774](#)
- anxiolytics, [1566–1568](#)
  - benzodiazepines, [576–577](#), [1065](#), [1566–1568](#)
  - buspirone, [1568](#)
- benztropine, [1566](#)
- botulinum toxin, [868](#)
- diphenhydramine, [1566](#)
- dosage management for, [1548–1549](#), [1570](#)
- dose–effect relationship for, [210](#)
- FDA reproductive safety ratings for, [1547–1548](#), **[1548](#)**
- future directions and recommendations for, [1568–1570](#)
- informed consent for, [1569](#)
- medication selection for, [1569–1570](#)
- monitoring of nursing infants, [1570](#)
- mood stabilizers, [1555–1562](#)
  - carbamazepine, [959](#), [1549](#), [1559–1560](#)
  - eslicarbazepine acetate, [960](#)
  - lamotrigine, [1002](#), [1011–1012](#), [1549](#), [1560–1562](#)
  - lithium, [901–902](#), [1555–1556](#)
  - oxcarbazepine, [960](#)
  - topiramate, [1030](#)
  - valproate, [935](#), [1549](#), [1556–1559](#)
- opioids
  - buprenorphine maintenance treatment, [1294](#)
  - methadone, [1293–1294](#), [1390](#)
- PTSD in, [1545](#), [1546](#)
- Pregnancy and Lactation Labeling Rule for drugs, [1547–1548](#)
- Premature ejaculation
  - fluoxetine for, [344](#)
  - paroxetine for, [344](#), [399](#)
  - sertraline for, [370](#)
- Premenstrual dysphoric disorder (PMDD) treatment
  - fluoxetine, [343](#)
  - MAOIs, [289](#)
  - paroxetine, [397](#)
  - sertraline, [364–365](#)
  - venlafaxine, [519](#)
- Premenstrual syndrome (PMS), [166–167](#)
  - buspirone for, [593](#)
  - sertraline for, [365](#)
- Prenylation, [13](#), [34](#)
- Prepulse inhibition deficit, in schizophrenia, [626–627](#), [656](#), [710](#)

Preschool ADHD Treatment Study (PATs), 1453, 1505

Presenilin 1 (PS1) and presenilin 2 (PS2)  
in Alzheimer's disease, 1039  
in transgenic mice, 27

Presystemic elimination of drug, 214-216

Priapism, drug-induced, 1615-1616  
antipsychotics, 612, 619  
clozapine, 640  
trazodone, 458, 1369, 1615  
treatment of, 1608, 1616

Primidone-drug interactions  
carbamazepine and oxcarbazepine, 963, 965, 968  
lamotrigine, 1012

Principal components analysis, for population stratification, 135

Pro-opiomelanocortin (POMC), 64, 99, 158, 342

Procainamide, interaction with iloperidone, 818

Procarbazine, interaction with MAOIs, 293

Prochlorperazine, 605, 607

Procyclidine, 857, 861

Profile of Mood States (POMS), 988

Progesterone, 166-167

Prolactin, 165-166. *See also* Hyperprolactinemia  
borderline personality disorder and, 1326  
circadian pattern of release of, 165  
depression and, 165-166  
dopamine-inhibited release of, 607  
drug effects on level of  
antipsychotics, 608-609, 612, 618-619, 1257-1258, 1499-1500  
brexpiprazole, 748  
classic antipsychotics, 609, 612, 618-619, 733  
iloperidone, 810, 818  
lurasidone, 825, 1257  
olanzapine, 672, 1439, 1462  
paliperidone, 720, 721, 722, 1247, 1257, 1463  
quetiapine, 696  
risperidone, 718, 720-721, 722, 1180, 1247, 1257, 1441, 1457, 1458  
buspirone, 588-589  
fluoxetine, 346  
psychosis and, 166

Prolixin. *See* Fluphenazine

Promazepam, 566

Promethazine, 1068

- for opioid withdrawal, 1614
- Propafenone, interaction with fluoxetine, 350
- Propofol, for ECT, 1121, 1122
  - in cardiac disease patients, 1125
  - for postictal agitation, 1123
- Propoxyphene, 964, 1384
- Propranolol
  - in children and adolescents, 1452
  - dosing of, 1660
  - drug interactions with, 866
    - fluvoxamine, 425
  - indications for, 865
    - acute stress disorder, 1219
    - akathisia, 864, 865, 865, 1607, 1614
      - vs. mirtazapine, 486
    - behavioral complications of dementia, 1524, 1612
    - migraine prophylaxis, 1414
  - PTSD
    - in children and adolescents, 1452
    - drug-enhanced exposure therapy, 1218
    - ICU-induced, 76
    - restless legs syndrome, 864
    - serotonin syndrome, 1615
    - trauma victims, 77
    - tremor, 865
  - pharmacokinetics and disposition of, 864
  - side effects of, 1452
- ProSom. See Estazolam
- Prostaglandins, 188, 189, 1382
  - in depression, 182, 182
- Prostate cancer, 370
- Prostatic hypertrophy, trazodone in, 458
- Protease inhibitor-drug interactions, 1507
  - benzodiazepines, 572
  - carbamazepine and oxcarbazepine, 963, 967
- Protein(s)
  - activator, 8
  - cAMP response element-binding (CREB), 9, 10, 11, 48, 101
  - CREB-binding (CBP), 10, 11
  - DNA coding for, 5
  - dominant-negative, 25, 27
  - G, 7, 25, 50, 61, 62

- green fluorescent, 19
- histone, 8
- regulatory, 6
- repressor, 6
- RNA translation into, 4, 5, 6, 7
- SNARE, 51
- TATA binding, 9, 9
- Protein binding. *See* Plasma protein binding of drugs
- Protein kinase A (PKA), 11, 49, 53, 81
- Protein kinase C (PKC), 53, 60, 61, 73, 81, 891
- Protein tyrosine phosphatase (PTP1D), 82-83
- Proteomics, 25, 33-34, 136
- Protriptyline, 306, 307, 308, 310, 311, 1632
- Prozac. *See* Fluoxetine
- Pruritus
  - citalopram-induced, 1470
  - doxepin for, 320
  - sertraline for, 370
- Pseudoakathisia, 856
- Pseudobulbar affect, sertraline for, 368
- PSM (pain self-management), 1396, 1397
- Psychiatric emergencies, 1593-1616
  - clinician training for, 1595
  - conditions that require minimal or adjunctive pharmacological intervention, 1601-1605, 1603
    - acute trauma, 1602-1604
    - adjustment disorders, 1602
    - conditions that require medical evaluation, 1604-1605
      - catatonia, 1605
      - conversion disorder, 1605
      - dissociative episodes, 1604-1605
      - mania or psychosis, 1605
      - panic disorder, 1604
  - conditions that usually require pharmacological intervention, 1605-1616, 1607-1608
    - assaultive, aggressive, or violent behavior, 1606-1609
    - bipolar disorder, 1610
    - delirium, 1612
    - dementia, 1612
    - psychotropic drug side effects, 1614-1616
      - antidepressants, 1615-1616
      - antipsychotics, 1614-1615

- schizophrenia, [1609–1610](#)
- substance intoxication, [1610–1612](#)
- substance withdrawal states, [1612–1614](#)
  - alcohol and sedative-hypnotics, [1612–1613](#)
  - opiates, [1613–1614](#)
- confidentiality in, [1594](#), [1597](#), [1601](#)
  - HIPAA and, [1594](#)
- decision making in, [1594](#)
- emergency department visits for, [1593](#)
- situations that do not require pharmacological intervention, [1595–1601](#), [1596](#)
  - evaluating need for hospitalization, [1595–1596](#)
  - grave disability and inability to care for self, [1601](#)
  - homicidal state, [1600–1601](#)
  - notification of third parties, [1601](#)
  - suicidal state, [1596–1600](#), [1597](#)
- sources of information in, [1593–1594](#)
- telemedicine systems for, [1594–1595](#)
- Psychiatric Genomics Consortium (PGC), [138](#), [140](#), [141](#), [143](#)
- Psychodynamic psychotherapy, short-term, for depression, [1164](#)
- Psychological debriefing after trauma exposure, [1602–1603](#)
- Psychomotor performance effects of drugs
  - barbiturates, [1068](#)
  - benzodiazepines, [570](#), [577–578](#), [1205](#), [1353](#), [1364](#)
  - buspirone, [594](#)
  - nonbenzodiazepine hypnotics, [1365](#)
  - opioids, [1385](#), [1386](#)
  - topiramate, [1028](#)
- Psychoneuroendocrinology, [157–169](#)
  - of depression, [158–162](#), [165–167](#), [1153](#), [1156–1157](#)
  - endocrine effects of drugs
    - antipsychotics, [608–609](#)
    - buspirone, [588–589](#)
    - opioids, [1385](#)
  - growth hormone and hypothalamic-pituitary-somatotrophic axis, [165](#)
  - hypothalamic-pituitary-adrenal axis, [157–164](#)
  - hypothalamic-pituitary-gonadal axis, [166–168](#)
  - hypothalamic-pituitary-thyroid axis, [164–165](#)
  - prolactin, [165–166](#)
  - of schizophrenia, [162–163](#), [165](#)
- Psychoneuroimmunology, [189](#). *See also* [Immune system](#)
- Psychosis. *See also* [Delusions](#); [Hallucinations](#); [Schizophrenia](#)



- during alcohol withdrawal, 1613
- during benzodiazepine withdrawal, 573
- in dementia, 1515, 1516, 1518–1519
  - aripiprazole for, 744
  - neurobiological mechanisms of, 1519–1520
  - olanzapine for, 663
- depression and, 1259–1260
- drug-induced
  - ketamine, 84, 86, 555
  - phencyclidine, 84
  - psychostimulants, 1502–1503
    - amphetamines, 1086, 1087, 1611
    - cocaine, 1611
  - topiramate, 1022
- HPA axis and, 162–163
- medical evaluation of, 1605
- paranoid, 1087
- in Parkinson's disease, 1528
  - clozapine for, 633
  - quetiapine for, 692–693
- postpartum, 167–168, 1545
- in pregnancy, 1545, 1546
- prolactin and, 166
- in PTSD, 667–668
- in schizophrenia, 1242, 1243, 1244–1246

Psychosocial interventions. *See also Psychotherapy*

- for adjustment disorders, 1602
- for pain, 1396
- for personality disorders, 1313
- for schizophrenia, 1245, 1248, 1250–1253, 1262
- for substance use disorders, 1284, 1292

Psychostimulants, 1083–1097. *See also Wakefulness-promoting agents; specific drugs*

- amphetamines, 1083–1087
- in children and adolescents, 1452–1453, 1455–1457, 1459–1460, 1502–1504
  - dosage and monitoring for, 1502, 1503
- FDA classification of, 1084
- formulations of, 213, 1503
- indications for, 1083, 1084, 1091–1097
  - ADHD, 214, 503, 1084, 1087, 1091–1092, 1452–1453, 1455–1456
  - atomoxetine and, 1454, 1456

- clonidine and, [1455](#), [1456](#), [1459–1460](#)
- with disruptive behavior disorders and aggression, [1456](#), [1457](#), [1459–1460](#)
- guanfacine and, [1455](#), [1456](#)
- risperidone and, [1457](#), [1458](#)
- alcohol use disorder, [1093](#)
- cocaine and stimulant abuse, [1093](#)
- drug-induced somnolence, [1398](#)
- fatigue, [1094](#)
- narcolepsy, [1093–1094](#)
- schizophrenia, [1096–1097](#)
- stroke and traumatic brain injury patients, [1092–1093](#)
- interaction with MAOIs, [293](#)
- lisdexamfetamine, [1087–1088](#)
- methylphenidate, [1088–1089](#)
- side effects of, [1502–1504](#)
  - growth effects in children, [1504](#)
- stimulant-related disorders, [1301–1303](#), [1611–1612](#)
  - bupropion for, [504](#)

Psychotherapy. *See also specific psychotherapies*

- for adjustment disorders, [1602](#)
- for anorexia nervosa, [1344](#)
- for binge-eating disorder, [1023](#), [1337](#), [1344](#)
- for bipolar disorder, [1183](#), [1186](#)
- for bulimia nervosa, [1337](#), [1339–1340](#)
- for children and adolescents, [1432](#)
- for depression, [1163–1165](#), [1166](#)
- for generalized anxiety disorder, [1210](#)
- for insomnia, [1350](#)
- for OCD, [1211](#)
- for pain, [1395–1397](#), [1396](#)
- for panic disorder, [1198–1199](#)
- for personality disorders, [1313](#)
- for PTSD, [1218](#)
- for schizophrenia, [1245](#), [1251](#), [1252](#)
- for social anxiety disorder, [1202–1203](#)
- for specific phobia, [1204](#)
- for substance use disorders, [1284](#)
- for suicidality, [1600](#)

Psychotic depression treatment, [1159](#), [1166](#)

- clozapine, [633](#)
- ECT, [1162](#), [1530](#)

in elderly patients, [1530](#)  
fluvoxamine, [421](#)  
MAOIs, [296](#)  
TCAs, [317](#)  
PTP1D (protein tyrosine phosphatase), [82-83](#)  
PTSD. *See* [Posttraumatic stress disorder](#)  
PTSD Checklist (PCL), [1213](#)  
Purine receptors, [96-97](#)  
Pyridoxine deficiency, MAOI-induced, [290](#)  
1-(2-Pyrimidinyl)piperazine (1-PP), [588](#), [594](#)

QIDS-SR (Quick Inventory of Depressive Symptomatology, Self-Report), [436](#), [437](#)

Qsymia. *See* [Phentermine-topiramate combination](#)

QTc interval, drug effects on

antidepressants

citalopram, [370](#), [431](#), [444](#), [446](#), [1525](#)

escitalopram, [446](#)

fluvoxamine, [425](#)

nefazodone, [462](#)

paroxetine, [401](#)

sertraline, [369](#), [370](#)

TCAs, [323](#), [370](#)

venlafaxine, [522](#), [1514](#)

vortioxetine, [473](#)

atypical antipsychotics, [1500](#)

asenapine, [804](#)

iloperidone, [815](#), [818](#), [1248](#)

lurasidone, [825](#)

olanzapine, [672](#)

paliperidone, [1248](#)

quetiapine, [721](#)

risperidone, [721](#), [722](#), [1517](#)

ziprasidone, [755](#), [781–782](#), [1248](#), [1469](#)

classic antipsychotics, [607](#), [608](#), [612](#), [618](#), [780–781](#)

dofetilide, [233](#)

eslicarbazepine acetate, [960](#)

methadone, [1289–1290](#), [1292](#), [1390](#)

sotalol, [233](#)

Quality of Life Scale, [767](#)

Quazepam, [565](#), [1064](#), [1353](#), [1642](#)

QUEST (Quetiapine Experience with Safety and Tolerability) study, [689](#)

Quetiapine, [685–697](#)

abuse potential of, [697](#)

in children and adolescents, [659](#), [687](#), [689](#), [1438](#), [1439–1440](#), [1441](#), [1442](#), [1452](#), [1462](#), [1463](#), [1469](#), [1499](#)

dosing of, [686](#), [687](#), [688](#), [690](#), [1180](#), [1523](#), [1649](#)

in children and adolescents, [1499](#)

in elderly persons, [1525](#)

drug interactions with, [686](#)

carbamazepine and oxcarbazepine, [963](#), [966](#)

in elderly persons, [687](#), [692](#), [1523](#), [1524](#), [1525](#), [1529–1530](#)

- extended-release, 685, 686–687, 690
- history and discovery of, 685
- indications for, 687–693
  - aggression in children and adolescents, 1458
  - agitation, 692, 693
  - antisocial personality disorder, 1328
  - anxiety disorders, 690–691
    - generalized anxiety disorder, 691, 1209
    - social anxiety disorder, 691
  - augmentation of antidepressant treatment, 685, 690
  - autism spectrum disorder, 1469
  - behavioral complications of dementia, 692, 1523, 1524, 1525, 1624
  - bipolar disorder, 685, 687, 689–690
    - in children and adolescents, 1438, 1439–1440, 1441, 1442
    - depressive episodes, 689–691, 894, 1005, 1181
    - maintenance treatment, 690, 896, 1185
    - mania, 689, 892, 1180, 1610
  - borderline personality disorder, 693, 1316, **1318–1319**
  - diffuse Lewy body dementia, 1528
  - insomnia, **1370**, 1371
  - OCD, 692, 1212
    - citalopram and, 1211
  - panic disorder, 1198
  - Parkinson's disease psychosis, 692–693, 1528
  - PTSD, 692, 1217
    - in children and adolescents, 1452
  - schizophrenia, 685, 687–689
    - CATIE study, 620, 688, 696, 697, 713, 1246–1247
    - in children and adolescents, 659, 687, 689, 1462, 1463
    - in elderly persons, 1529–1530
    - vs. lurasidone, 823
    - vs. olanzapine, 659, 688–689
    - vs. risperidone, 688
    - with substance use disorder, 689, 1259
    - treatment-resistant illness, 631, 1249
  - pharmacokinetics and disposition of, 686–687, 1523
  - pharmacological profile of, 624, 1523
  - side effects and toxicology of, 688, **693**, 693–697, 1180, 1248, 1316, **1370**, 1440, 1463
    - cardiovascular effects, 697, 1516
    - cataracts, 697

- extrapyramidal side effects, [669](#), [688](#), [697](#), [720](#), [871](#), [872–873](#), [1255](#), [1523](#)
- somnolence, sedation, and dizziness, [688](#), [694](#), [804](#), [823](#), [1180](#), [1248](#), [1316](#), [1440](#), [1463](#), [1525](#)
- thyroid hormone abnormalities, [697](#)
- weight gain/metabolic effects, [637](#), [689](#), [691](#), [694–696](#), [695](#), [718](#), [823](#), [1180](#), [1253](#), [1254](#)
- structure–activity relations for, [624](#), [625](#), [685–686](#), [686](#)
- use in pregnancy and lactation, [697](#), [1564](#)

Quetiapine Experience with Safety and Tolerability (QUEST) study, [689](#)

Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR), [436](#), [437](#)

Quillivant XR. *See* [Methylphenidate](#)

Quinidine

- combined with dextromethorphan, for agitation in elderly patients, [1628](#)
- drug interactions with, [312](#)
  - aripiprazole, [749](#)
  - brexpiprazole, [749](#)
  - carbamazepine, [963](#)
  - classic antipsychotics, [620](#)
  - fluoxetine, [350](#)
  - iloperidone, [818](#)
  - oxcarbazepine, [963](#)

TCAs, [325](#)

Quinupristin/dalfopristin, interaction with carbamazepine, [964](#)

Rabbit syndrome, [1256](#)

Race/ethnicity

- CYP2D6 and, [312](#)
- depression risk and, [1153](#)
- genetic testing for carbamazepine use
  - HLA-A\*3101*, [958](#)
  - HLA-B\*1502*, [957](#)
- 5-HTTLPR polymorphism and, [128](#)
- metabolic ratio and, [228](#), [229](#)
- suicide and, [1598](#)

Racemic mixtures, [226](#)

Raclopride, [629](#), [707](#), [710](#)

RAISE (Recovery After an Initial Schizophrenia Episode) study, [696](#)

Ramelteon, for insomnia, [1052](#), [1071](#), [1355–1356](#), [1366](#), [1642](#)

- in adjustment disorders, [1602](#)
- interaction with fluvoxamine, [425](#)

Rapamycin, [1218](#)

Rape victims, [1603](#)

Rapid eye movement (REM) sleep, [55](#)

- drug effects on
  - alcohol-type hypnotics, [1069](#)
  - amphetamines, [1084–1085](#)
  - barbiturates, [1062](#), [1067](#)
  - benzodiazepines, [1061–1062](#), [1062](#)
  - fluoxetine, [346](#)
  - γ-hydroxybutyrate, [1069](#)
  - nefazodone, [460](#)
  - nonbenzodiazepine hypnotics, [1057](#)
  - prazosin, [1217](#)
  - ramelteon, [1071](#)
- in narcolepsy, [1094](#)

Rapstinel, [553](#)

Rash, drug-induced

- benzodiazepines, [1065](#)
- bupropion, [504](#), [1436](#), [1498](#)
- carbamazepine, [957–958](#), [1179](#), [1440](#)
- classic antipsychotics, [616](#), [619](#)
- eslicarbazepine acetate, [960](#)
- ketamine, [555](#)
- lamotrigine, [1008–1009](#), [1010](#), [1441](#), [1502](#)
- modafinil, [1090](#)
- oxcarbazepine, [958](#), [960](#), [1440](#), [1502](#)
- TCAs, [324](#)
- ziprasidone, [775](#)

Reboxetine

- for autism spectrum disorder, [1471](#)
- for depression, [391](#)
- for panic disorder, [1197](#)

Receptors, [46–54](#). *See also specific types*

- adenosine, [96–98](#)
- adrenergic, [76–77](#)
- agonist binding to, [46](#)
- γ-aminobutyric, [47](#), [93–96](#)
- autoreceptors, [50–51](#)
- cannabinoid, [98](#), [247](#), [1394](#)
- CRH, [98–99](#)
- dopamine, [70–72](#)
- functions of, [46](#)

- G protein-coupled, 25, 34, 47, **48-49**, 50-53, **52**
- glutamate, 47, **82**, 85-91
  - AMPA receptors, 88-89
  - kainate receptors, 89-90
  - metabotropic, 90-91
  - NMDA receptors, 85-88
- glycine, 91-92
- heteroreceptors, 50, 90
- $\gamma$ -hydroxybutyrate, 1069
- ionotropic, 47-50, **48**
- melatonin, 1071, 1355, 1356
- muscarinic, **62**, **79**, 80
- neurotensin, 654, 656
- nicotinic, 47, **79**, 80-81, 97
- nuclear, 47, **48-49**, 53-54
- opioid, 76, 101
- orexin, 1072, 1358
- oxytocin, 99
- PET imaging of, 244-245, **246-247**
- receptor tyrosine kinases, 47, **48-49**, 53, 81
- serotonin, 59-64
- sigma-1, 420, 421, 424
- subtypes of, 47, **48-49**
- vasopressin, 99
- Recovery After an Initial Schizophrenia Episode (RAISE) study, 696
- Reduction in ADHD Rating Scale IV (ADHD-RS-IV), 1455
- REM sleep. See [Rapid eye movement sleep](#)
- Remifentanyl, for ECT, 1122
- REMIT (Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment) study, 442-443
- Renal disease patients, psychotropic drug use in
  - amantadine, 862, 863
  - asenapine, 799
  - benzodiazepines, 1285
  - bupropion, 498, 1508
  - buspirone, 588
  - cariprazine, 837
  - desvenlafaxine, 516
  - fluoxetine, 340
  - fluvoxamine, 420
  - gabapentin, 984, 989
  - lamotrigine, 1002



- lithium, [900](#), [903](#), [904–905](#), [1178](#)
- lurasidone, [822](#)
- memantine, [1043](#)
- mirtazapine, [480](#)
- olanzapine, [654](#)
- paroxetine, [387](#), [393](#)
- pharmacokinetics of, [1507](#), [1507–1508](#)
- pregabalin, [991](#), [995](#)
- sertraline, [362](#)
- topiramate, [1019](#)
- tramadol, [1383](#), [1384](#)
- venlafaxine, [516](#), [1508](#)
- vortioxetine, [468](#)
- ziprasidone, [760](#)
- Renal effects of drugs
  - antipsychotics, [618](#), [1516](#)
  - gabapentin, [989](#)
  - ketamine, [555](#)
  - lithium, [900](#), [902](#), [904–905](#), [962](#), [1178](#), [1501](#), [1507](#)
    - in pregnancy, [1556](#)
  - in neuroleptic malignant syndrome, [1614](#)
  - topiramate, [1029](#)
- Renal excretion of drugs, [217](#), [218](#), [225](#), [227](#)
  - in elderly persons, [1507–1508](#)
- Repaglinide, interaction with carbamazepine and oxcarbazepine, [963](#), [968](#)
- Repetitive transcranial magnetic stimulation (rTMS), [268](#)
  - for depression, [1129–1130](#), [1163](#)
    - compared with ECT, [1130–1131](#)
  - for OCD, [1212](#)
  - for PTSD, [1217](#)
- Reserpine, [283](#), [315](#)
  - for tardive dystonia, [1257](#)
- Respiratory arrest or depression, drug-induced
  - alcohol-type hypnotics, [1069](#)
  - barbiturates, [1067](#), [1068](#)
  - benzodiazepines, in neonates, [576](#)
  - clozapine, [639](#)
  - ketamine, [552](#), [555](#)
  - methadone, [1289](#)
  - TCA's, [324](#)
    - in infants exposed during breast feeding, [1555](#)
- Responses of Mental Stress Induced

Myocardial Ischemia to Escitalopram Treatment (REMIT) study, [442–443](#)

Restless legs syndrome

- benzodiazepines for, [866](#)
- $\beta$ -blockers for, [864](#)

Restlessness

- during benzodiazepine withdrawal, [573](#), [1065](#)
- drug-induced
  - anticholinergic agents, [859](#)
  - cariprazine, [848](#)
  - fluoxetine, [1470](#)
  - haloperidol, [816](#)
  - iloperidone, [816](#)
  - sertraline, [1444](#)
  - tranylcypromine, [295](#)
  - ziprasidone, [775](#)

Restoril. *See* [Temazepam](#)

Restraint. *See* [Physical restraint of patient](#)

Retrocollis, antipsychotic-induced, [614](#)

Retrovirus vectors for gene transfer, [18](#)

Reverse transcriptase, [14](#), [15](#)

RGH-188. *See* [Cariprazine](#)

Rhabdomyolysis

- amphetamine-induced, [1086](#)
- in neuroleptic malignant syndrome, [1614](#)

Rheumatoid arthritis, [183](#), [190](#), [191](#), [193](#), [393](#), [1384](#), [1402](#), [1407](#)

Rhinitis

- during benzodiazepine withdrawal, [573](#)
- drug-induced
  - citalopram, [1434](#)
  - haloperidol, [719](#)
  - risperidone, [719](#)
  - sertraline, [371](#)

Rhinorrhea, during opioid withdrawal, [1613](#)

Ribonucleic acid (RNA), [5–6](#)

- adenosine deaminases that act on, [12](#)
- antisense, [27](#)
- CRISPR (crRNA), [22](#)
- double-stranded (dsRNA), [12](#), [19](#), [20](#), [21](#)
- editing of, [6](#), [11–13](#), [63](#)
- heterogeneous nuclear (hnRNA), [9](#), [10](#), [11](#)
- long noncoding (lncRNA), [13](#)
- messenger (mRNA), [4](#)

- differential display to identify region specific expression of, 17
- posttranscriptional modification of, 10-11
- translation of, 5, 7
- microRNA (miRNA), 4, 6, 13, 19-20
  - as Alzheimer's disease biomarker, 1039
- noncoding (ncRNA), 13, 20, 136
- Piwi-interacting (piRNA), 13
- ribosomal (rRNA), 6, 7, 9, 13
- RNA interference (RNAi), 19-20, 20
  - applications of, 21
  - knockdown of gene expression by, 20-21
- small hairpin (shRNA), 20, 21
- small interfering (siRNA), 13, 19-21, 20
- small nuclear (snRNA), 6, 13
- small nucleolar, 13
- structure of, 6
- transfer (tRNA), 6, 7, 9, 12, 13
  - aminoacyl-tRNA, 7
- Ribosomes, 5, 7
- Rifampin-drug interactions
  - brexpiprazole, 749
  - ketamine, 556
  - lurasidone, 822
  - propranolol, 866
- Riluzole
  - for autism spectrum disorder, 1474
  - effects on brain AMPA receptors, 89
  - for generalized anxiety disorder, 1209
  - for OCD in children and adolescents, 1450
  - side effects of, 1474
- RISC (RNA-induced silencing complex), 19, 20, 21
- RISC loading complex (RLC), 19
- Risperidone, 705-723
  - in children and adolescents, 659, 712, 899-900, 930, 1438, 1439, 1441-1442, 1452, 1457-1458, 1462-1463, 1464-1465, 1466-1468, 1474-1475, 1499
  - dosing of, 709, 712-713, 721-722, 1180, 1649-1650
    - in children and adolescents, 1499
    - in elderly persons, 1522, 1525
  - drug interactions with, 722
    - carbamazepine and oxcarbazepine, 963, 966
  - in elderly persons, 715, 717, 1521-1524, 1525, 1526, 1529, 1530

formulations of, [1249](#)  
intramuscular, [706](#), [1608](#), [1610](#)  
microspheres (long-acting injectable), [706](#), [708](#), [709](#), [712](#), [713–714](#), [723](#),  
[1247](#)  
high dose and overdose of, [721–722](#)  
history and discovery of, [705–706](#)  
indications for, [712–717](#)  
acute stress disorder, [1218–1219](#)  
assaultive, aggressive, or violent behavior, [1606](#)  
augmentation of antidepressant treatment, [716](#)  
autism spectrum disorder, [716–717](#), [1466–1468](#)  
N-acetylcysteine and, [1475](#)  
amantadine and, [1474](#)  
buspirone and, [593](#), [1474](#)  
celecoxib and, [1474](#)  
memantine and, [1474](#)  
pentoxifylline and, [1474–1475](#)  
riluzole and, [1474](#)  
behavioral complications of dementia, [717](#), [1521–1522](#), [1525](#), [1526](#), [1624](#)  
vs. haloperidol, [1523–1524](#)  
switching from haloperidol to, [1525](#)  
behavioral emergencies, [1610](#)  
bipolar mania, [716](#), [1179–1180](#), [1610](#)  
in children and adolescents, [899–900](#), [930](#), [1438](#), [1439](#), [1441–1442](#)  
borderline personality disorder, [1318](#), [1327](#)  
clozapine augmentation, [634](#)  
disruptive behavior disorders and aggression in children and adolescents,  
[1457–1458](#)  
generalized anxiety disorder, [717](#)  
OCD, [717](#), [1212](#)  
panic disorder, [1198](#)  
PTSD, [1216–1217](#)  
in children and adolescents, [1452](#)  
schizoaffective disorder, [712](#)  
schizophrenia, [712–715](#)  
for behavioral emergencies, [1610](#)  
vs. cariprazine, [840](#), [841](#), [843](#)  
CATIE study, [620](#), [713](#), [714](#), [715](#), [720](#), [721](#), [722](#), [1246–1247](#)  
in children and adolescents, [659](#), [712](#), [1462–1463](#), [1464–1465](#)  
for cognitive deficits, [659](#), [714–715](#)  
in elderly persons, [1529](#), [1530](#)  
first-episode patients, [715](#)

- vs. haloperidol, 712–715, **714**
- vs. iloperidone, 811, **812**
- vs. lurasidone, 823
- maintenance treatment, 713–714
- mirtazapine and, 486
- vs. olanzapine, 659
- vs. quetiapine, 688
- with substance use disorder, 1259
- treatment-resistant illness, 631, 715, 1248
- valproate and, 931
- schizotypal personality disorder, 1329
- Tourette syndrome, 1461
- mechanism of action of, 63, 710–712
- pharmacokinetics and disposition of, 212, 709–710
- pharmacological profile of, 706–709, **708**, 1521
- side effects and toxicology of, **693**, 717–721, **719**, 722, **816**, 1179–1180, 1439, 1441, 1457–1458, 1463, 1522
  - cardiovascular effects, 718, 721, 722, 1516
  - extrapyramidal side effects, 669, 712, 713, 718–720, 722, 872, 1179–1180, 1247, 1457, 1458, 1522
  - hyperprolactinemia, 718, 720–721, 722, 1180, 1247, 1257, 1441, 1457, 1458
  - weight gain/metabolic effects, 637, 669, **695**, 716, 718, 931, 1253, 1441, 1457, 1458, 1467
- structure–activity relations for, 706, **707**
- use in pregnancy and lactation, 1563–1564
- Ritalin LA, Ritalin SR. *See* **Methylphenidate**
- Ritanserin, 705, 708, 710–711
- Ritonavir–drug interactions
  - bupropion, 506
  - carbamazepine, **964**, 967
  - quetiapine, 686
  - suvorexant, 1072
- Rivastigmine, 1040, 1041, **1659**
  - antipsychotics and, 1521
  - transdermal, 1041
- RLC (RISC loading complex), 19
- RNA. *See* **Ribonucleic acid**
- RNA-induced silencing complex (RISC), 19, **20**, 21
- RNA polymerases, 6, 8, **9**, 9–10, **20**
- Rocuronium
  - for ECT, 1122

- interaction with carbamazepine and oxcarbazepine, [963](#)
- Rofecoxib, [1382](#)
- Rosmarinus officinalis*, [1045](#)
- Routes of drug administration
  - absorption and, [212](#), [213](#), [214](#)
  - presystemic elimination and, [215](#)
- rTMS. See [Repetitive transcranial magnetic stimulation](#)
- RTS (Rubinstein-Taybi syndrome), [10](#)
- RU486, [166](#)
- Rubia cordifolia*, [1045](#)
- Rubinstein-Taybi syndrome (RTS), [10](#)

S-100 $\beta$ , [60](#)  
SAD. *See* [Social anxiety disorder](#)  
SAD (synapses of amphiDs defective) kinases, [51](#)  
SADHART (Sertraline Antidepressant Heart Attack Randomized Trial), [369](#)  
Safety Planning Intervention (SPI), for suicidal patients, [1599–1600](#)  
Sakel, Manfred, [1106](#)  
Salicylates, topical, [1393](#), [1394](#)  
Salience network (SN), [260](#)  
Salsalate, [1413](#), [1415](#) *Salvia lavandulaefolia*, [1045](#)  
SAM-e (*S*-adenosylmethionine), for depression, [1165](#)  
SAMHSA (Substance Abuse and Mental Health Services Administration),  
[1292](#), [1295](#)  
SANS (Scale for the Assessment of Negative Symptoms), [658–659](#)  
Sarcoidosis, [1094](#)  
SAS (Simpson-Angus Scale), [746](#), [748](#), [848](#)  
Scale for the Assessment of Negative Symptoms (SANS), [658–659](#)  
Scale for the Assessment of Positive Symptoms (SAPS), [1021](#)  
Schedule for Affective Disorders and Schizophrenia for School-Aged Children  
—Lifetime Version (Kiddie-SADS-L), [1435](#)  
Schedule for Affective Disorders and Schizophrenia for School-Aged Children  
—Present Episode Version (Kiddie-SADS-P), [1434](#)  
Schedule I–V drugs, [1383](#)  
Schizoaffective disorder  
  smoking cessation medications in, [1299](#)  
  suicide and, [1260](#), [1261](#)  
  treatment of  
    aripiprazole, [738](#)  
    asenapine, [801](#)  
    in children and adolescents, [1465](#)  
    classic antipsychotics, [611](#)  
    clozapine, [630](#), [632](#), [633](#)  
    iloperidone, [811](#), [812–813](#)  
    olanzapine, [661](#)  
      injectable, for agitation, [1609](#)  
      metformin and, [670](#)  
    paliperidone, [706](#), [712](#)  
    quetiapine, [689](#), [692](#)  
    risperidone, [712](#), [713](#)  
    topiramate, [1022](#)  
    ziprasidone, [755](#), [756](#), [757](#), [758](#), [759](#), [761](#), [762–763](#), [765](#), [766–767](#), [769](#),  
      [773](#), [777](#), [783](#)

## Schizophrenia, 1241–1245

age at onset of, 1244, 1462

late onset, 1529

in children and adolescents, 1462

clinical features of, 1242–1243

negative symptoms, 611, 614, 1242–1243, 1244

vs. depression, 1159

vs. extrapyramidal side effects, 1243

phencyclidine intoxication as model for, 652

primary vs. secondary, 1243

neurocognitive deficits, 611, 659, 766, 1242–1244

rating scales for, 826–827

positive symptoms, 611, 1242, 1244

amphetamine intoxication as model for, 610

prodromal symptoms, 1244, 1262

sleep disturbances, 1075

social deficits, 767–768

course of, 1241, 1243, 1244–1245

diagnosis of, 1242, 1243

in elderly persons, 1515, 1528–1529

employment and, 1252

family high expressed emotions and, 1250

gender and, 1244

genetics of, 14, 121

COMT genotype, 130

copy number variants, 127

cross-disorder studies, 143

*DISC1* and *DISC2* genes, 125, 130–131

genomewide association studies, 138–140, 139, 141, 142

immune system in, 185

mortality in, 618

neurodegeneration hypothesis of, 1244

neuroendocrinology of

growth hormone, 165

HPA axis, 162–163

neuroimaging in, 262

MRI, 262

PET, 93, 244, 267

SPECT, 266

neurotransmitters and receptors in

adenosine receptors, 97–98

dopamine, 84, 266, 610–611, 710, 732



- GABA, 93
- glutamate, 84
- neurochemical hypotheses, 654
- obstetrical factors and, 185, 1243, 1546
- in pregnancy, 1546
- prepulse inhibition deficit in, 626–627, 656, 710
- prevalence of, 1241
- psychiatric comorbidity with
  - depression, 766–767, 1244, 1259–1260
  - obsessive-compulsive symptoms, 1261
  - substance use disorders, 632, 1258–1259
  - smoking, 81, 1254–1255, 1299
  - suicidality, 632, 1260–1261
- relapses of, 1246, 1248
- Schizophrenia Cognition Rating Scale (SCoRS), 826–827
- Schizophrenia treatment, 1241–1262
  - for acute psychosis, 1245–1246
    - first-episode psychosis, 1245–1246
    - hospitalization, 1245
  - antidepressants, 320
  - antipsychotics, 267, 611, 1241–1242, 1245–1249, **1249**
    - for acute psychosis, 1245
    - aripiprazole, 738–741
    - asenapine, 799, 800–802
    - brexpiprazole, 745
    - buspirone and, 592–593
    - cariprazine, 840–844, **841–843**
    - CATIE study, 604, 620, 631, 637, 658, 661, 669, 688, 694, **695**, 696, 697, 713, 714, 715, 718, 720, 721, 722, 764–765, 766, 767, 776, 778, 779–780, 871, 875, 1106, 1246–1247, 1250, 1253, 1254, 1255, 1524
    - in children and adolescents, 1462–1466
    - choice of, 1246–1248, **1249**
    - clozapine, 630–632
    - in elderly persons, 1528–1530
    - for first-episode psychosis, 1246
    - galantamine and, 1042
    - iloperidone, 809, 811–815, **812–813**
    - lurasidone, 823, 825, 826–827
    - new drug development, 1261–1262
    - noncompliance with, 1245, 1248
    - olanzapine, 657–661
    - paliperidone, 706, 712, 715–716

- quetiapine, 685, 687-689
- relapse risk after discontinuation of, 1246, 1529
- risperidone, 712-715
- topiramate and, 1021-1022
- valproate and, 931
- ziprasidone, 758-759, 761-769
- for behavioral emergencies, 1609-1610
- in children and adolescents, 1462-1466
  - atypical antipsychotics, 1462-1465
    - aripiprazole, 739-740, 1462, 1463, 1465
    - asenapine, 1462, 1464
    - clozapine, 634, 1464
    - comparison of, 1464-1465
    - olanzapine, 634, 659-660, 1462, 1464-1465
    - paliperidone extended release, 1462, 1463, 1465
    - quetiapine, 659, 687, 689, 1462, 1463
    - risperidone, 659, 712, 1462-1463, 1464-1465
    - ziprasidone, 773, 1462, 1463-1464
  - classic antipsychotics, 1464, 1465
  - clinical recommendations for, 1465-1466
  - maintenance treatment, 1466
- deinstitutionalization and, 603-604
- delay from onset of symptoms to, 1246
- for depression, sertraline, 371
- dihydropyridine, 70
- dual-diagnosis treatment, 1245
- early intervention, 1245, 1246
- ECT, 1111-1112
- in elderly persons, 1528-1530
  - dosing of, 1530
  - quetiapine, 1529-1530
  - risperidone, 1529, 1530
- future directions for, 1261-1262
- lamotrigine, 1007
- maintenance therapy/relapse prevention, 1248
  - aripiprazole, 738, 739, 740-741
  - asenapine, 799, 801-802
  - in children and adolescents, 1466
  - clozapine, 634-635
  - ECT, 1111
  - goals of, 1248
  - olanzapine, 801, 1248

- risperidone, 713-714, 1248
- ziprasidone, 762-766
- for medical comorbidity, 1253-1258
  - extrapyramidal side effects, 1255-1256
  - hyperprolactinemia, 1257-1258
  - neuroleptic malignant syndrome, 1257
  - obesity, diabetes mellitus, and metabolic syndrome, 1253-1254
  - tardive dyskinesia and tardive dystonia, 1256-1257
  - tobacco use disorder, 1254-1255
- mirtazapine, 486
- for negative symptoms, 731-732, 1244, 1262
  - aripiprazole, 737, 739
  - armodafinil, 1096
  - asenapine, 801
  - brexpiprazole, 737
  - buspirone, 593
  - cariprazine, 831, 836, 850, 851
  - classic antipsychotics, 608, 611, 731, 1241
  - clozapine, 634
  - idazoxan, 712
  - iloperidone, 812-813, 814
  - modafinil, 1096
  - olanzapine, 652, 656, 657, 658-659, 801
  - quetiapine, 687
  - risperidone, 659, 705, 710, 712, 713, 714
  - setoperone, 705
  - ziprasidone, 755, 756, 763, 765, 768, 769
- for neurocognitive deficits, 611, 1242-1244, 1249-1250, 1262
  - armodafinil, 1096
  - cariprazine, 843
  - in CATIE trial, 1250
  - lurasidone, 826-827
  - modafinil, 1096
  - olanzapine, 659
  - olanzapine vs. risperidone, 659
  - perphenazine, 1250
  - risperidone, 659, 714-715
  - ziprasidone, 766, 827
- physical restraint, 1245, 1257
- for positive symptoms, 1244
  - aripiprazole, 737
  - brexpiprazole, 737

- cariprazine, 846
- classic antipsychotics, 611, 612, 733, 1241
- clozapine, 628, 634
- ECT, 1111
- iloperidone, 812-813, 814
- olanzapine, 657, 658, 659, 668
- risperidone, 713, 714
- valproate, 931
- ziprasidone, 755, 761, 765, 768, 769
- for prodromal symptoms, 1262
- for psychiatric comorbidity, 1258-1261
  - depression, 1259-1260
  - obsessive-compulsive symptoms, 1261
  - substance use disorders, 632, 1258-1259
  - suicidality, 1260-1261
- psychosocial interventions, 1245, 1248, 1250-1253, 1262
  - cognitive-behavioral therapy, 1251, 1252, 1261
  - to improve psychosocial functioning, 1251-1253
  - for relapse prevention, 1250-1251
- psychostimulants, 1096-1097
- trazodone, 458
- for treatment-resistant illness, 1248-1249
  - aripiprazole, 738, 739, 740-741, 1249
  - clozapine, 604, 623, 630-631, 1247, 1248, 1249
    - in children and adolescents, 1466
  - ECT and, 1111
  - olanzapine, 631, 658
  - quetiapine, 631, 1249
  - risperidone, 631, 715
  - ziprasidone, 768, 1249
- trials of
  - Comparison of Atypicals in First Episode Psychosis (CAFE), 687, 696
  - Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study—band 2 (CUtLASS-2), 631, 1247
  - European First Episode Schizophrenia Trial (EUFEST), 765-766
  - Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO), 631
  - Monitoring of Oral Ziprasidone As Rescue Therapy (MOZART), 768
  - Quetiapine Experience with Safety and Tolerability (QUEST), 689
  - Recovery After an Initial Schizophrenia Episode (RAISE), 696
  - Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication (SPECTRUM), 697

Use of Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia (METS), [670](#)

Ziprasidone Experience in Schizophrenia in Germany/Austria (ZEISIG), [765](#)

Ziprasidone Extended Use in Schizophrenia (ZEUS), [763](#), [778](#)

Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), [781](#)

Schizotypal personality disorder (SztPD), [162](#), [1328–1329](#)

SCL-90 (Symptom Checklist-90), [665](#)

SCL-90-R (Symptom Checklist-90—Revised), [774](#), [1027](#)

SCN. *See* [Suprachiasmatic nucleus](#)

Scopolamine, [79](#), [80](#), [309](#)

SCoRS (Schizophrenia Cognition Rating Scale), [826–827](#)

Seasonal affective disorder

- bright light therapy for, [1163](#), [1166](#)
- bupropion for, [501](#)
- immune system in, [185](#)

Second-dose effect, [216](#)

Second messengers, [47](#), [50](#)

- antidepressant effects on, [195](#)
- cholinergic receptors and, [80](#)
- cytokines and, [189](#)
- dopamine D<sub>1</sub> receptor activation of, [70](#)
- in heterologous desensitization, [53](#)
- opioid effects on, [101](#)
- psychotropic drug effects on, [34](#)
- regulation of transcription factors by, [10](#)
- time to drug effects and, [226](#)

Secretase inhibitors, [1045](#)

Secretin, [100](#)

Sedation, drug-induced. *See also* [Somnolence](#)

- antipsychotics, [1516](#)
- atomoxetine, [1499](#)
- atypical antipsychotics, [1500](#)

  - aripiprazole, [737](#), [1461](#), [1468](#)
  - asenapine, [804](#), [1248](#), [1464](#)
  - brexpiprazole, [737](#)
  - clozapine, [626](#), [639](#), [1248](#), [1521](#)
  - iloperidone, [810](#)
  - olanzapine, [672](#), [1248](#), [1370](#), [1439](#), [1522](#), [1523](#), [1525](#)
  - quetiapine, [688](#), [694](#), [823](#), [1248](#), [1316](#), [1370](#), [1440](#), [1525](#)
  - risperidone, [718](#), [722](#)
  - ziprasidone, [1248](#), [1440](#)

barbiturates, 1066  
benzodiazepines, 567, 570, 572, 1196, 1205, **1364**, 1627  
carbamazepine, 946, 957  
classic antipsychotics, 424, 607, 612, 614, **615**, 1458, 1465, 1469, 1516  
clonidine, 871, 1500  
diphenhydramine, 862, **1368**  
doxylamine, **1368**  
eszopiclone, **1365**  
gabapentin, 989  
guanfacine, 1501  
γ-hydroxybutyrate, 1069  
ketamine, 552  
milnacipran, 541  
mirtazapine, 484, 487, **1369**, 1471  
pregabalin, 995  
propranolol, 1452  
SSRIs, 346, 1445, 1449  
suvorexant, 1359, **1367**  
TCAs, 320, 322, **1367**, **1368**, **1369**  
trazodone, 457-458, **1369**  
trihexyphenidyl, 860  
valproate, 933, 1501  
Sedative-hypnotics, 1051-1076. *See also specific drugs and classes*  
  alcohol-type hypnotics, 1068-1069  
  antihistamines, 1069-1070  
  barbiturates, 1065-1068  
  for behavioral complications of dementia, 1520, 1524, 1526  
  benzodiazepines, 1053-1065, 1353-1354  
  coadministered with antidepressants, 230  
  considerations in treatment of insomnia, 1073-1076  
  in elderly persons, 1075-1076, 1526  
  history of development of, **1052**  
  γ-hydroxybutyrate/sodium oxybate, 1069  
  interaction with carbamazepine, 966  
  mechanism of action, pharmacokinetics, and dosage as determinants of  
    effects on sleep, 1350-1352  
  mechanism of action of, 1076  
  melatonin receptor agonists, 1071-1072, 1355-1356  
    melatonin, 1070-1071, 1355-1356  
    ramelteon, 1071, 1355-1356  
  nonbenzodiazepine hypnotics, 1057, **1058**, 1060, 1064, **1064**, 1353-1355  
  pharmacokinetics of, 213

suvorexant, [1072–1073](#)

treatment of withdrawal from, [1607](#), [1612–1613](#)

## Seizures

during alcohol withdrawal, [1285](#), [1286](#)

during barbiturate withdrawal, [1068](#)

during benzodiazepine withdrawal, [570](#), [573](#)

drug-induced

amantadine, [864](#)

amphetamine, [1086](#)

bupropion, [221](#), [496](#), [504](#), [505](#), [506](#), [1297](#), [1498](#)

cariprazine, [848](#)

classic antipsychotics, [614](#), [616](#)

clozapine, [221](#), [633](#), [635](#), [638](#), [640](#), [641](#), [875](#), [1248](#), [1464](#), [1500](#), [1521](#)

dihydroxidine, [70](#)

γ-hydroxybutyrate, [1069](#)

lurasidone, [825](#)

sertraline, [372](#)

TCAs, [314](#), [320](#), [321](#), [324](#), [1615](#)

venlafaxine, [522](#)

drug-resistant, [227](#)

glycine receptors and, [91](#)

kainate receptors and, [90](#)

in neonates exposed to drugs in utero, SSRIs, [403](#)

neuroimaging during, [242](#)

neuromodulation treatment-induced ECT, [1113–1121](#)

ketamine effects on, [554](#)

focal electrically administered seizure therapy, [1132](#)

magnetic seizure therapy, [268](#), [1132](#), [1163](#)

norepinephrine transporter and, [76](#)

sertraline for mood symptoms in patients with, [368](#)

synchronous dural activity during, [264](#)

treatment of

benzodiazepines, [568](#), [866](#), [1060](#)

carbamazepine, [942](#), [944](#), [949–950](#), [964](#)

ECT, [1112](#)

eslicarbazepine acetate, [943](#), [949](#), [960](#)

gabapentin, [983](#), [984–985](#), [989](#)

lamotrigine, [1001](#), [1003](#)

oxcarbazepine, [942](#), [947](#), [949–950](#)

pregabalin, [990](#), [991](#), [1393](#)

topiramate, [638.1017](#), [1019](#)

vagus nerve stimulation, [1130](#)

valproate, 932–933, 935

Selective serotonin reuptake inhibitors (SSRIs), 335–446. *See also specific drugs*

acute tryptophan depletion-induced depressive relapse in patients receiving, 55

augmentation of, 1160

atypical antipsychotics, 1160

  aripiprazole, 500, 742, 1449–1450

  quetiapine, 692

  ziprasidone, 772

bupropion, 495, 500

buspirone, 591

lithium, 898, 1160

mirtazapine, 482, 1160

thyroid hormone, 1160, 1216

topiramate, 1021

valproate, 927

in children and adolescents, 1433–1435, 1437, 1438, 1444–1445, 1451, 1452, 1497, **1498**

citalopram, 431–446

coadministered with benzodiazepines, 230

cognitive effects in children exposed in utero to, 1550

discontinuation syndrome with, 340, 348–349, 372–373, 401, 420, 444–445, 1196, **1608**, 1615

dosing of

  in children and adolescents, **1498**

  in pregnancy, 1549

drug interactions with, 233, 1196

  antipsychotics, 350, 404, **404**, 1261

  MAOIs, 230, **293**, 297, 346, 373, **404**, 405, 425, 446

  St. John's wort, 1165

  TCAs, 350, 373, **404**, 425, 1615

in elderly persons, 1508, 1512–1514

escitalopram, 431–446

familial aggregation of response to, 124

fluoxetine, 335–350

fluvoxamine, 419–426

indications for

  acute stress disorder, 1219

  agitation in elderly patients, 1627–1628

  autism spectrum disorder, 345, 1469–1470

  binge-eating disorder, 371, 423–424, 1342–1343



- bipolar depression, 1183
  - valproate and, 927
- borderline personality disorder, 343, 665, 1316, 1320, **1321-1322**, 1327
- bulimia nervosa, 342-343, 1338, 1339
- depression, 1159
  - with anxiety, 341, 441-442, 501
  - with atypical features, 288, 1159
  - vs. bupropion, 499
  - in children and adolescents, 1433-1435, 1437, 1438
  - vs. duloxetine, 534-535, **536-537**
  - vs. milnacipran, 535, **538**
  - persistent depressive disorder (dysthymia), 318, 1159
- generalized anxiety disorder, 1206-1207, 1210
  - nonbenzodiazepine hypnotics and, 1208
- mixed anxiety disorders in children and adolescents, 1445-1446
- OCD, 318, 1211
  - augmentation strategies, 1211-1212
  - in children and adolescents, 367, 396, 1211, 1447-1450
  - cognitive-behavioral therapy and, 1211
  - olanzapine and, 668
  - quetiapine and, 692, 1211
- pain syndromes, 344, 345, 424, 1391
- panic disorder, 569, 1195-1196
  - atypical antipsychotics and, 1198
  - in children and adolescents, 1445
  - clonazepam and, 1196
  - maintenance treatment, 1198
- premature ejaculation, 344, 370, 399
- PTSD, 1214-1215
  - in children and adolescents, 1451, 1452
  - olanzapine and, 667
  - quetiapine and, 692
  - thyroid hormone and, 1216
- separation anxiety disorder, 1202-1203, 1445, 1446
- social anxiety disorder, 1199-1200
  - in children and adolescents, 1202, 1444-1445
- mechanism of action of
  - fMRI studies of, 269
  - 5-HT<sub>1A</sub> receptor effects, 59, 60, 245
  - serotonin transporter binding, 55, 58, 70, 245
- overdose of, 347, 349, 350, 401-402, 425, 1159, 1497, 1514
- paroxetine, 385-406

- pharmacogenomics of response to, 128, 388–389
- sertraline, 359–373
- side effects and toxicology of, 345, 1159, 1196
  - in elderly persons, 1514
  - sexual dysfunction, 345, 346, 371, 372, 398–399, 424, 443, 444, 1159, 1196, 1449
  - bupropion for, 503
  - mirtazapine for, 482–483
  - teratogenic effects, 1550–1551
- structure–activity relations for, 336, 337
- suicidality and, 346–347, 372, 393–395, 399–400, 425, 445–446
- switching to other antidepressants, 1161
  - MAOIs, 340, 346, 405
  - vortioxetine, 473, 474
- use in pregnancy and lactation, 347–348, 364, 373, 402–403, 1549, 1550–1553
  - autism risk in children after in utero exposure, 348, 1551
  - persistent pulmonary hypertension of the newborn and, 348, 403, 1552–1553
- Selegiline, 283, 284, 297–298
  - dietary interactions with, 297
  - discontinuation of, 297
  - dosing of, 297
  - drug interactions with, 297–298
  - formulations of, 215
  - indications for, 297
    - Alzheimer’s disease, 297
    - depression, 297
    - Parkinson’s disease, 289, 297, 299
  - mechanism of action of, 215
  - pharmacokinetics of, 297
  - pharmacological profile of, 286
  - side effects of, 297
  - structure of, 287
- Selegiline transdermal system (STS), 297, 298, 299, 1640
  - for depression, 298
    - in children and adolescents, 1436
  - dietary interactions with, 298
  - drug interactions with, 298–299
    - carbamazepine, 965
  - pharmacokinetics of, 298
  - pharmacological profile of, 298

- side effects of, 298, 1436
- strengths of patches, 298
- Self-injurious behavior, 1593. *See also* Suicide and suicidal behavior
  - in autism spectrum disorder, 1466, 1475
    - mirtazapine for, 1471
    - olanzapine for, 1468
  - in borderline personality disorder, 1320, **1321-1322**, 1599
  - in dementia, 1518
  - emergency department visits for, 1593
  - in schizotypal personality disorder, 1329
- Separation anxiety disorder, 1202-1203, 1443, 1445, 1446
- Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, 63, 288, 312, 435, 436, 445, 482, 500, 591, 898, 1106
- Serentil. *See* Mesoridazine
- D-Serine, 85, 86, 92
- Seroquel. *See* Quetiapine
- Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication (SPECTRUM) study, 697
- Serotonin (5-HT), 54-55, **56-57**, 335-336
  - brain distribution of, 54, **56**, 335
  - cytokine effects on, 191-192
  - drug effects on
    - buspirone, 587
    - citalopram, 431, 433, 434-435
    - clomipramine, 1210
    - cyclic antidepressants, 305, 306-309, 315, 319
    - desvenlafaxine, 515, 517
    - duloxetine, 531-532, 542
    - escitalopram, 433
    - fluoxetine, 336-338, 339, 340
    - fluvoxamine, 419-420
    - gabapentin, 984
    - levomilnacipran, 531, 533
    - lithium, 890
    - MAOIs, 54
    - milnacipran, 531, 532, 533, 542
    - mirtazapine, 479
    - moclobemide, 295
    - nefazodone, 460-461
    - paroxetine, 385, 389
    - sertraline, 359-360, 362
    - tramadol, 1383

- trazodone, 455–456
- venlafaxine, 515, 517
- ECT effects on, 1107
- metabolism of, 55
- PET studies of, 245, 248
- in sleep–wake cycle, 1350, **1351**
- in specific disorders, 55
  - alcohol dependence, 55
  - anger/aggression, 55, 343
  - anxiety, 585
  - bipolar disorder, 55, 59
  - depression/suicidality, 55, 59, 61, 192, 245, 263, 346–347
  - eating disorders, 342
  - impulsivity, 55
  - psychotic dementia, 1519
  - schizophrenia, 732
- synthesis of, 54, 336
- Serotonin receptors, 59–64
  - in Alzheimer’s disease with psychosis, 1520
  - autoreceptors, 51, **57**, 61, 245, 340, 533, 585
  - drug effects on
    - antidepressants
      - citalopram, 435
      - cyclic antidepressants, 307–309, **308**, 336, 338
      - fluoxetine, 336–338, 340
      - fluvoxamine, 419
      - MAOIs, 286, 338
      - mirtazapine, 479, 485
      - nefazodone, 459, 460
      - paroxetine, 389
      - sertraline, 359–360, 362
      - trazodone, 455–456
      - vortioxetine, 467–468, 472, 474
  - antipsychotics, 869–870, 1242, 1518
    - aripiprazole, 731, 732, 734, **735**, 737, 831, 833, **834**, 836
    - asenapine, 797, 798
    - brexpiprazole, 731, 734, **735**, 737, 831, **834**, 836
    - cariprazine, 831, 833, 834, **834**, 836, 851
    - clozapine, 624–626, 628–629
    - iloperidone, 809–810
    - lurasidone, 821–822
    - olanzapine, 650, 652, 655, 1522

- quetiapine, 686, 1523
- risperidone, 705–706, 708, **708**, 710–712, 1521
- ziprasidone, 756–757, **758**, 775, 783
- buspirone, 585–586, 587, 588
- lamotrigine, 1001
- families of, 59
- 5-HT<sub>1</sub>, 59–61
  - 5-HT<sub>1A</sub>, 59–61, **83**, 245, 585–586
    - agonists and antagonists of, 60, 61, 585, 586, 587
    - antidepressant efficacy related to downregulation of, 245
    - brain distribution of, 59, 585–586
    - drug effects on density of, 59–60
    - knockout studies of, 60
    - PET imaging of, 61, **246**
    - role in anxiety and depression, 586
    - signaling mechanisms used by, 60–61
  - 5-HT<sub>1B</sub>, **57**, 61, **246**
  - 5-HT<sub>1C</sub>, 61
  - 5-HT<sub>1D</sub>, 61
  - lithium affinity for, 890
- 5-HT<sub>2</sub>, 59, 61–64
  - antidepressant antagonism of, 34, 63
  - antipsychotic antagonism of, 34, 63, 705, 869–870, 1242
    - asenapine, 797, 798
    - cariprazine, 831, 833, 834, **834**, 836
    - clozapine, 624, 628–629
    - iloperidone, 809
    - lurasidone, 821–822
    - olanzapine, 655
    - quetiapine, 686
    - risperidone, 705–706, 708, **708**, 710–712
    - ziprasidone, 756–757, **758**, 775, 783
  - brain distribution of, 62
  - in depression/suicidality, 347
  - ECT downregulation of, 1107
  - ECT upregulation of, 63
- 5-HT<sub>2A</sub>, 59–64, 262
- 5-HT<sub>2B</sub>, 61, 62
- 5-HT<sub>2C</sub>, 61, 62, **62**, 63, 64
  - RNA-edited, 12–13
  - role in antipsychotic-induced weight gain, 63, 64

- 5-HT<sub>3</sub>, [47](#), [59](#), [64](#)
- 5-HT<sub>4</sub>, [57](#), [59](#), [64](#)
- 5-HT<sub>5</sub>, [59](#), [64](#)
- 5-HT<sub>6</sub>, [59](#), [64](#)
- 5-HT<sub>7</sub>, [59](#), [64](#)
- PET studies of, [61](#), [63–64](#), [246](#), [248](#)
- Serotonin syndrome, [230](#), [233](#), [346](#), [1615](#)
  - drugs associated with, [1615](#)
    - buspirone, [587](#), [594](#)
    - desvenlafaxine, [523](#)
    - duloxetine, [542](#)
    - levomilnacipran, [542](#)
    - MAOIs, [292](#), [293](#), [298](#), [373](#), [405](#), [446](#), [523](#), [542](#)
    - milnacipran, [542](#)
    - SSRIs, [346](#), [373](#), [405](#), [425](#), [446](#), [1497](#)
    - St. John's wort, [1165](#)
    - trazodone, [459](#)
    - venlafaxine, [522](#), [523](#)
  - treatment of, [1607](#), [1615](#)
- Serotonin transporter (5-HTT; SERT), [55–59](#), [57](#)
  - brain distribution of, [58](#)
  - drug effects on
    - aripiprazole, [734](#)
    - atomoxetine, [76](#)
    - BMS-820836, [69](#)
    - cyclic antidepressants, [55](#), [306](#), [307–309](#), [308](#), [315](#)
    - duloxetine, [529–533](#), [531](#)
    - levomilnacipran, [529](#)
    - milnacipran, [529](#), [531](#)
    - nefazodone, [460–461](#)
    - SSRIs, [55](#), [58](#), [338](#), [359–360](#), [386](#), [388](#), [419–420](#), [432](#), [434](#)
    - trazodone, [455](#)
    - venlafaxine, [517](#)
    - vortioxetine, [467](#), [473](#), [474](#)
    - ziprasidone, [757](#)
  - PET studies of, [59](#), [245](#), [467](#), [532](#)
  - serotonin binding to, [58](#)
  - in specific disorders
    - depression, [121](#), [245](#)
    - suicidality, [58–59](#)
  - structure of, [58](#)

suicidality related to genetic polymorphisms of, [58-59](#)

Serotonin-transporter-linked polymorphic region (5-HTTLPR), [59](#), [127-128](#), [134](#), [388](#)

Serotonin-norepinephrine reuptake inhibitors (SNRIs). *See also specific drugs*

- antinociceptive effects of, [319](#)
- duloxetine, milnacipran, and levomilnacipran, [529-543](#)
- indications for
  - anxiety disorders, [563](#)
  - panic disorder, [569](#)
  - borderline personality disorder, [1320](#), [1322](#)
  - depression, [391](#)
  - generalized anxiety disorder, [1207-1208](#)
- interaction with St. John's wort, [1165](#)
- mechanism of action of, [517](#), [533](#)
- PET studies of receptor binding affinity of, [59](#)
- structure-activity relations for, [515](#), [516](#), [529](#), [530](#)
- switching to vortioxetine from, [473](#), [474](#)
- venlafaxine and desvenlafaxine, [515-523](#)

SERT. *See* [Serotonin transporter](#)

Sertraline, [359-373](#)

- in children and adolescents, [361](#), [367](#), [371](#), [1202-1203](#), [1211](#), [1434-1435](#), [1444](#), [1447](#), [1451](#), [1498](#)
- discontinuation syndrome with, [349](#), [372-373](#)
- dosing of, [363](#), [1636-1637](#)
  - in children and adolescents, [1498](#)
- drug interactions with, [373](#)
  - bupropion, [362](#), [506](#)
  - carbamazepine and oxcarbazepine, [963](#), [965](#)
- in elderly persons, [361](#), [364](#), [368-369](#), [1506](#), [1512-1513](#)
- generic, [335](#)
- history and discovery of, [359](#)
- indications for, [362-371](#)
  - autism spectrum disorder, [1470](#)
  - bipolar depression, valproate and, [927](#)
  - borderline personality disorder, [1321-1322](#)
  - depression, [362-364](#)
    - in Alzheimer's disease, [485](#)
    - with anxiety, [501](#)
    - vs. bupropion, [499](#)
  - in cancer, [370](#)
  - in cardiovascular disease, [369-370](#)
  - in children and adolescents, [361](#), [371](#), [1434-1435](#)

- and cognitive dysfunction in elderly persons, 368–369
- iSPOT-D study, 437–438
- maintenance treatment, 363–364
- vs. paroxetine, 390
- persistent depressive disorder (dysthymia), 318
- postpartum depression, 363, 364
- with psychotic features, 1530
- in schizophrenia, 371
- generalized anxiety disorder, 371, 372, 1207
  - in children and adolescents, 1444
- hot flashes, 370
- mixed anxiety disorders in children and adolescents, 1446
- mood symptoms in neurological conditions, 368
- OCD, 366, 1211
  - in children and adolescents, 367, 1211, 1447
  - maintenance treatment/relapse prevention, 1211
- other uses, 370–371
- panic disorder, 365–366, 1195, 1604
  - clonazepam and, 1200
  - maintenance treatment, 1198
- premenstrual dysphoric disorder, 364–365
- PTSD, 367–368
  - in children and adolescents, 1451
- social anxiety disorder, 365, 1199–1200
  - in children and adolescents, 1202–1203, 1444
- substance use disorders, 369
- mechanism of action of, 362
- pharmacokinetics and disposition of, 360–362
  - in elderly persons, 1506
- pharmacological profile of, 59, 360
- side effects and toxicology of, 371–372, 1435, 1444, 1447
- structure–activity relations for, 337, 359–360, 360
- suicidality and, 372
- thyroid hormone augmentation of, 165
- use in hepatic or renal disease, 362
- use in pregnancy and lactation, 364, 373, 1549, 1550–1553

Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), 369

Serum sickness, bupropion-induced, 504

SET-C (Social Effectiveness Therapy for Children), 1444

Setoperone, 705, 707

Sexual behavior therapy, 344

Sexual dysfunction



- drug-induced
  - antipsychotics, [609](#), [618–619](#), [718](#)
  - benzodiazepines, [1065](#)
  - classic antipsychotics, [609](#), [612](#), [616](#), [619](#), [720](#)
  - clozapine, [640](#)
  - desvenlafaxine, [521](#)
  - duloxetine, [540](#)
  - MAOIs, [290](#), [1159](#)
  - milnacipran, [541](#)
  - mirtazapine, [487](#)
  - opioids, [1385](#)
  - risperidone, [718](#), [720](#)
  - SSRIs, [345](#), [346](#), [371](#), [372](#), [398–399](#), [424](#), [443](#), [444](#), [1159](#), [1196](#), [1449](#)
  - TCAs, [324](#), [1159](#)
  - trazodone, [458](#)
  - venlafaxine, [521](#), [1208](#)
  - vilazodone, [1159](#)
  - vortioxetine, [472](#), [474](#), [1159](#)
- hyperprolactinemia and, [618](#)
- treatment of, [399](#)
  - bupropion, [372](#), [399](#), [503–504](#), [1160](#)
  - cypheptadine, [290](#), [399](#)
  - ephedrine, [399](#)
  - mirtazapine, [482–483](#)
  - phosphodiesterase inhibitors, [372](#), [399](#), [1160–1161](#)
- SFS (Social Functioning Scale), [659](#)
- SGAs (second-generation antipsychotics). *See* [Antipsychotics, atypical](#)
- Sheehan Disability Scale, [689](#), [846](#)
- Sheehan Panic and Anticipatory Anxiety Scale (PAAS), [1195](#)
- Shift work sleep disorder, [1074](#)
  - melatonin for, [1070](#)
  - melatonin receptor agonists for, [1072](#)
  - modafinil and armodafinil for, [1084](#), [1089](#), [1097](#)
- Short PTSD Rating Instrument (SPRINT), [1213](#)
- Short tandem repeats (STRs), [128](#)
- SIADH. *See* [Syndrome of inappropriate antidiuretic hormone](#)
- Sibutramine, for binge-eating disorder, [1343–1344](#)
- Sickness behavior, cytokine-induced, [189](#), [190–191](#)
  - antidepressant efficacy for, [195](#), [196](#)
  - CRH and, [193](#)
- Sigma-1 receptor, fluvoxamine affinity for, [420](#), [421](#), [424](#)
- Signal transducers and activators of transcription (STATs), [95](#), [186](#), [194](#)

Signal transduction pathways, 47, 102  
  in CREB activation, 11  
  G protein-coupled receptor endocytosis for, 53  
  for glucocorticoid receptors, 194  
  for opioid receptors, 101  
  for P1 adenosine receptors, 96

Sildenafil, 372, 399, 1160–1161

Silenor. *See* Doxepin

Simpson-Angus Scale (SAS), 746, 748, 848

Simvastatin, interaction with eslicarbazepine acetate, 969

Sinequan. *See* Doxepin

Single nucleotide polymorphisms (SNPs), 129–130, 145  
  genomewide association studies of, 136–141  
    in bipolar disorder, 140–141  
    in depression, 140  
    methodology for, 136–138  
    results of, 138–141  
    in schizophrenia, 138–140, 139  
  5-HTTLPR and, 128  
  iloperidone efficacy and side effects associated with, 815

Single photon emission computed tomography (SPECT), 239–240  
  dopamine imaging, 69, 129, 246  
    in schizophrenia, 266  
  GABA imaging, 248  
    in PTSD and panic disorder, 248  
  receptor-labeling studies, 246–247

Sinusitis, risperidone-induced, 719

Sirolimus, interaction with carbamazepine and oxcarbazepine, 963, 967

*SIRT1* gene, 140

Skeletal muscle relaxants  
  benzodiazepines, 1051  
  cyclobenzaprine, 1393, 1403  
  for ECT, 1122, 1124  
  interaction with carbamazepine and oxcarbazepine, 963, 967  
  for neuroleptic malignant syndrome, 1257  
  for pain, 1393, 1413  
    fibromyalgia, 1403  
    low back pain, 1406

Skin-picking disorder, fluoxetine for, 342

Skin reactions. *See* Cutaneous effects of drugs

*SLC6A3* gene, 69, 129

*SLC6A4* gene, 127, 1158. *See also* 5-HTTLPR

*SLCO3A1* gene, [815](#)

Sleep apnea

drug use in

barbiturates, [1067](#)

benzodiazepines, [1064–1065](#)

ramelteon, [1356](#)

suvorexant, [1359](#)

HPA effects of, [158](#)

treatment of

armodafinil, [1084](#), [1090–1091](#)

CPAP and, [1091](#)

mirtazapine, [484](#)

modafinil, [1084](#), [1089](#), [1094–1095](#)

CPAP and, [1095](#)

trazodone, [458](#)

Sleep deprivation

for depression, [1165](#)

drug effects after

benzodiazepines, [1061](#)

modafinil, [1090](#)

Sleep disturbances. *See also* [Insomnia](#)

in adjustment disorders, [1602](#)

in anxiety disorders, [1075](#), [1349](#)

circadian rhythm-based

delayed sleep phase disorder, [1070](#), [1072](#)

jet lag, [1070](#), [1072](#), [1074](#)

melatonin for, [1070](#)

melatonin receptor agonists for, [1071–1072](#)

non-24-hour sleep-wake cycle, [1070](#), [1071](#)

shift work sleep disorder, [1070](#), [1072](#), [1074](#), [1084](#), [1089](#), [1097](#)

classification of, [1073](#), [1074](#)

in depression, [182](#), [1073](#), [1075](#), [1349](#)

in elderly persons, [1070](#)

medical illness and, [1349–1350](#)

during opioid withdrawal, [1613](#)

in schizophrenia, [1075](#)

suicide and, [1349](#), [1350](#)

Sleep effects of drugs

$\alpha_1$ -adrenergic receptor antagonists, [1359](#)

prazosin, [1217](#), [1359–1361](#), [1368](#)

alcohol-type hypnotics, [1069](#)

amphetamine, [1086](#)

antidepressants, 1362–1363  
    bupropion, 504  
    desvenlafaxine, 521  
    duloxetine, 540  
    MAOIs, 290  
    mirtazapine, 482, 1362, **1369**  
    selegiline transdermal system, 298  
    SSRIs, 1196, 1497  
        citalopram, 1470  
        escitalopram, 444, 1434  
        fluoxetine, 345, 346, 1470  
        fluvoxamine, 423, 1448  
        paroxetine, 1445  
        sertraline, 371, 1435, 1447  
    TCAs, 320, 1362, **1368**–1369  
        doxepin, 1351–1352, 1356–1358, **1367**, **1369**  
    trazodone, 290, 457–458, 1362–1363, **1369**  
    venlafaxine, 472, 521  
antihistamines, 1068, 1361–1362, **1368**  
antipsychotics, **615**, **719**, **816**, 1363, 1371–1372  
    aripiprazole, 746, 747, 1180  
    asenapine, 1464  
    brexpiprazole, 748  
    cariprazine, 847, **847**, 848  
    iloperidone, **816**, 817  
    olanzapine, **1370**  
    paliperidone, 1463  
    quetiapine, **1370**  
    ziprasidone, 774, 775  
atomoxetine, 1472  
barbiturates, **1062**, 1067  
benzodiazepines, 569, 570, 1060–1062, **1062**, 1353–1354, **1364**  
 $\beta$ -blockers, 864, 866  
buspirone, 593  
clonidine, 1500  
 $\gamma$ -hydroxybutyrate, 1069  
lamotrigine, 1471  
mechanism of action, pharmacokinetics, and dosage as determinants of,  
    1350–1352  
melatonin, 1070, 1355–1356, **1366**  
modafinil, 1092  
nonbenzodiazepine hypnotics, 1057, 1354–1355, **1365**

- psychostimulants, 1088, 1472, 1502
- ramelteon, 1071, 1355–1356, **1366**
- suvorexant, 1072–1073, 1358–1359
- topiramate, 1029
- venlafaxine, 1498
- Sleep hygiene, 1074
- Sleep log, 1074
- Sleep Problems Questionnaire, 988
- Sleep restriction, 1074
- Sleep–wake cycle, 1350–1353
  - mechanism of action, pharmacokinetics, and dosage as determinants of drug effects on, 1350–1352
  - melatonin in, 1070, 1350, **1351**
  - neurotransmitters in, 1350, **1351**
  - orexins in, 73, **101**, 1350, **1351**, 1352
  - transient vs. persistent disturbances of, 1074
- Smoking cessation, 1295–1300
  - bupropion for, 495, 497, 501–502, 1297, 1298
  - bupirone for, 592
  - in children and adolescents, 1299
  - comorbid disorders and, 1299–1300
    - schizophrenia, 1255, 1259
    - substance use disorders, 1300
  - counseling strategies for, 1295–1296
  - nicotine replacement therapies for, 1296–1297
  - second-line medications for, 1298
  - topiramate for, 1025–1026
  - varenicline for, 1297–1298
  - in women who are pregnant or are trying to conceive, 1298–1299
- Smoking/tobacco-related disorders, 1295
  - bipolar disorder and, 1299
  - in children and adolescents, 1299
  - depression and, 1300
  - drug use and
    - $\beta$ -blockers, 865
    - clozapine, 641
    - olanzapine, 673–674
  - e-cigarettes, 1299
  - genetics of nicotine addiction, **121**
  - incidence of, 1283, 1295
  - medical complications of, 1254–1255
  - nicotine–drug interactions

- antipsychotics, 620
- TCAs, 326
- other substance use disorders and, 1300
- during pregnancy, 1299
- schizophrenia and, 81, 1254–1255, 1299
- vascular cognitive impairment and, 1043

SN (salience network), 260

SNPs. *See* [Single nucleotide polymorphisms](#)

SNRIs. *See* [Serotonin–norepinephrine reuptake inhibitors](#)

Social anxiety disorder (SAD)

- bulimia nervosa and, 1338
- genetics of, **121**
- prevalence of, 1199
- rating scales for, 1199

Social anxiety disorder treatment, 1199–1203

antidepressants

- bupropion, 1199
- MAOIs, 289, 294, 296, 1199, 1201
- mirtazapine, 483, 1199, 1200
- nefazodone, 1199, 1200
- SSRIs, 1199–1200
  - in children and adolescents, 1444–1445
  - citalopram, 441, 1444–1445
  - escitalopram, 441, 1200, 1444
  - fluoxetine, 1200, 1444
  - fluvoxamine, 422–423, 1199
  - paroxetine, 395, 1200, 1444
  - sertraline, 365, 1199–1200, 1444
- TCAs, 1199
- venlafaxine, 519, 1199, 1200, 1445

benzodiazepines, 569, 1199, 1200, 1339

β-blockers, 1199, 1202

botulinum toxin, 1202

buspirone, 1201–1202

in children and adolescents, 1202–1203, 1444–1445

- citalopram, 1444–1445
- escitalopram, 1444
- fluoxetine, 1444
- paroxetine, 1202, 1444
- sertraline, 1202–1203, 1444
- venlafaxine, 1202, 1445

cognitive-behavioral therapy, 1203

- with D-cycloserine, [1202](#)
- with sertraline in children and adolescents, [1202-1203](#)
- gabapentin, [986-987](#), [1200-1201](#)
- GR205171, [1202](#)
- maintenance therapy, [1199](#), [1203](#)
- olanzapine, [1201](#)
- ondansetron, [1201](#)
- pregabalin, [994](#), [1201](#)
- quetiapine, [691](#)
- Social cognition and interaction training, for schizophrenia, [1252](#)
- Social deficits
  - in autism spectrum disorder, [1466](#)
  - in schizophrenia, [767-768](#), [1242](#), [1250-1253](#)
- Social Effectiveness Therapy for Children (SET-C), [1444](#)
- Social Functioning Scale (SFS), [659](#)
- Social phobia. *See* [Social anxiety disorder](#)
- Social Phobia Inventory (SPIN), [1199](#)
- Social skills training (SST)
  - for autism spectrum disorder, [1432](#)
  - for schizophrenia, [1245](#), [1251-1252](#)
- Sodium ion channels, [33](#), [47](#), [49](#), [58](#), [85](#), [97](#)
  - drug effects on
    - carbamazepine, [949](#)
    - eslicarbazepine acetate, [949](#)
    - lamotrigine, [1001](#), [1002](#)
    - topiramate, [1017](#), [1018](#)
- Sodium oxybate, [1069](#)
- Somatic therapies, [1105-1134](#)
  - bright light therapy, [1163](#), [1166](#)
  - for depression, [1162-1163](#)
  - ECT, [1105-1129](#), [1162](#), [1163](#)
  - investigational techniques, [1131-1134](#), [1163](#)
    - deep brain stimulation, [1133-1134](#), [1163](#)
    - focal electrically administered seizure therapy, [1132](#)
    - magnetic seizure therapy, [268](#), [1132](#), [1163](#)
    - transcranial direct current stimulation, [1132-1133](#)
  - repetitive transcranial magnetic stimulation, [1129-1131](#), [1163](#)
  - vagus nerve stimulation, [1130-1131](#), [1162-1163](#)
- Somatostatin, [100](#), [949](#)
- Somatotropin. *See* Growth hormone
- Somnolence, drug-induced. *See also* [Drowsiness](#); [Sedation](#)
  - antihistamines, [861](#)

aripiprazole, [746](#), [747](#), [1439](#), [1463](#), [1468](#)  
asenapine, [804](#), [805](#), [806](#), [1439](#), [1464](#)  
carbamazepine, [944](#), [957](#), [1179](#)  
clomipramine, [1449](#)  
clonidine, [1454](#)  
duloxetine, [472](#), [540](#), [1436](#), [1498](#)  
eslicarbazepine acetate, [960](#)  
gabapentin, [987](#), [1401](#), [1404](#)  
haloperidol, [719](#), [816](#), [1465](#)  
iloperidone, [816](#), [816](#)  
lithium, [1178](#)  
lurasidone, [825](#)  
mirtazapine, [487](#), [1498](#)  
nefazodone, [462](#), [1436](#)  
olanzapine, [804](#), [1179](#), [1316](#), [1439](#)  
opioids, [1385](#)  
oxcarbazepine, [1440](#), [1502](#)  
paliperidone, [1463](#)  
pregabalin, [992](#), [1393](#), [1401](#), [1404](#)  
quetiapine, [693](#), [694](#), [804](#), [1180](#), [1440](#), [1463](#)  
risperidone, [693](#), [718](#), [719](#), [816](#), [1180](#), [1439](#), [1457](#), [1463](#)  
SSRIs, [398](#), [424](#), [443](#), [1435](#), [1447](#), [1449](#), [1497](#)  
topiramate, [1028](#), [1029](#), [1440](#), [1502](#)  
trazodone, [457](#)  
valproate, [1178](#)  
venlafaxine, [1498](#)  
ziprasidone, [774](#), [1180](#), [1440](#), [1464](#)  
zolpidem, [1365](#)  
Sonata. See [Zaleplon](#)  
Sorine. See [Sotalol](#)  
Sotalol, [233](#), [818](#), [865](#)  
SPECT. See [Single photon emission computed tomography](#)  
SPECTRUM (Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication) study, [697](#)  
Speech-language disturbances, drug-induced benzodiazepines, [572](#)  
    carbamazepine, [944](#)  
    MAOIs, [290](#)  
    sertraline, [372](#)  
    topiramate, [1028](#)  
SPI (Safety Planning Intervention), for suicidal patients, [1599–1600](#)  
Spielberger State-Trait Anxiety Inventory (STAI), [666](#)  
SPIN (Social Phobia Inventory), [1199](#)



Sipiperone, [587](#), [589](#)  
Spironolactone challenge, in depression, [160](#)  
Spousal abuse, [1596](#)  
SPRINT (Short PTSD Rating Instrument), [1213](#)  
SSRIs. *See* [Selective serotonin reuptake inhibitors](#)  
SST. *See* [Social skills training](#)  
St. John's wort, [1507](#)  
    for depression, [1165](#)  
    drug interactions with, [556](#), [1165](#), [1507](#)  
    for OCD, [1212](#)  
STAI (Spielberger State-Trait Anxiety Inventory), [666](#)  
STAR\*D (Sequenced Treatment Alternatives to Relieve Depression) study, [63](#),  
    [288](#), [312](#), [435](#), [436](#), [445](#), [482](#), [500](#), [591](#), [898](#), [1106](#)  
State-Trait Anger Expression Inventory (STAXI), [774](#), [1027](#)  
Statins, for vascular cognitive impairment, [1044](#)  
STATs (signal transducers and activators of transcription), [95](#), [186](#), [194](#)  
Status epilepticus, [1112](#), [1123](#)  
STAXI (State-Trait Anger Expression Inventory), [774](#), [1027](#)  
Steady-state drug concentration, [219](#), [219–221](#), [221](#). *See also* [Plasma drug concentration](#)  
    drug interactions affecting, [231](#), [232](#)  
    of metabolites, [225–226](#)  
Stelazine. *See* [Trifluoperazine](#)  
Stellate ganglion block, for PTSD, [1218](#)  
Stereotypes  
    amphetamine-induced, [1086](#), [1087](#)  
    in autism spectrum disorder, [1466](#), [1475](#)  
        atomoxetine for, [1473](#)  
        celecoxib for, [1474](#)  
        haloperidol for, [1469](#)  
        olanzapine for, [1468](#)  
        pentoxifylline for, [1475](#)  
    in catatonia, [1605](#)  
    in children and adolescents with schizophrenia, [1465](#)  
Steroids  
    interaction with carbamazepine and oxcarbazepine, [963](#), [967](#)  
    metabolism of, [1507](#)  
Stevens-Johnson syndrome  
    carbamazepine and, [957](#)  
    lamotrigine and, [1008](#), [1502](#)  
    modafinil and, [1090](#)  
Stimulants. *See* [Psychostimulants](#)

Stool softeners, [1398](#)

Strabismus, botulinum toxin for, [867](#), [868](#)

Stress

acute stress disorder and, [1212–1213](#), [1218–1219](#), [1602](#)

adjustment disorders and, [1602](#)

definition of, [179](#)

depression and, [1153](#) (*See also* [Childhood abuse/trauma](#); [Early life stress](#))

downregulation of 5-HT<sub>1A</sub> receptor expression by, [60](#)

PTSD and, [1212–1218](#)

Responses of Mental Stress Induced

Myocardial Ischemia to Escitalopram Treatment study, [442–443](#)

Stress response

in depression, [99](#), [158–162](#), [181](#), [1156–1157](#)

fight-or-flight, [179](#), [180](#)

HPA axis in, [99](#), [157–158](#), [159](#), [179](#), [187](#), [435–436](#)

effects on HPG axis, [168](#)

escitalopram effects on, [436](#)

immune system effects of, [179–181](#)

locus coeruleus noradrenergic neurons in, [72](#)

prefrontal cortex in, [54](#), [73](#), [80](#)

protective effects of, [180](#)

Stress urinary incontinence, duloxetine for, [539–540](#)

Stroke, [122](#)

antipsychotic-associated risk in elderly dementia patients, [660](#), [825](#), [848](#),  
[1370](#), [1517](#)

depression and, [1153](#), [1154](#)

fluoxetine for, [345](#)

sertraline for, [370](#)

lithium and reduced risk of, [901–902](#)

NSAIDs and, [1382](#)

psychostimulants and, [1092–1093](#)

STRs (short tandem repeats), [128](#)

STS. *See* [Selegiline transdermal system](#)

Stuttering, sertraline-induced, [372](#)

Sublingual drugs, [213](#)

Substance Abuse and Mental Health Services Administration (SAMHSA),  
[1292](#), [1295](#)

Substance P, [100](#), [186](#), [949](#)

Substance P receptor antagonists, for depression, [391](#)

Substance-related disorders, [1283–1303](#). *See also* *specific substances of abuse*  
anticholinergic abuse, [860](#)

barbiturate abuse/dependence, [1068](#)

- benzodiazepine abuse/dependence, [573–575](#), [590](#), [1065](#), [1205](#)
- cocaine use disorder, [1301](#), [1611](#)
- designer drugs, [1610–1611](#)
- economic cost of, [1283](#)
- γ-hydroxybutyrate abuse, [1069](#), [1611](#)
- incidence of, [1283](#)
- insomnia and, [1349](#)
- laboratory screening for, [1611](#)
- psychiatric comorbidity with ADHD, bupropion for, [503](#)
  - depression, [1154](#), [1165](#)
    - suicide and, [1155](#)
  - schizophrenia, [1258–1259](#)
    - clozapine for, [632](#), [1259](#)
    - quetiapine for, [689](#)
  - suicide, [1597–1598](#)
- smoking cessation in, [1300](#)
- substance dependence, [573](#)
- treatment of, [1283–1303](#)
  - for acute intoxication with violent behavior, [1610–1612](#)
  - for alcohol-related disorders, [1284–1289](#), [1611](#)
  - buspirone, [592](#)
  - ketamine, [554–555](#)
  - for opioid-related disorders, [1289–1295](#), [1386–1387](#)
  - psychosocial interventions, [1284](#)
  - sertraline, [369](#)
  - for stimulant-related disorders, [1301–1303](#), [1611–1612](#)
  - for tobacco-related disorders, [1295–1300](#)
  - topiramate, [1023–1026](#)
- Substantia nigra
  - D<sub>2</sub> receptors in, [834](#)
  - dopaminergic neurons in, [65](#)
  - 5-HT<sub>7</sub> receptors in, [64](#)
  - norepinephrine in, in Alzheimer's disease with psychosis, [1519](#)
- Succinylcholine, [81](#)
  - for ECT, [1122](#), [1124](#)
- Sudden cardiac death
  - psychostimulants and, [1503–1504](#)
  - TCAs and, [319](#), [323](#)
- Suicide and suicidal behavior, [1596–1600](#)
  - age distribution of, [1598](#)
  - anorexia nervosa and, [1344](#)
  - assessing risk for, [1595](#), **[1596](#)**, [1596–1599](#)

- acute risk factors, [1597](#), [1597-1598](#)
- chronic risk factors, [1597](#), [1598-1599](#)
- lethality of attempts, [1598](#)
- previous suicide attempts, [1598](#)
- protective factors, [1599](#)
- in schizophrenia, [1260-1261](#)
- bipolar disorder and, [55](#), [59](#), [898-899](#), [907](#), [1598](#)
- borderline personality disorder and, [1599](#)
- depression and, [1151](#), [1154](#), [1155](#)
- drug-related
  - antidepressants, [1437](#), [1497](#)
    - bupropion, [1298](#)
    - SSRIs, [346-347](#), [372](#), [393-395](#), [399-400](#), [405](#), [425](#), [445-446](#)
    - venlafaxine, [521](#), [522](#)
  - atomoxetine, [1499](#)
  - barbiturates, [1068](#)
  - benzodiazepines, [1065](#)
  - carbamazepine, [958](#)
  - cariprazine, [848](#)
  - eslicarbazepine acetate, [958](#), [960](#)
  - lurasidone, [825](#)
  - oxcarbazepine, [958](#), [960](#)
  - psychostimulants, [1502-1503](#)
    - methamphetamine, [1611](#)
  - topiramate, [1030](#)
  - varenicline, [1298](#)
- in elderly persons, [1509](#), [1598](#)
- emergency department visits for, [1593](#)
- firearm access and, [1598](#), [1599](#), [1600](#)
- gender and, [1155](#), [1509](#), [1598](#)
- HPA axis and, [99](#)
- insomnia and, [1349](#), [1350](#)
- management of, [1599-1600](#)
  - cognitive-behavioral therapy, [1600](#)
  - hospitalization, [1599](#)
  - ketamine, [86](#), [553](#), [1600](#)
  - no-harm contracts, [1599](#)
  - Safety Planning Intervention, [1599-1600](#)
- mortality from, [1155](#), [1596](#)
- neurotransmitters and receptors in
  - glutamate, [87](#)
  - metabotropic glutamate receptors, [91](#)

- norepinephrine, 55
- serotonin, 55, 59, 346–347
- serotonin 5-HT<sub>1A</sub> receptor, 61
- serotonin transporter, 58–59, 245
- during or after psychiatric hospitalization, 1596–1597
- PET studies of, 59, 61, 69, 243, 245, 248
- race/ethnicity and, 1598
- schizophrenia and, 1260–1261
  - assessment and management of, 1260–1261
  - clozapine for, 632, 1261
  - ECT for, 1261
  - risk factors for, 1260
- suicidal ideation, attempted suicide, and completed suicide, 1596
- Sulindac, 1413
- Sulpiride, 608
  - for generalized anxiety disorder, 1209
- Sumatriptan, 405, 1414, 1615
- Supported employment, for schizophrenia patients, 1252
- Supported housing, for schizophrenia patients, 1252
- Suprachiasmatic nucleus (SCN)
  - benzodiazepine actions in, 1061
  - melatonin receptors in, 1071
  - regulation of circadian pattern of HPA activity by, 158
- Surgical interventions
  - for chronic pain, 1377
  - for OCD, 1212
  - for osteoarthritis, 1407
  - for PTSD, 1218
- Sustenna. *See* Paliperidone palmitate
- Suvorexant, for insomnia, 1052, 1072–1073, 1358–1359, 1367
  - contraindications to, 1072
  - dosing of, 1072, 1642
  - drug interactions with, 1072, 1073
  - pharmacokinetics of, 1072–1073
  - side effects of, 1359, 1367
  - use in hepatic disease, 1072
- Sweating
  - during alcohol or sedative-hypnotic withdrawal, 573, 1285, 1613
  - anticholinergic-induced decrease in, 858, 859
  - drug-induced
    - duloxetine, 540
    - levomilnacipran, 541

- prazosin, [1368](#)
- SSRIs, [345](#), [398](#), [401](#), [443](#), [1196](#), [1451](#)
- TCAs, [324](#)
- venlafaxine, [521](#), [522](#), [1498](#)
- in neuroleptic malignant syndrome, [1614](#)
- during opioid withdrawal, [1613](#)
- in serotonin syndrome, [346](#)
- Symmetrel. *See* [Amantadine](#)
- Sympathetic nervous system, [72](#), [179](#), [186](#)
  - in depression, [181–182](#), [195](#)
  - drug effects on, sertraline, [360](#)
  - HPA axis and, [187](#)
- Sympathomimetic amines, interaction with MAOIs, [292–294](#), [293](#)
- Symptom Checklist-90 (SCL-90), [665](#)
- Symptom Checklist-90—Revised (SCL-90-R), [774](#), [1027](#)
- Synapses of amphids defective (SAD) kinases, [51](#)
- Synaptic plasticity, [102](#)
  - AMPA receptors in regulation of, [84](#), [86](#), [88](#)
  - in bipolar disorder, [89](#)
  - cytokines and, [189](#)
  - in depression, [1157](#)
  - genome-wide association studies of calcium signaling in, [140](#)
  - glutamate in, [83](#)
  - kainate receptors in regulation of, [89](#)
  - ketamine-enhanced, [268](#)
  - long-term depression, [86](#)
  - long-term potentiation, [59](#), [86](#)
  - NMDA receptors in regulation of, [30](#), [86–87](#)
- Syncope, clozapine-induced, [636](#)
- Syndrome of inappropriate antidiuretic hormone (SIADH), drug-induced
  - in elderly persons, [1508](#)
  - SSRIs, [1508](#)
    - fluoxetine, [346](#)
    - paroxetine, [401](#)
    - sertraline, [371–372](#)
  - tranylcypromine, [295](#)
  - venlafaxine, [1508](#)
- Systemic lupus erythematosus, [87](#), [178](#), [1113](#)
- Systems family therapy, for anorexia nervosa, [1344](#)
- SztPD (schizotypal personality disorder), [162](#), [1328–1329](#)

T cells, 178  
in depression, 182, **182**  
glucocorticoid effects on, 158  
helper, 158, 178  
suppressor, 178

T<sub>3</sub>. See **Triiodothyronine**

T<sub>4</sub>. See **Thyroxine**

Tachycardia  
during alcohol or sedative-hypnotic withdrawal, 1613  
after clonidine discontinuation, 1500  
drug-induced  
antipsychotics, 1516  
classic antipsychotics, 612, **615**, **719**  
clozapine, 626, 636, 637, 1464  
ketamine, 555  
lamotrigine, 1011  
milnacipran, 541  
modafinil, 1090  
quetiapine, **1370**  
risperidone, 718, **719**, 721  
TCAs, 321, 322–323  
in panic disorder, 1604  
in serotonin syndrome, 346

Tacrine, 425, 1041

Tacrolimus, interaction with carbamazepine and oxcarbazepine, **963**, 967

Tai chi, **1396**

Tamoxifen  
for hot flashes, 370  
interaction with paroxetine, 398, 404, **404**, 405

*Tarasoff v. Regents of the University of California*, 1600–1601

Tardive dyskinesia (TD), 856  
amoxapine-induced, 321  
antipsychotic-induced, 875–876, 1256–1257, 1316, 1516, 1518, 1525  
cariprazine, 848  
classic antipsychotics, 617, 720, 875, 1247  
in elderly patients, 617, 663, 1257, 1516, 1518, 1626  
exclusion from CATIE study, 620  
lurasidone, 825  
olanzapine, 651, 669, 875  
risperidone, 717, 720, 875, 1522  
monitoring for, 1528

- prevention of, [875](#)
- risk factors for, [876](#), [1257](#)
- treatment of, [874–875](#), [1257](#)
  - buspirone, [593](#)
  - clonazepam, [866](#), [867](#), [874–875](#)
  - clozapine, [617](#), [635](#), [875](#), [876](#), [1257](#)
  - valbenazine, [875](#)
  - vitamin E, [868–869](#), [875](#)
- Tardive dystonia, antipsychotic-induced, [856](#), [1256–1257](#)
  - treatment of, [875](#), [876](#), [1257](#)
- Tasimelteon, [1071–1072](#), [1643](#)
- Tau protein
  - in Alzheimer's disease, [248](#), [1519](#)
  - expression in transgenic mice, [27](#)
  - PET imaging of, [247](#), [248](#)
- TCAs (tricyclic antidepressants). *See* [Antidepressants, tricyclic](#)
- TD. *See* [Tardive dyskinesia](#)
- tDCS (transcranial direct current stimulation), [1132–1133](#)
- TDT (transmission disequilibrium test), [134–135](#)
- TEAM (Treatment of Early Age Mania) study, [899](#), [1441](#)
- Tegretol; Tegretol-XR. *See* [Carbamazepine](#)
- Telemedicine systems, for psychiatric emergencies, [1594–1595](#)
- Temazepam
  - dosing of, [1642](#)
  - in elderly patients, [1076](#)
  - for insomnia, [1064](#), [1351](#), [1353](#), [1364](#)
  - pharmacokinetics of, [566](#), [567](#), [572](#), [1060](#), [1061](#), [1064](#)
  - side effects of, [1364](#)
  - structure of, [565](#), [1053](#)
  - use in pregnancy, [1567](#)
- Temporomandibular joint disorder, [1401](#)
- Tenormin. *See* [Atenolol](#)
- Tension-type headache (TTH), [1408](#), [1411](#)
- Teratogenic effects of drugs, [1546–1547](#). *See also* [Pregnancy and lactation](#)
  - amantadine, [864](#), [1566](#)
  - benzodiazepines, [576](#), [1566–1567](#)
  - benztropine, [1566](#)
  - bupropion, [1553](#)
  - carbamazepine, [959](#), [1559–1560](#)
  - cariprazine, [849–850](#)
  - clozapine, [1562](#)
  - diphenhydramine, [1566](#)



- duloxetine, 1553
- FDA reproductive safety ratings, 1547–1548, **1548**
- fluoxetine, 1549
- lamotrigine, 1011, 1561
- lithium, 901, 1555
- mirtazapine, 1553
- nefazodone, 1553
- olanzapine, 1563
- paroxetine, 402–403, 1549
- phenothiazines, 1565
- risperidone, 1564
- sertraline, 1549, 1550
- TCAs, 324–325, 1554
- topiramate, 1030
- trazodone, 1553
- valproate, 935, 1556–1559
- venlafaxine, 1553
- Terfenadine, 861, 1507
  - interaction with nefazodone, 462
- Testosterone, 166, 934
- Tetrabenazine, 874, 875, 1257
- TH (tyrosine hydroxylase), 65, **66–67**, 72, **74–75**
- Theobromine, 97
- Theophylline, 97, 1506, 1507
  - drug interactions with, 233
    - carbamazepine, **963**, 967
    - fluvoxamine, 425
    - lithium, 907
    - oxcarbazepine, **963**
    - propranolol, 866
- Thiamine, for alcoholism, 1613
- Thiopental, 1067
- Thioridazine
  - dosing of, **1645**
  - interaction with fluvoxamine, 425
  - for mood disorders, 611
  - receptor affinities of, **613**
  - for schizophrenia in children and adolescents, 1465
  - side effects of, **615–616**
    - cardiovascular effects, 618, 780, 1516, 1517
    - ocular effects, 619
    - weight gain, 618, 637

- structure-activity relations for, [605](#), [607](#)
- Thiothixene
  - dosing of, [1645](#)
  - indications for
    - borderline personality disorder, [1317](#)
    - schizophrenia in children and adolescents, [1465](#)
    - schizotypal personality disorder, [1329](#)
  - interaction with carbamazepine and oxcarbazepine, [963](#), [966](#)
  - receptor affinities of, [613](#)
  - side effects of, [615](#)–[616](#)
  - structure-activity relations for, [606](#), [607](#)
- Thioxanthenes. *See also* [Antipsychotics](#)
  - side effects of, [615](#)–[616](#)
  - structure-activity relations for, [606](#), [607](#)
- Thirst, lithium-induced, [1439](#), [1501](#)
- 30-Item Inventory of Depressive Symptomatology—Clinician-Rated (IDS-C30), [1096](#)
- Thorazine. *See* [Chlorpromazine](#)
- Threohydrobupropion, [498](#)
- Thrombocytopenia, drug-induced
  - carbamazepine, [957](#), [1179](#)
  - valproate, [933](#), [1179](#), [1502](#)
- Thrombocytopenic purpura, antipsychotic-induced, [619](#)
- Thyroid disorders
  - depression and, [192](#)
  - euthyroid sick syndrome, [192](#)
  - lithium-induced, [903](#)–[904](#), [1178](#), [1501](#)
  - mood disorders and, [165](#)
- Thyroid hormones, [49](#), [53](#), [164](#)–[165](#)
  - drug interactions with
    - carbamazepine and oxcarbazepine, [963](#)
    - quetiapine, [697](#)
- Thyroid-stimulating hormone (TSH), [164](#)–[165](#)
  - in euthyroid sick syndrome, [192](#)
  - lithium effects on, [903](#)
- Thyrotropin-releasing hormone (TRH), [100](#), [164](#)–[165](#)
- Thyroxine (T<sub>4</sub>), [165](#)
  - in euthyroid sick syndrome, [192](#)
  - lithium effects on, [903](#)
- Tiagabine
  - in generalized anxiety disorder, [1209](#)
  - interaction with carbamazepine and oxcarbazepine, [963](#), [965](#)

- mechanism of action of, [96](#), [990](#)
- in panic disorder, [1197](#)
- for PTSD, [1216](#)

Ticlopidine–drug interactions

- carbamazepine, [964](#)
- ketamine, [556](#)

Tics

- ADHD and
  - atomoxetine for, [1454](#)
  - guanfacine for, [1455](#)
- drug-induced
  - psychostimulants, [1502](#)
  - SSRIs, [1497](#)
- Tourette syndrome, [1460–1462](#)

Timolol, interaction with paroxetine, [404–405](#)

Tinnitus

- during benzodiazepine withdrawal, [573](#)
- drug-induced
  - sertraline, [371](#)
  - venlafaxine, [1208](#)
- treatment of
  - sertraline, [370](#)
  - TCAs, [319](#)

Tizanidine

- interaction with fluvoxamine, [425](#)
- for pain, [1393](#), [1413](#)

TMS. See [Repetitive transcranial magnetic stimulation](#)

TNF- $\alpha$ . See [Tumor necrosis factor  \$\alpha\$](#)

Tobacco-related disorders. See [Smoking/tobacco-related disorders](#)

$\alpha$ -Tocopherol. See [Vitamin E](#)

Tolbutamide, [1507](#)

Topiramate, [1017–1031](#)

- in children and adolescents, [1019](#), [1440](#), [1501](#)
- dosing of, [1653](#)
- drug interactions with, [1030](#)
  - carbamazepine, [963](#), [965](#), [1019](#), [1030](#)
  - hormonal contraceptives, [1030](#)
  - lithium, [905](#), [1030](#)
  - oxcarbazepine, [963](#), [968](#)
  - phenytoin, [1019](#), [1030](#)
- history and discovery of, [1017](#)
- indications for, [1017](#), [1019–1028](#), [1031](#)

- binge-eating disorder, [1022-1023](#), [1343](#), [1346](#)
- bipolar disorder, [1019](#), [1020](#)
  - in children and adolescents, [1440](#)
- borderline personality disorder, [1027](#), [1323](#), **[1325](#)**
- bulimia nervosa, [1022](#), [1339](#)
- depression, [1020-1021](#)
- drug-associated weight gain, [1027-1028](#), [1254](#)
- migraine prophylaxis, [1017](#), [1019](#), **[1411](#)**, **[1415](#)**
- obesity, [1017](#), [1019](#), [1028](#)
  - combined with phentermine, [503](#), [1017](#), [1019](#), [1028](#)
- OCD, [1026-1027](#), [1212](#)
- PTSD, [1026](#), [1216](#)
  - with alcohol use disorder, [1026](#)
- schizoaffective disorder, [1022](#)
- schizophrenia, [1021-1022](#)
- seizures, [638](#), [1017](#), [1019](#)
- substance use and addictive disorders, [1023-1026](#)
  - alcohol use disorder, [1023-1024](#), [1026](#), [1288-1289](#), [1302](#)
  - cocaine use disorder, [1024-1025](#)
  - gambling disorder, [1026](#)
  - methamphetamine use disorder, [1025](#)
  - smoking cessation, [1025-1026](#)
- mechanism of action of, [1019](#), [1288](#)
- pharmacokinetics and disposition of, [1018-1019](#), [1507](#)
- pharmacological profile of, [1017-1018](#)
- side effects and toxicology of, [1021](#), [1028-1030](#), [1339](#), [1440](#), [1502](#)
- structure of, **[1018](#)**
- suicidality and, [1030](#)
- use in pregnancy, [1030](#)
- use in renal or hepatic disease, [1019](#)

TORDIA (Treatment of SSRI-Resistant Depression in Adolescents) trial, [1437](#)

Torsades de pointes, [233](#)

- antipsychotic-induced, [618](#), [780](#), [781-782](#), [1517](#)

Torticollis

- antipsychotic-induced, [614](#), [1256](#)
- botulinum toxin for, [868](#)

Tourette syndrome, [1460](#)

- treatment of, [1460-1462](#)
  - antipsychotics, [612](#), [1461](#)
    - aripiprazole, [735](#), [738](#), [743-744](#), [750](#), [1461](#)
    - brexpiprazole, [749](#)
    - haloperidol, [1461](#), [1462](#)

- pimozide, [608](#), [612](#), [1461](#), [1462](#)
- risperidone, [1461](#)
- in children with ADHD, [1462](#)
- clinical recommendations for, [1461–1462](#)
- clonidine, [1460–1461](#), [1500](#)
- guanfacine, [1460–1461](#)
- habit reversal training, [1461–1462](#)
- Toxic epidermal necrolysis
  - carbamazepine and, [957](#)
  - lamotrigine and, [1008](#)
- TPH2 gene, [1158](#)
- TRAAY (Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth), [1460](#)
- Tramadol, [1383–1384](#), [1414](#)
  - abuse potential of, [1387](#)
  - combined with acetaminophen, [1398](#), [1408](#)
  - dosing of, [1383](#)
  - drug interactions with
    - bupropion, [506](#)
    - carbamazepine and oxcarbazepine, [963](#)
  - in elderly patients, [1384](#)
  - for fibromyalgia, [1403](#), [1403](#)
  - for low back pain, [1406](#), [1406](#)
  - for neuropathic pain, [1400](#), [1401](#)
  - for osteoarthritis, [1408](#)
  - pharmacological profile of, [1383](#)
  - use in renal or hepatic disease, [1383](#), [1384](#)
- Tramiprosate, [1045](#)
- Transcranial direct current stimulation (tDCS), [268](#), [1132–1133](#)
- Transcranial magnetic stimulation (TMS). *See* [Repetitive transcranial magnetic stimulation](#)
- Transcription, [6](#)
- Transcription (*trans*-acting) factors, [6](#), [8](#), [9](#), [10](#), [22](#)
  - alteration by chronic drug treatment, [224](#)
  - glucocorticoid interactions with, [188](#)
  - interactions of RNA polymerases with, [9](#)
  - nuclear receptors, [53](#)
  - opioid dependence and, [101](#)
  - regulation by second messengers, [10](#)
- Transdermal drugs, [213](#)
  - clonidine, in children and adolescents, [1451](#), [1461](#), [1472](#), [1500](#)
  - fentanyl, [1387](#), [1388](#), [1388](#)

- ketamine, 550
- methylphenidate, **1503**
- nicotine replacement therapy, 1296, 1297, 1298
- rivastigmine, 1041
- selegiline, 215, 297, 298–299
  - in adolescents, 1436
- topical analgesics, 1393–1394, **1415**
  - capsaicin, 1394, 1400
  - lidocaine, 1393, 1400
- Transfection, 14, 19, **20**
  - stable vs. transient, 17
  - vectors for, 17–18
- Transforming growth factor  $\beta$ , 179
- Transgenic mice, 21, 25–30, **27**
- Translocations, chromosomal, 125
  - balanced, 125, 130, 141
- Translocator protein (TSPO), 249
- Transmembrane signaling, 46–47, 102. *See also* [Signal transduction pathways](#)
- Transmission disequilibrium test (TDT), 134–135
- Transporters
  - dopamine, 68–70
  - drug, 211–212, 227–228
  - excitatory amino acid, 84
  - GABA, 58, 92
  - glutamate, 83–84
  - serotonin, 55–59
- Tranylcypromine, 283, **284**, 295
  - contraindications to, 295
  - dietary interactions with, 291
  - discontinuation of, 295
  - dosing of, **1640**
  - drug interactions with
    - meperidine, 292
    - phenylephrine, 294
  - familial aggregation of response to, 124
  - indications for, 295
    - borderline personality disorder, **1321**
    - depression, 288
    - in bipolar disorder, 317, 1183
    - social anxiety disorder, 289
  - pharmacokinetics of, 295
  - pharmacological profile of, 286

- physical dependence on, 295
- side effects of, 290, 295
- stimulant effects of, 286, 295
- structure of, **287**
- withdrawal from, 295

#### Trauma exposure

- acute stress disorder after, 1212–1213, 1218–1219, 1602
- benzodiazepines after, 1603–1604
- in childhood (See [Childhood abuse/trauma](#))
- emergency interventions after, 1218–1219, 1602–1604, **1603**
- psychological debriefing after, 1602–1603
- PTSD after, 1212–1218

#### Traumatic brain injury. See [Head injury](#)

#### Trazodone, 455–459, 462–463

- dosing of, 458, **1639**
- drug interactions with, 459
  - carbamazepine, 965
  - paroxetine, 404, 405
- in elderly persons, 457
- formulations of, 455
- generic, 455
- history and discovery of, 455
- indications for, 456–458
  - agitation and aggression in elderly patients, 1626–1627
  - akathisia, 458
  - Alzheimer's disease, 457
  - bulimia nervosa, 1338
  - depression, 456–457
    - lithium and, 898
  - generalized anxiety disorder, 457
  - insomnia, 290, 457–458, 1362–1363, **1369**
    - in adjustment disorders, 1602
  - panic disorder, 1197
  - schizophrenia, 458
- mechanism of action of, 456
- overdose of, 458
- pharmacokinetics and disposition of, 456
- pharmacological profile of, 455–456
- side effects and toxicology of, 458–459, **1369**
  - priapism, 458, 1616
- structure of, **456**
- use in medical illness, 458

- use in pregnancy and lactation, 1553
- TRD. See [Depression, treatment-resistant](#)
- Treatment of Early Age Mania (TEAM) study, 899, 1441
- Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial, 1437
- Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY), 1460
- TREK-1, 51
- Tremor
  - during alcohol or sedative-hypnotic withdrawal, 573, 1068, 1285, 1613
  - drug-induced
    - amantadine, 863
    - antipsychotics, 614, 856, 1256
      - aripiprazole, 746, 747, 1439, 1463, 1468
      - cariprazine, **848**, 1180
      - paliperidone, 1463
    - carbamazepine, 944
    - clomipramine, 1448, 1449
    - desvenlafaxine, 521
    - lithium, 903, 905, 1458, 1472, 1501
    - SSRIs, 345, 398, 443, 1196, 1447
    - TCAs, 321
    - topiramate, 1029
    - valproate, 933, 1178, 1501
    - venlafaxine, 521
  - after SSRI discontinuation, 1615
  - treatment of
    - deep brain stimulation, 1134, 1163
    - gabapentin, 986, 990
- TRH. See [Thyrotropin-releasing hormone](#)
- Triazolam
  - dosing of, **1642**
  - drug interactions with
    - modafinil, 1089
    - nefazodone, 462
  - for insomnia, 1351, 1353, **1364**
    - in elderly patients, 1076
  - pharmacokinetics of, **566**, 1060, 1064, **1064**, 1507
    - in elderly persons, 1506
  - side effects of, 570, **1364**
  - structure of, **565**, **1053**
- Triazole dione, 460
- Triazolopyridazines, 1057



Trichloroethanol, [1069](#)

Trichotillomania

- fluvoxamine for, [423](#)
- sertraline for, [371](#)

Tricyclic antidepressants (TCAs). *See* [Antidepressants, tricyclic](#)

Trier Social Stress Test, [161](#), [162](#)

Trifluoperazine

- for borderline personality disorder, [1317](#)
- dosing of, [1645](#)
- receptor affinities of, [613](#)
- for schizophrenia in children and adolescents, [1465](#)
- side effects of, [615](#)–[616](#)
- structure–activity relations for, [605](#)
- use in pregnancy and lactation, [1565](#), [1566](#)

Triflupromazine, [605](#)

Trigeminal neuralgia, [1400](#)

- carbamazepine for, [943](#), [949](#), [1393](#)
- oxcarbazepine for, [943](#)

Triglyceride levels, drug effects on antipsychotics, [618](#), [695](#), [696](#)

- aripiprazole, [747](#)
- asenapine, [805](#)
- cariprazine, [850](#)
- clozapine, [638](#)
- iloperidone, [818](#)
- lurasidone, [825](#)
- olanzapine, [670](#), [695](#), [696](#), [747](#), [1462](#)
  - melatonin and, [671](#)
  - metformin and, [670](#)
- quetiapine, [695](#), [696](#)
- risperidone, [695](#), [696](#)
- ziprasidone, [695](#), [696](#), [780](#)

$\beta$ -blockers, [864](#)

Trihexyphenidyl, [856](#)–[860](#)

- abuse of, [860](#)
- dosing of, [858](#), [1660](#)
- drug interactions with, [859](#)–[860](#)
- for extrapyramidal side effects, [857](#), [858](#), [1607](#)
- history and discovery of, [856](#)
- mechanism of action of, [858](#)
- pharmacokinetics and disposition of, [858](#)
- pharmacological profile of, [858](#)
- side effects and toxicology of, [858](#)–[859](#)

- structure-activity relations for, 856, 858
- Triiodothyronine (T<sub>3</sub>), 164–165
  - antidepressant augmentation with, 165, 1160, 1162
  - in euthyroid sick syndrome, 192
  - for PTSD, 1217
- Trilafon. *See* Perphenazine
- Trimethadione, 1066
- Trimipramine
  - dosing of, 311, 1634
  - indications for
    - depression, 306
    - insomnia, 1362, 1369
  - pharmacokinetics of, 311
  - pharmacological profile of, 308
  - side effects of, 1369
  - structure-activity relations for, 306, 307
- Trintellix. *See* Vortioxetine
- Triptans
  - drug interactions with
    - SSRIs, 405
    - vortioxetine, 473
  - for migraine, 1411, 1411, 1414
- Trisomies, 124–125
- TrkB (tyrosine kinase receptor B), 435, 445, 553, 556, 1108
- Troleandomycin, interaction with carbamazepine, 964
- Tryptophan
  - acute depletion of, 55
    - depression and, 55, 192, 263, 315
    - panic disorder and, 55
  - for depression, 1165
  - interaction with MAOIs, 293
  - in serotonin synthesis, 54, 57, 192
- Tryptophan hydroxylase, 54, 57
- TSH. *See* Thyroid-stimulating hormone
- TSPO (translocator protein), 249
- TTH (tension-type headache), 1408, 1411
- Tuberohypophyseal dopamine circuit, 65
- Tuberoinfundibular dopamine circuit, 65, 66
  - effect of antipsychotic D<sub>2</sub> receptor blockade of, 608, 612, 618, 732
    - clozapine, 629
    - ziprasidone, 756
- Tuberous sclerosis, 245

Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), [186](#), [189](#)  
    in depression, [162](#), [184](#), [1157](#)  
        antidepressant effects on, [184](#), [195](#)  
    in fibromyalgia, [185](#)  
    HPA axis and, [188](#), [194](#)  
Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) antagonists, [191](#)  
Turner syndrome, [125](#)  
12-Step facilitation, for alcohol use disorder, [1284](#)  
22q11 syndrome, [125](#), [130](#)  
Twin studies, [117–122](#), [118](#), [120](#), [123](#)  
    in conduct disorder, [123](#)  
    in depression, [123](#), [140](#), [1153](#)  
    in schizophrenia, [123](#), [124](#), [142](#)  
    in substance use disorders, [123](#)  
    of suicidality, [445](#)  
Tyramine in diet, MAOI interactions with, [283](#), [291](#), [296](#), [297](#), [298](#)  
L-Tyrosine  
    in dopamine synthesis, [65](#), [66–67](#)  
    in norepinephrine synthesis, [72](#), [74–75](#)  
Tyrosine hydroxylase (TH), [65](#), [66–67](#), [72](#), [74–75](#)  
Tyrosine kinase receptor B (TrkB), [435](#), [445](#), [553](#), [556](#), [1108](#)  
  
UCLA PTSD-I (University of California, Los Angeles Post-Traumatic Stress Disorder Index for DSM-IV), [1451](#)  
UGT (uridine diphosphate-glucuronosyltransferase), [944](#), [1002](#)  
U.K. Epilepsy and Pregnancy Register, [1561](#)  
Ulcerative colitis, [188](#), [194](#)  
Unifiram, [1045](#)  
Unisomies, [124](#)  
United Parkinson's Disease Rating Scale, [986](#)  
University of California, Los Angeles Post-Traumatic Stress Disorder Index for DSM-IV (UCLA PTSD-I), [1451](#)  
University of California San Diego Performance-Based Skills Assessment (UPSA), [469](#)  
    Brief version (UPSA-B), [827](#)  
Upper respiratory infection, drug-induced  
    doxepin, [1367](#)  
    sertraline, [1435](#)  
UPSA (University of California San Diego Performance-Based Skills Assessment), [469](#)  
    Brief version (UPSA-B), [827](#)  
Urecholine. *See* [Bethanechol](#)

Uridine diphosphate-glucuronosyltransferase (UGT), [944](#), [1002](#)

Urinary abnormalities, drug-induced anticholinergic agents, [858](#), [859](#)

- antipsychotics, [612](#), [1516](#)
- clozapine, [640](#)
- diphenhydramine, [1368](#)
- doxylamine, [1368](#)
- levomilnacipran, [541](#)
- lithium, [1439](#), [1458](#), [1459](#), [1501](#)
- MAOIs, [290](#)
- risperidone, [722](#)
- sertraline, [372](#)
- TCAs, [321](#), [1368](#), [1369](#)
- venlafaxine, [1471](#)

Urine drug screening, [1611](#)

Use of Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia (METS) study, [670](#)

Vaccines, immune responses to, [178](#), [180](#), [181](#)

Vagus nerve stimulation (VNS), [268](#), [1130](#)

- for depression, [1130](#), [1162–1163](#)
  - compared with ECT, [1131](#)
- immune system effects of, [186](#)

Valbenazine (NBI-98854), [875](#)

Valproate, [923–936](#)

- in children and adolescents, [899–900](#), [930](#), [1440](#), [1441–1442](#), [1459](#), [1471](#), [1501](#), [1501](#)
- dosing of, [926](#), [936](#), [1178](#), [1653](#)
  - in children and adolescents, [1501](#)
  - in pregnancy, [1557](#)
- drug interactions with, [924](#), [935–936](#)
  - antipsychotics, [619](#)
  - carbamazepine, [934](#), [962–964](#), [963](#), [964](#)
  - lamotrigine, [936](#), [1012](#)
  - lithium, [905](#)
  - oxcarbazepine, [963](#)
  - paroxetine, [405](#)
- in elderly persons, [930–931](#), [934](#), [1075–1076](#), [1524](#), [1612](#), [1627](#)
- epigenetic mechanisms of response to, [124](#)
- formulations of, [923](#), [925](#), [933](#), [936](#), [1178](#)
- history and discovery of, [923](#)
- indications for, [926–932](#)
  - ADHD, [930](#)

- aggression in children and adolescents, 1459
- antipsychotic augmentation in schizophrenia, 931
- autism spectrum disorder, 1471
- behavioral complications of dementia, 930-931, 1524, 1612, 1627
- bipolar disorder
  - with alcohol use disorder, 932
  - in children and adolescents, 899-900, 930, 1440, 1441-1442
  - depressive episodes, 927, 1182
  - maintenance treatment, 895, 896, 927-929, 936, 1184-1185
  - mania, 738, 741, 803, 923, 926-927, 942, 1178-1179
  - mania secondary to head trauma or neurodevelopmental/neurodegenerative disorders, 929-930
  - predictors of response to, 932, 936
- borderline personality disorder, 1320, 1323, 1324-1325, 1327
- clozapine-induced seizures, 638
- conduct disorder, 930, 1459
- irritability and aggression, 931
- migraine prophylaxis, 1411, 1415
- oppositional defiant disorder, 930, 1459
- panic disorder, 1197
- PTSD, 1026, 1216
- mechanism of action of, 926
- neurodevelopmental outcome of children exposed in utero to, 1556-1557
- overdose of, 935
- pharmacokinetics and disposition of, 923-926, 925, 926
- pharmacological profile of, 923
  - effect on brain GABAergic neurons, 92
  - effect on brain glutamate receptors, 88, 89
- side effects and toxicology of, 932-935, 1178-1179, 1440, 1501-1502
  - cognitive effects, 934
  - gastrointestinal effects, 933, 1178, 1440, 1501
  - hair loss, 935, 1502
  - hematological effects, 933, 1179, 1502
  - hepatic effects, 933-934, 1179, 1502
    - in neonates after in utero exposure, 1558
  - lipid profile effects, 934
  - monitoring for, 1501
  - pancreatitis, 933, 1179, 1502
  - polycystic ovarian syndrome, 934, 1185, 1501, 1502
  - sedation, 933, 1501
  - teratogenic effects, 935, 1556-1559
  - tremor, 933, 1178, 1501

- weight gain, [934](#), [1185](#)
- structure-activity relations for, [923](#), [924](#)
- use in pregnancy and lactation, [935](#), [1549](#), [1556–1559](#)
  - fetal valproate syndrome, [1557](#), [1558](#)
  - folate supplementation and, [1558](#)
  - monitoring of nursing infants, [1570](#)
  - vitamin K supplementation and, [1559](#)
- Varenicline, for smoking cessation, [81](#), [1297–1298](#), [1661](#)
  - combined with bupropion, [1298](#)
  - combined with nicotine replacement therapies, [1298](#)
  - dosing of, [1298](#), [1661](#)
  - in patients with psychiatric disorders, [1299–1300](#)
  - in schizophrenia, [1259](#)
  - suicidality and, [1298](#)
- Variable number tandem repeats (VNTRs), [128–129](#)
  - SLC6A3* gene, [69](#), [129](#)
- Vascular cognitive impairment
  - Alzheimer's disease and, [1044](#)
  - risk factors for, [1043](#)
  - treatment of, [1043–1044](#)
    - acetylcholinesterase inhibitors, [1044](#)
    - aspirin, [1043](#), [1044](#)
    - CDP-choline, [1044](#)
    - NSAIDs, [1044](#)
    - statins, [1044](#)
- Vasoactive intestinal peptide, [100](#), [186](#)
- Vasomotor menopausal symptoms
  - desvenlafaxine for, [520](#)
  - fluoxetine for, [345](#)
  - mirtazapine for, [485](#)
  - paroxetine for, [385](#), [398](#)
  - sertraline for, [370](#)
  - venlafaxine for, [520](#)
- Vasopressin, [99](#), [100](#)
  - for borderline personality disorder, [1323](#)
  - receptors for, [99](#)
  - in stress response, [159](#)
- VCFS (velocardiofacial syndrome), [125](#)
- Vecuronium, interaction with carbamazepine and oxcarbazepine, [963](#), [967](#)
- Velocardiofacial syndrome (VCFS), [125](#)
- Venlafaxine, [515–523](#)

in children and adolescents, 520–521, 1202, 1435–1436, 1438, 1443–1444, 1445, 1446, 1471, 1498, **1498**

*CYP2D6* screening before initiation of, 127

discontinuation syndrome with, 522, 1208, 1615

dosing of, 516, 517, 518, **1637–1638**

in children and adolescents, **1498**

drug interactions with, 522–523

bupropion, 506

MAOIs, 523

in elderly persons, 1508, 1514

formulations of, 213, 515, 516

extended-release, 515, 516–517, 518, 519, 520–521, 523

generic, 523

history and discovery of, 515

indications for, 517–521, 523

autism spectrum disorder, 1471

borderline personality disorder, 1320, **1322**

depression, 515, 517–519, 1159

in bipolar disorder, 518

vs. bupropion, 499, 518

in children and adolescents, 520–521, 1435–1436, 1438

vs. duloxetine, **536**

iSPOT-D study, 437–438

maintenance treatment, 391, 518–519

vs. milnacipran, 535

mirtazapine and, 288, 481–482

vs. paroxetine, 391

vs. trazodone, 457

vs. vortioxetine, 469, **470**, 518

generalized anxiety disorder, 519, 1207–1208, 1210

in children and adolescents, 1443–1444

with comorbid depression, 1207

vs. pregabalin, 994

menopausal vasomotor symptoms, 520

OCD, 520

pain syndromes, 1392, **1414**

panic disorder, 519, 1197

maintenance treatment, 1198

premenstrual dysphoric disorder, 520

PTSD, 519

social anxiety disorder, 519, 1199, 1200

in children and adolescents, 1202, 1445

mechanism of action of, [517](#)  
overdose of, [522](#)  
pharmacokinetics and disposition of, [516–517](#)  
    in elderly persons, [1508](#)  
pharmacological profile of, [515–516](#)  
    PET studies of receptor binding affinity, [59](#), [517](#)  
racemic, [226](#)  
side effects and toxicology of, [521–522](#), [1208](#), [1404](#), [1436](#), [1471](#), [1498](#),  
    [1514](#)  
structure–activity relations for, [515](#), [516](#)  
suicidality and, [521](#), [522](#)  
switching to/from MAOIs, [523](#)  
switching to vortioxetine from, [474](#)  
use in hepatic or renal disease, [516](#), [1508](#)  
use in pregnancy and lactation, [522](#), [1553](#), [1554](#)  
Ventral tegmental area (VTA), [65](#), [68](#), [73](#), [88](#), [834](#)  
Verapamil  
    interaction with carbamazepine, [964](#), [966](#), [969](#)  
    P-glycoprotein inhibition by, [312](#)  
Vertigo, drug-induced. *See also* [Dizziness](#)  
    amantadine, [863](#)  
    eslicarbazepine acetate, [960](#)  
Vesicular monoamine transporter 2 (VMAT2), [496](#)  
Veterans Administration Cooperative Study of Disulfiram Treatment of  
    Alcoholism, [1286](#)  
Vigabatrin, [990](#)  
    for cocaine and methamphetamine dependence, [1302](#)  
Vilazodone  
    dosing of, [1639](#)  
    interaction with carbamazepine, [965](#)  
    use in pregnancy and lactation, [1554](#)  
Violent behavior. *See also* [Aggression](#)  
    in bipolar disorder, [1606](#)  
    childhood exposure to  
        ADHD and, [1432](#)  
        borderline personality disorder and, [1326](#)  
        PTSD and, [1326](#)  
    in dementia, [1518](#)  
    duty to warn potential victims of, [1600–1601](#)  
    emergency treatment of, [1606–1609](#), [1607](#)  
    homicidal, [1600–1601](#)  
    interventions for victims of, [1603](#), [1603](#)



- opioid use and, [1289](#)
- in postpartum OCD, [1545](#)
- in schizophrenia, [1606](#)
- substance intoxication and, [1610](#)
- suicide and, [1598](#)
- Vioxx. *See* [Rofecoxib](#)
- Viral vectors for gene transfer, [18](#), [21](#)
- Visken. *See* [Pindolol](#)
- Visual disturbances
  - during benzodiazepine withdrawal, [573](#)
  - drug-induced
    - antipsychotics, [1516](#)
    - carbamazepine, [957](#), [1179](#)
    - classic antipsychotics, [612](#), [619](#)
    - diphenhydramine, [1368](#)
    - doxylamine, [1368](#)
    - eslicarbazepine acetate, [960](#)
    - ketamine, [555](#)
    - MAOIs, [290](#)
    - nefazodone, [462](#)
    - oxcarbazepine, [1440](#), [1502](#)
    - paroxetine, [386](#)
    - pregabalin, [995](#)
    - risperidone, [722](#)
    - TCAs, [321](#), [1368](#), [1369](#)
    - topiramate, [1029](#)
    - trazodone, [1369](#)
- Vitamin C, as cognitive enhancer, [1044](#)
- Vitamin E
  - as cognitive enhancer, [1044](#)
  - drug interactions with, [869](#)
  - side effects of, [869](#)
  - for tardive dyskinesia, [868–869](#), [875](#)
- Vitamin K
  - interaction with vitamin E, [869](#)
  - supplementation of, for valproate use in pregnancy, [1558](#)
- VMAT2 (vesicular monoamine transporter 2), [496](#)
- VNS. *See* [Vagus nerve stimulation](#)
- VNTRs. *See* [Variable number tandem repeats](#)
- Vortioxetine, [467–474](#)
  - discontinuation of, [472](#)
  - dosing of, [469](#), [470–471](#), [473](#), [1639](#)

- drug interactions with, 473, 474
- in elderly persons, 469
- history and discovery of, 467
- indications for, 468–469
  - depression, 468–469, 470–471
  - with cognitive dysfunction, 469
  - generalized anxiety disorder, 468
- mechanism of action of, 64
- overdose of, 473
- pharmacokinetics and disposition of, 468
- pharmacological profile of, 467–468
- side effects and toxicology of, 472–473, 474
- structure–activity relations for, 467, 468
- switching from SSRIs or SNRIs to, 473, 474
- use in hepatic or renal disease, 468

Vraylar. *See* [Cariprazine](#)

VTA (ventral tegmental area), 65, 68, 73, 88, 834

Vyvanse. *See* [Lisdexamfetamine](#)

Wakefulness-promoting agents. *See also* [Psychostimulants](#)

- armodafinil, 1090–1091

- FDA classification of, 1084

- modafinil, 1089–1090

Warfarin–drug interactions, 1507

- antipsychotics, 619

- barbiturates, 1068

- carbamazepine, 963, 967

- eslicarbazepine acetate, 969

- fluoxetine, 1508

- fluvoxamine, 425, 1508

- methylphenidate, 1089

- oxcarbazepine, 963, 968

- paroxetine, 404, 405

- sertraline, 373

- TCAs, 326

- trazodone, 459

Weakness

- during benzodiazepine withdrawal, 573

- drug-induced

  - botulinum toxin, 868

  - MAOIs, 290

Wechsler Memory Scale, 859

## Weight changes

in anorexia nervosa, 168, 666, 667, 1344

in bulimia nervosa, 1337

drug-induced, 168, 666, 667

antidepressants

bupropion, 502–503, 505

duloxetine, 540

isocarboxazid, 290

milnacipran, 541

mirtazapine, 484, 487, **1369**, 1498

SSRIs, 345, 371, 424, 1196, 1449

TCAs, 322, 324, **1368**, **1369**

antipsychotics, 777, 1246, 1253, 1499, 1516 (*See also* Metabolic effects of antipsychotics)

aripiprazole, 696, 737, 742, 747, 1461

asenapine, 804, 805, 1180, 1253, 1464

brexpiprazole, 737, 748

cariprazine, 847, **847**, 848, 849, **850**

in children and adolescents, 671, 1253, 1439, 1441, 1457

classic antipsychotics, 63, 64, 612, **616**, 618, 669, **695**, 718, 1253

clozapine, 626, 628, 637–638, 639, 669, 718, 1248, 1253, 1464, 1516

in elderly patients, 1516

iloperidone, 810, 817–818, 1253

lurasidone, 823, 825, 1253

olanzapine, 34, 637, 666, 667, 669–672, **695**, 718, 747, 805, 823, 931, 1179, 1185, 1216, 1248, 1253, **1370**, 1439, 1468, 1516, 1522, 1523, 1525

paliperidone, 1463

quetiapine, 637, 689, 691, **693**, 694, **695**, 718, 823, 1180, 1253, **1370**

risperidone, 637, 669, **693**, **695**, 716, 718, 931, 1253, 1441, 1457, 1458, 1467

ziprasidone, **695**, 696, 757, 777–778, **779**, 1253

benzodiazepines, 1065

carbamazepine, 957, 958

gabapentin, 1401, 1404

histamine H<sub>1</sub> receptor antagonism and, 757

lamotrigine, 1009

lithium, 902–903, 1178, 1501

olanzapine, 1316

pregabalin, 995, 1393, 1401, 1404

riluzole, 1474

topiramate, 1027–1028, 1029, 1339, 1343, 1502

- treatment of, 1254
  - melatonin, 671
  - metformin, 670–671, 1254
  - topiramate, 1027–1028, 1254
  - valproate, 931, 933, 934, 1178, 1185, 1501
- Weinberger Adjustment Inventory, 1459
- Wernicke-Korsakoff syndrome, 1613
- Withdrawal from substance. *See also* Discontinuation of drug
  - alcohol, 1285–1286, 1612–1613
  - barbiturates, 1068
  - benzodiazepines, 570, 572–573, 574, 1065, 1205, 1613, 1627
    - neonatal, 576
  - opioids, 1290–1291, 1613
    - neonatal, 1294
  - sedative-hypnotics, **1607**, 1612–1613
- Wnt signaling pathway, 891, 935
- World Federation of Societies of Biological Psychiatry, 1005
- World Health Organization, 1377, 1378, 1390
- Wound healing, 178, 180, 181, 183
  
- Xerostomia. *See* Dry mouth
- XKR4* gene, 815
- Xynem. *See* Sodium oxybate
  
- Yale-Brown Obsessive Compulsive Scale (Y-BOCS), 366, 367, 422, 423, 668, 692, 1026, 1027, 1210, 1211
  - Children’s version (CY-BOCS), 1447–1449, 1450, 1470
- Yale Global Tic Severity Scale (YGTSS), 744, 1461
- Yawning, drug-induced
  - duloxetine, 540
  - sertraline, 371
- YGTSS (Yale Global Tic Severity Scale), 744, 1461
- YMRS (Young Mania Rating Scale), 661–662, 689, 741, 742, 802–803, 824, **844–845**, 927, 930, 950, 987, 1019, 1020, 1438, 1439, 1440, 1441, 1442
- Yoga, **1396**, 1404, **1406**
- Yohimbine, **75**, 76, **308**, 399, 1218
- Young Mania Rating Scale (YMRS), 661–662, 689, 741, 742, 802–803, 824, **844–845**, 927, 930, 950, 987, 1019, 1020, 1438, 1439, 1440, 1441, 1442
  
- Zaleplon, for insomnia, 1057, **1365**
  - in adjustment disorders, 1602
  - dosing of, **1643**

- in elderly patients, 1076, 1526
- mechanism of action of, 1351
- pharmacokinetics of, 1064
- side effects of, 1365
- structure-activity relations for, 1057, 1058
- ZEISIG (Ziprasidone Experience in Schizophrenia in Germany/Austria) study, 765
- ZEUS (Ziprasidone Extended Use in Schizophrenia) study, 763, 778
- Zinc finger nucleases, 22
- Ziprasidone, 755-783
  - in children and adolescents, 773, 1438, 1440, 1462, 1463-1464, 1469, 1499
  - dosing of, 758-759, 761, 775, 1180, 1650
    - in children and adolescents, 1499
  - drug interactions with, 760, 782, 783
    - carbamazepine and oxcarbazepine, 963, 966
  - formulations of, 1249
    - intramuscular, 1608, 1609, 1610
  - history and discovery of, 755
  - indications for, 755, 761-773, 783
    - acute psychosis, 1245
    - aggression in children and adolescents, 1458
    - agitation, 772-773
    - antidepressant augmentation, 772
    - autism spectrum disorder, 1469
    - behavioral complications of dementia, 1624
    - behavioral emergencies, 1608, 1609
    - bipolar disorder, 758, 770-772
      - in children and adolescents, 1438, 1440
      - depressive episodes, 771
      - maintenance treatment, 771-772, 929, 1185
      - mania, 770, 770-771, 773, 892-893, 1180, 1610
    - borderline personality disorder, 1319
    - in children and adolescents, 773
    - generalized anxiety disorder, 1209
    - schizophrenia and schizoaffective disorder, 758-759, 761-769
      - for behavioral emergencies, 1609, 1610
      - CATIE study, 620, 713, 764-765, 766, 767, 776, 778, 779, 780, 1246-1247
      - in children and adolescents, 773, 1462, 1463-1464
      - for cognitive deficits, 766, 827
      - for depressive symptoms, 766-767

- vs. iloperidone, [813](#), [814](#)
- vs. lurasidone, [823](#)
- maintenance treatment, [762–766](#)
- for social deficits and improvement in quality of life, [767–768](#)
- switching from other antipsychotics to, [768–769](#)
- treatment-resistant illness, [768](#), [1249](#)
- overdose of, [781](#)
- pharmacokinetics and disposition of, [759–761](#)
  - food effects on, [759](#), [760–761](#)
- pharmacological profile of, [755–759](#), [783](#)
  - 5-HT<sub>1A</sub>, 5-HT<sub>1D</sub>, and 5-HT<sub>2C</sub> receptor activity, [756–757](#)
  - D<sub>2</sub> and 5-HT<sub>2A</sub> receptor activity, [756](#)
  - PET receptor occupancy studies, [757–758](#), [758](#)
  - serotonin and norepinephrine transporter activity, [757](#)
- side effects and toxicology of, [773–782](#), [783](#), [1180](#), [1248](#), [1440](#), [1464](#)
  - activation effects, [774–775](#)
  - cardiovascular effects, [755](#), [780–782](#), [1248](#)
  - DRESS syndrome, [775](#)
  - extrapyramidal side effects, [669](#), [756](#), [769](#), [774](#), [776–777](#), [871](#), [873](#), [1180](#), [1255](#), [1464](#)
  - mortality risk in elderly dementia patients, [774](#)
  - tolerability profile in clinical trials, [773–774](#)
  - weight gain/metabolic effects, [695](#), [696](#), [757](#), [777–780](#), [779](#), [1253](#)
- structure–activity relations for, [755](#), [756](#)
- use in pregnancy and lactation, [774](#), [1564–1565](#)
- use in renal or hepatic disease, [760](#)
- Ziprasidone Experience in Schizophrenia in Germany/Austria (ZEISIG) study, [765](#)
- Ziprasidone Extended Use in Schizophrenia (ZEUS) study, [763](#), [778](#)
- Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), [781](#)
- ZODIAC (Ziprasidone Observational Study of Cardiac Outcomes), [781](#)
- Zolmitriptan, [1414](#)
- Zoloft. *See* [Sertraline](#)
- Zolpidem
  - in adjustment disorders, [1602](#)
  - dosing of, [1643](#)
  - in elderly patients, [1076](#), [1526](#)
  - for insomnia, [1052](#), [1076](#), [1365](#)
  - interaction with carbamazepine, [966](#)
  - mechanism of action of, [1351](#)
  - pharmacokinetics of, [213](#), [1064](#)
  - pharmacological profile of, [96](#)

side effects of, **1365**

with SSRIs for generalized anxiety disorder, **1208**

structure-activity relations for, **1057**, **1058**

Zonalon. *See* **Doxepin**

Zonisamide

for alcohol use disorder, **1023**

for binge-eating disorder, **1343**

interaction with carbamazepine and oxcarbazepine, **963**, **965**

Zopiclone, **1057**

in elderly patients, **1076**

pharmacokinetics of, **1064**

*S*-enantiomer of (*See* **Eszopiclone**)

ZT-1, as cognitive enhancer, **1042**

Zyban. *See* **Bupropion**

Zyprexa Zydis. *See* **Olanzapine**